

CONTINUOUS

VIABLE

PARTICLE MONITORING

FOR CRITICAL ENVIRONMENTS

Annex 1



A PRACTICAL GUIDE



Clean Air Monitoring Solutions

CHOOSING A COMPLIANT MONITORING SYSTEM



Since the introduction of EU GMP Annex 1, considerable attention is understandably focused on its requirement for continuous viable monitoring during critical Grade A operations.

However, simply selecting a monitoring method because it is mentioned in Annex 1 risks overlooking an equally important requirement: **the chosen method must be scientifically justified, its recovery performance understood, and the monitoring strategy must be capable of detecting microbiological contamination during the period of risk.**

Annex 1 tells us what is required, however, the standards help determine whether the chosen method is capable of achieving it. The final task on this journey is validation.

Don't choose a monitoring method and then try to prove that it works. Start with the validation requirements and work backwards.

Define the performance your viable monitoring system will ultimately have to demonstrate — including sampling accuracy, physical and biological collection efficiency, recovery of low concentrations, flow calibration, microbiological recovery and performance over the intended sampling duration. Then select a technology that you **know can be objectively tested and validated against those requirements.**

This approach turns validation from a final hurdle into a design criterion and provides confidence that the monitoring method selected today will withstand scientific scrutiny, qualification and regulatory inspection tomorrow.

ESSENTIAL REQUIREMENTS

Annex 1 | EN 17141 | ISO 14698

1

VALIDATION

Can you scientifically justify your method?

Your monitoring method must be capable of being scientifically justified and validated to demonstrate reliable and reproducible recovery of viable microorganisms under actual conditions of use.



2

CONTINUOUS MONITORING

Throughout the process and setup.

Monitoring should cover the full duration of critical processing, including equipment setup, interventions and dynamic conditions.

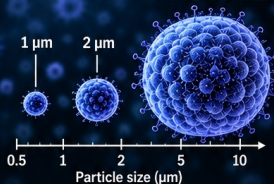


3

PARTICLE CAPTURE EFFICIENCY

Detect and capture the small particles that matter.

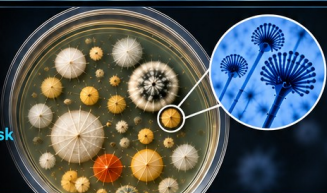
The method must efficiently capture particles down to **1–2 μm** , the size range capable of carrying viable microorganisms.



4

MICRO-ORGANISM IDENTIFICATION

Micro-organisms detected in the Grade A and B areas should be identified to species level and a risk assessment carried out on their potential impact.



5

GRADE A: NO GROWTH EXPECTED

If 1 CFU matters, your method must capture it.

The Annex 1 action limit for Grade A is “no growth”. This means your monitoring system must be capable of capturing that 1 CFU. Biological collection efficiency is therefore a critical consideration.

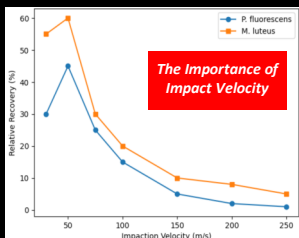
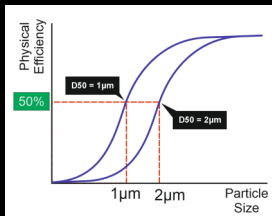


UNDERSTANDING THE TECHNICAL REQUIREMENTS

Particle Collection Efficiency (D50):

Capturing particles of certain sizes is referred to as the Physical Efficiency, and the term D50 is used to measure it. 'D' is the particle size (Diameter) at which the collection efficiency is 50%.

EN-17141 requires a D50 of 2µm or better.



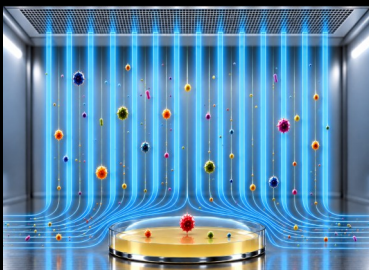
For media based systems, **impact velocity** is also important to ensure adhesion of the smallest particles onto the media surface. A minimum of 30m/s is recommended with an optimum recovery seen in the range 40-60m/s.

Identification: Even today, with modern methods, identification to species level is best achieved using media, allowing organisms to grow into colonies for counting and identification. Media is the most practical, well established and trusted method for this.

Units of Measure: When considering final validation and the need to *scientifically prove* the efficacy of a chosen method, units of measure become a major factor. **CFU per m³** is a clear definition of what is expected, Colony Forming Units, i.e. viable organisms, not for example 'autofluorescent events' and per cubic metre of air. For settle plates **CFU per 4 hours** is less defined. It is therefore essential to be able to prove the volumetric measurement of the air sampled using a calibration supported method.

METHODS — SETTLE PLATES

Settle Plates: The generally accepted view of settle plates is that they rely on particles ‘dropping’ onto the surface. In an environment with **no moving air, and the only downward force is gravity**, this can be assumed. All particles, regardless of size, have an equal probability of landing on the plate.



