Cherwell

Environmental Monitoring Processes and Validation guide

How to ensure your EM Program complies with the new EU GMP Annex 1

Updated December 2022

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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 new 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 newly revised 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).

While the intent of these regulatory guides is clear, a common complaint is that they can appear both excessively prescriptive and open to interpretation.

However, they are ultimately intended to be used across many pharmaceutical 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 must make in order to determine the right path for them.

Adopting a business-efficient approach to EM

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' operations, complexity and product, will not necessarily be viable for another. How can an organisation still 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 facility, will help you achieve and maintain quality risk assessment on your 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 1971, 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.

Since the last revision in 2008, pharmaceutical manufacturing has seen significant changes in process and technology, therefore, an update was much overdue. The new 2022 revision, published in late August, delivers increased focus on a quality risk management (QRM) approach and the creation of a well-designed facility wide contamination control strategy (CCS).

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. The new 59-page 2022 revision seeks to elicit a greater understanding by pharmaceutical manufacturers of these new technologies.

Ultimately Annex 1 strives to remove any lingering potential risks to patient safety whilst moving 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.

How we are moving towards a global standard

With a definite emphasis on quality risk management, the revised EU GMP Annex 1 and other international standards collectively aim to create singular, up to date documentation.

Sterile manufacturing techology 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 to date.

Annex 1 now considers a range of additional aspects including: 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 and subjects such as viable and non-viable monitoring are also addressed in other standards, which of course have also been revised. For non-viable EM, there has been a change from ISO 14644 parts 1 and 2 1999 to the 2015 version.

Microbiological methods of monitoring are covered in ISO14698; however, it should be noted that a new European standard, EN 17141, has superseded the ISO standard for UK and European manufacturers.

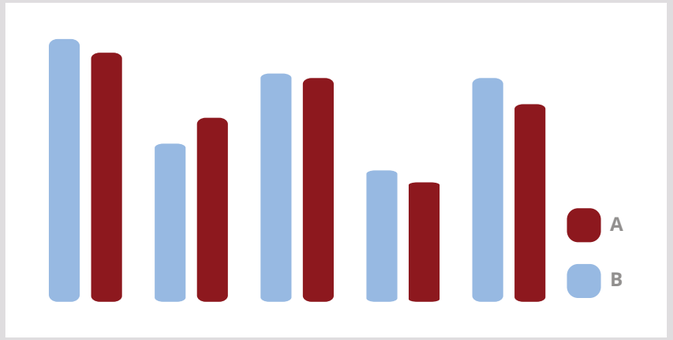
This duplication of standards undoubtedly provides greater complexity for international business. That said, Annex 1 does make reference to some of these aforementioned standards and how to apply them, as well as offering advice about best practices for EM, including continuous monitoring during filling operations.

Furthermore, it advises on how to approach data and the expectation to speciate isolates from grade A and grade B areas.

Changes to EM in the new Annex 1

Now that the Annex 1 revision is published and the deadline for it coming into operation is set as 25th August 2023, except for point 8.123 which is postponed until 25th August 2024, a key question is what are the main impacts to environmental monitoring?

In brief, these are some of the most notable changes relating to EM in the new Annex 1:

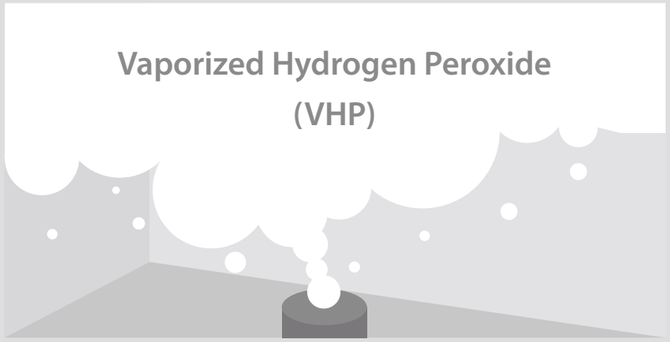


Trends monitoring

For both viable and non-viable environmental and process monitoring, ongoing routine monitoring should be undertaken with regards to the setting of appropriate alert and action limits and reviewing trending data to understand baseline flora of individual facilities and also continually develop the EM program.