In a ‘real’ pharma environment with unidirectional air flow, this is not the case. The settle plate is now part of a giant air sampler i.e. the HVAC is the pump, the rim of the dish is the inlet and a pocket of air forms above the media which acts as a barrier. Only the largest particles can break out of

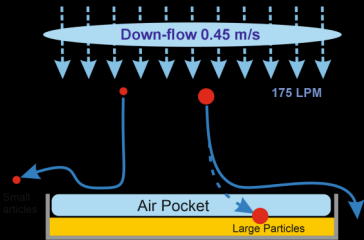
the airflow and fall into the dish, while smaller particles will follow the airflow to waste.

Many studies have shown lower recovery per cubic metre with a settle plate compared to an active air sampler. In a published study, the worst performing air sampler saw 19x more colony counts than settle plates. The

Sampler/ Method	CFU Count/m ³	CFU x SP
CAMS ImpactAir-90	130	x43
CAMS ImpactAir-140	105	x35
Sieve Sampler 1	78	x26
Sieve Sampler 2	57	x19
Settle Plates (SP)	3*	---

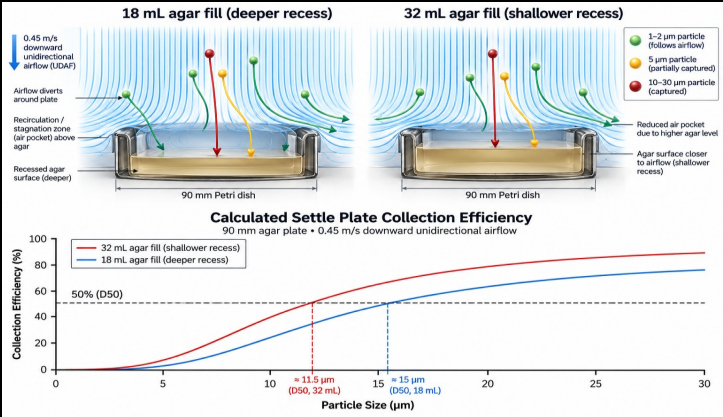
D50 value of a settle plate positioned below a 0.45m/s unidirectional airflow with different media fill volumes has a D50 value of, at best **11µm**. The standard specifies **2µm**.

METHODS — SETTLE PLATES



With the largest collection area at 61cm², the highest flow rate at 157 LPM and in a 0.45m/s unidirectional flow, a 9cm settle plate samples a massive 38m³ in 4 hours. Surely it should yield the best results — yet it has the poorest efficiency compared to active air samplers in trials.

The fill volume can also have an effect on the particle collection efficiency. The distance between the surface of the agar and the top of the dish rim creates a ‘stagnant air pocket’ which has an effect on the aerodynamic performance. This illustration serves to help explain the phenomenon which contributes to the reasons that settle plates are not as effective as a true impactor active air sampler.



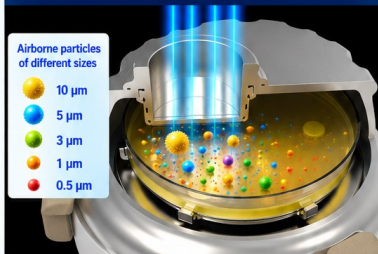
Key questions for settle plates

Can they really provide a scientifically validated method for viable air monitoring?



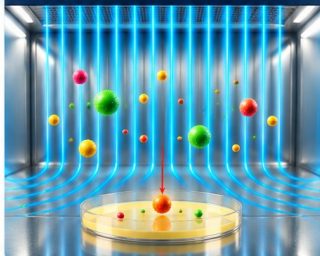
ACTIVE AIR SAMPLER

Known air volume, high collection efficiency, can be validated



SETTLE PLATE

No defined air volume, low and uncertain collection efficiency, cannot be validated



1	What is the D50 value?	✓ Defined and measurable. Collection efficiency can be characterised and expressed as a D50 value.	✗ No D50 can be defined or measured. There is no defined airflow, so a D50 cannot be determined for a settle plate.
2	What volume of air has been sampled?	✓ Known and controlled. A defined volume of air is pulled through the sampler (e.g. 1 m ³).	✗ No defined air volume. The amount of air "sampled" depends on uncontrolled factors such as air movement, turbulence, location and exposure time.
3	In what units are the results?	✓ CFU per cubic metre (CFU/m³). Results are converted to a concentration in air (CFU/m ³) because the sampled air volume is known.	✗ CFU per plate per time period. Results are typically reported as CFU per plate per exposure time (e.g. per 4 hours) and cannot be converted to a concentration in air because the air volume is unknown.
4	How is the method validated and calibrated?	✓ Validation & calibration is routine practice. Active air samplers can be validated to EN 17141 at globally recognised test laboratories, with full validation reports produced and routinely calibrated to traceable standards.	✗ Cannot be validated or calibrated. There is no standardised method to validate a settle plate. There is no defined air volume, no collection efficiency and no measurable performance characteristics.
5	How can you scientifically prove this method is effective?	✓ Demonstrated through validation at recognised test laboratories. The D50 collection efficiency and recovery can be demonstrated through validation at recognised test laboratories.	✗ No quantitative proof of effectiveness. There is no quantitative evidence that settle plates provide a reliable or representative measure of airborne viable contamination, especially when compared to validated active air samplers.
6	If an air sampler sees activity and a settle plate does not, how can that be justified?	✓ Consistent and defensible results. An active air sampler will detect low levels of contamination and small particle sizes because it samples a known volume of air with a defined collection efficiency (D50). Results are reproducible and scientifically defensible.	✗ It cannot be justified. A negative settle plate does not disprove contamination. Due to unknown air volume, poor sensitivity and low collection efficiency (particularly for small particles), a settle plate can easily miss viable organisms that are detected by an active air sampler.