Personnel training

The new Annex requires that personnel are appropriately trained, knowledgeable and qualified, not only in relation to facilities and processes, but that they should also fully understand EM. This is because it is their responsibility to correctly obtain the samples as part of the EM program to ensure the availability of accurate and relevant information for that cleanroom environment.



VHP fumigation

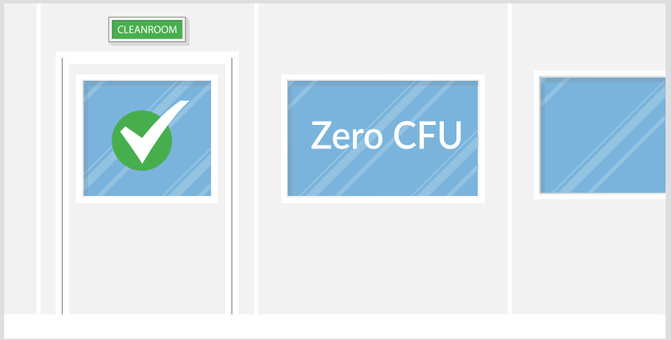
As the 2022 revision of Annex 1 now mentions vaporized hydrogen peroxide (VHP) for use in decontamination processes, consideration should be given as to whether EM products used can withstand this process in relation to protective packaging and media formulation.

Right methods for a facility

There is now a greater emphasis on risk-based management and a holistic approach to EM. So, using tools such as QMS (quality management system) and PQS (pharmaceutical quality system) will help to define locations for a facility's EM and what it is aiming to achieve. The new Annex 1 places more scrutiny on EM programs, requiring companies to fully understand their facility and processes to ensure they have a clear understanding of the right media and methods necessary to obtain the best data possible across their
entire facility.

Continuous EM

Viable air monitoring must now be undertaken throughout entire campaigns and processes in Grade A zones, however, there does remain ambiguity around what will be expected to achieve continuous EM. Along with the clear definition on expected zero CFU in Grade A, there is more emphasis on the quality of the result obtained. Consequently, the D50 that is being achieved must be considered, not only for active air sampling but for passive methods too. The clause on new technologies in the revised Annex 1 supports the use of alternative methodologies where appropriate, such as active continuous viable air monitors in place of passive sampling and active air samplers.



Zero CFU

The microbial limit for a Grade A space has changed from <1 CFU to zero CFU. This removes all previous ambiguity and companies must now have the confidence and assurances that their EM provides accurate results, therefore, monitoring devices must be capable of detecting a single CFU. Additionally, to achieve this stringent level of compliance, careful consideration must be given to the graded areas surrounding a Grade A critical zone as they will pose a risk of microbial ingress.

Further areas detailed in the latest EU guidelines include:

- Pharmaceutical Quality System (PQS) – specific requirements of the PQS when applied to sterile medicinal products.
- 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.
- Water treatment and testing – a dedicated section referring to the Pharmacopoeia, biofilms and water for injection.
- Production and specific technologies - specific requirements depending on the facilities processes and the different technologies implemented.

A more detailed overview and factsheet series on key changes in the 2022 version of Annex 1 are available on Cherwell's website.

Achieving Annex 1 compliance for your EM processes and program

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. These practices need to align with and be supportive of your facility wide contamination control strategy (CCS) that seeks to reduce the risk of product contamination at all stages. This involves a holistic approach to contamination risk management.

Start with a full EM audit.

- What methods are you currently using?
- Why do you use these methods?
- What sort of data are you gathering?
- How are you using that data to inform your compliance protocol?
- How does your current EM program support your CCS?

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 be 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. Analyse every part of your current EM program

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:

- Non-viable 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. Such areas include:

- Data trending and the setting of action and alert limits
- 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 gained from all of these activities must be used when evaluating possible changes in your control mechanisms in your facility.

3. 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.

As the EU GMP Annex 1 specifically demands a better and more holistic, facility-wide contamination control strategy, it is expected that you document this strategy formally. Therefore, every effort made to minimise the risk of contamination must be recorded and can be presented if necessary. 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.

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 elements, notably continuous monitoring, as well as passive elements. Annex 1 also instructs manufacturers to understand and be aware of real time monitoring solutions. Consider all areas of your operations and how you will monitor the following:

- 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. You must also recognise the impact of your facility on the viability of your EM program, notably, high airflow Restricted Access Barrier systems (RABs) and Isolators can desiccate agar and affect the recovery capabilities of your plates.

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 pharmaceutical industry; so for organisations operating in this sector, full compliance is imperative. Modern manufacturing spaces have clearly evolved with the increasing adoption of isolator technology and the advent of RABs. These highly contained spaces deliver improved aseptic performance with lower contamination risk and have led to the growing use of gassing systems for decontamination.

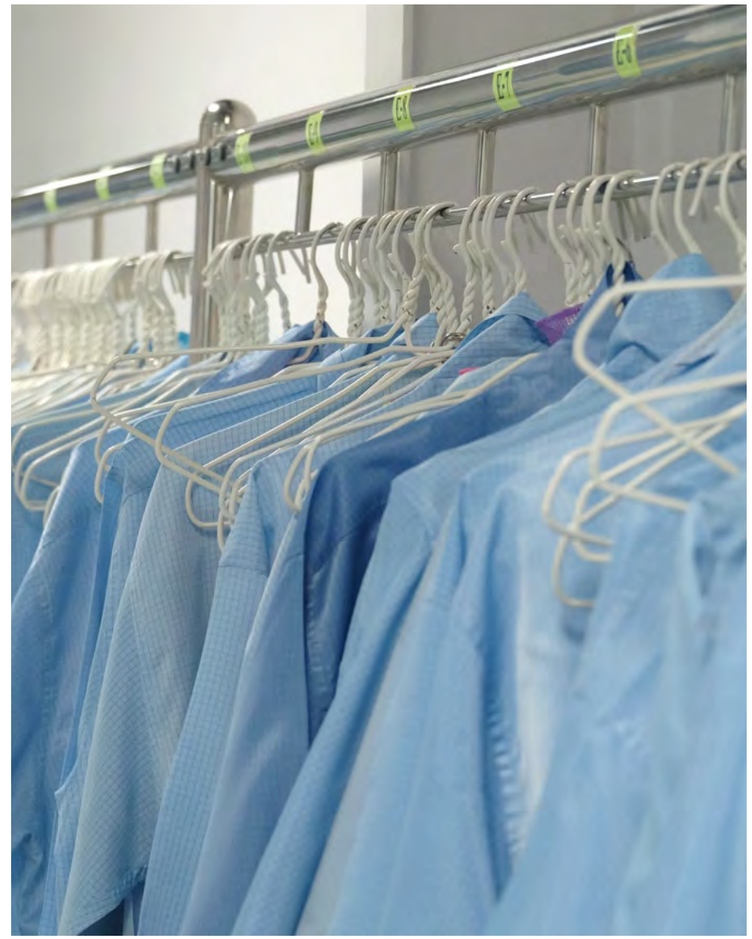
These new barrier technologies do present new challenges for achieving a highly effective EM program due to their restricted access. However, for this sector, contamination prevention is critical, as once contamination has occurred, the consequences can be devastating to both patients and the manufacturer, so it must be avoided at all costs. Therefore, airborne particulates, temperature and humidity should be monitored constantly using regularly calibrated equipment, while passive EM methods should also be used where appropriate.

Industrial pharmaceutical manufacturing processes can include non-sterile, aseptic fill products or employ a terminal sterilisation process. If non-sterile or aseptically filled products become contaminated, it will inevitably result in either 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. Therefore, having defined limits and constant analysis are paramount to identifying challenges and monitoring the potential impact of the environment on the final product. 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. You need to feel confident in every area of your environmental monitoring, including that all culture media has been manufactured in a strictly controlled environment and tested thoroughly, and also that all active air monitors and samplers are sampling defined air volumes.

So, any proposed process must incorporate external factors such media validation and supplier certification, and internal factors such as equipment calibration and multiple sampling methods. Regular reviews of your EM program are also very important in ensuring your processes are providing the data you need.



EM process must address the following challenges:

- A large manufacturing area with a high number of sample points
- Increasing use of barrier technologies to keep product segregated from operators
- A risk assessment must be performed to inform sampling regime
- Multiple methods of sample capture, e.g. 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 air monitor 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 pharmaceutical industry facilities. The main difference for this sector is size of operation and budget, but they still have the same obligation to avoid harm to patients.

Therefore, NHS hospital trusts are feeling increasing pressure to maintain the highest performance levels with minimal funding, yet also with increasing patient numbers. Furthermore, although aseptic compounders face all the regulation of large-scale pharmaceutical operations, they may have challenges on appropriate space and having adequate resources to meet regulatory requirements.

In commercial hospitals and aseptic compounders speed is also a factor, with quick and easy production of medications or parenteral fluids considered a priority in order to produce IV bags and infusion bags for antibiotics for instance. These patient specific preparations can typically have a short shelf life.

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

Any locations where sterile products are stored must also be carefully monitored because of the shorter shelf life of these products. 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 also an increased need to demonstrate that the environment is continuously and consistently well controlled. However, 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 and Biological Safety 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

Identifying the tools to run an effective EM program

Once you have a clearer idea of the kind of EM program your operation is going to require, the next step is to understand all the monitoring equipment you're going to need.

Only once you have concluded your requirements can you start to form a viable financial plan to acquire all the components you need that best suits your business model.

The best passive sampling methods include gamma irradiated settle plates. These offer improved pre-use sterility assurance and have an extended shelf life. There are a variety of media types and presentations to choose from, not only for passive monitoring but also active air monitoring. The widespread use of vapourised hydrogen peroxide gassing systems within Isolators and RABs setups also requires the use of specific barrier packaging.

To perform active air sampling, you need a microbial air sampler. The SAS range of air samplers are an excellent choice as they offer a proven active sampling method of direct, multi-point impaction on to a standard agar plate. The range offers high flow rate models which sample one cubic metre in under six minutes.

If you want to monitor within isolator cabinets or Grade A filling lines you must not only buy a tool to get the job done, but also standardise operator behaviour. Therefore, with isolator cabinets you need to reduce the number of transfers to reduce the risk of contamination.

Within filling lines, you must reduce interventions to reduce risk and production downtime.

The SAS Isolator sampling system provides an ideal monitoring solution for closed environments, as it can sit permanently inside the isolator cabinet with the control unit sitting externally. The connection between the two is purely electrical with no human interaction necessary. Alternatively, bespoke solutions can be created to meet your specific needs.

Monitoring compressed air and bottled gases for any microbial contamination has become a top priority with manufacturers. The SAS Super Pinocchio CR makes use of the proven SAS method of direct multi-point impaction on to an agar plate. This piece of equipment is compact and can be kept onsite within your facilities and offers up accurate reporting with minimal risk of false reporting.

For highly regulated industries, high performance, specialised continuous air monitoring devices will be required.

The BioAerosol Monitoring System (BAMS) is an airborne particle counter used to detect both inert and microbial particles in real-time. The first truly portable continuous, real-time microbial monitor, that uses Laser-Induced Fluorescence to differentiate biologic from inert particles, with viable particles emitting fluorescence. It's designed to meet exacting, pharmaceutical manufacturing standards while providing real-time data for immediate action and catastrophic loss avoidance.

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.

The publication of the new Annex 1 has reshaped expectations within pharmaceutical manufacturing. However, 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 which form part of that wider, holistic contamination control strategy. Achieving the perfect combination for your business can be very 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 by following risk management principles. Legislation will almost certainly continue to change; 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

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 tailored 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 pharmaceutical sector.

Since the early 80s, we have been the UK distributor for the SAS range of air samplers. Recognised across the industry, many of the leading pharmaceutical companies across the world use the distinctive yellow SAS as the cornerstone of their EM programs.

During the 40 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 BioAerosol Monitoring System to further meet the monitoring needs in critical environments.

With many, many years of insight and experience with environmental monitoring applications, we have intricate understanding 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.

Cherwell

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