SETTLE PLATES ARE NOT AND CANNOT BE SCIENTIFICALLY VALIDATED

METHODS — SIEVE SAMPLERS

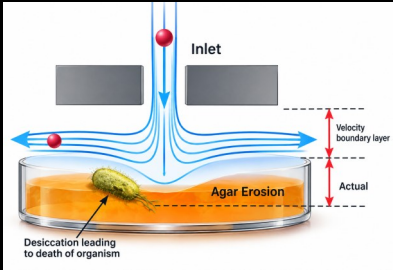
By far the **most common** active air sampler for many years. Designed to sample 1m³ as fast as possible, typically within just 10 minutes — and that is their weakness.



With the air constantly impacting on the same locations on the plate, media erosion and **desiccation** is a significant issue resulting in organism mortality i.e. poor **biological collection efficiency**. Sieve samplers generally already have low impact velocity and some manufacturers are reducing the flowrate in an attempt to increase the maximum run time, however that can **dramatically reduce the particle efficiency** (D50) and impact velocity.

Fundamentally, this style of sampler was designed for **speed, not monitoring**.

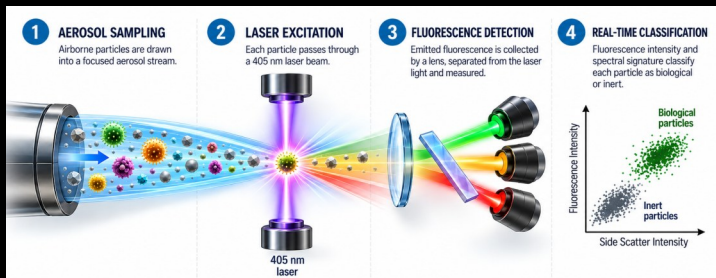
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The total inlet area of a typical sieve sampler with 300 holes is only around **1.5%** of the total media area.

METHODS — REAL-TIME LASER INDUCED FLUORESCENCE

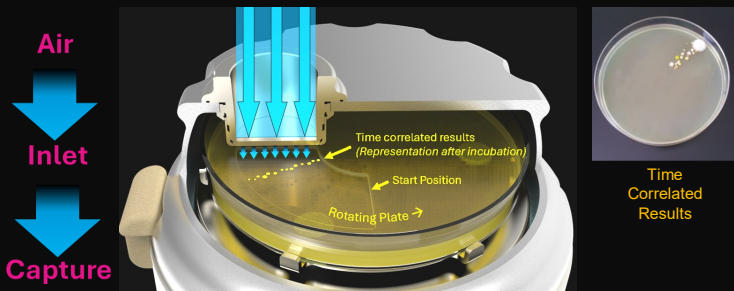
LIF detectors provide continuous, **near-real-time monitoring** of airborne particles. As each particle passes through a laser beam, naturally fluorescent biological compounds are excited and the resulting fluorescence is measured. This allows the instrument to classify particles as **potentially biological** without waiting for incubation and colony growth. EN 17141 recognises fluorescence-based real-time particle detection as an Alternative Microbiological Method (AMM) and notes that it can provide valuable information about the state of control.



LIF can provide immediate detection of biologically fluorescent particles, but fluorescence alone **does not demonstrate viability, culturability or microbial identity**. Annex 1 permits alternative technologies only where their suitability has been scientifically justified and validated, including equivalence or superiority to established methods and, where possible, correlation of non-CFU results to CFU. LIF can therefore be a **powerful supplementary monitoring technology**, but replacing established viable air monitoring presents significant validation and regulatory challenges.

SLIT-TO-AGAR

ESTABLISHED AND TRUSTED TECHNOLOGY



- Air is sampled on to Agar, a well **established and trusted method**, familiar to all pharma companies, with many years' experience and historic data. There is no need to change methods for **full Annex 1 compliance**.
- What is different? Unlike other air samplers, our equipment is designed to sample over very long periods onto a single plate. **4 hours is typical**, but 8+ hours is also possible. This also brings huge **cost savings** on plate usage.
- Our narrow slit inlet and rotating agar ensure the air is impacted onto fresh agar throughout the run, thus minimizing desiccation giving our method the best physical and biological efficiency of any method available. Our standard particle collection efficiency is **0.53µm (D50)**.
- By using agar, **identification to species level** is possible which is a key requirement of Annex 1. **Single organisms can be detected**, another key factor of the standards especially in Grade A and B areas. With agar, there is no 'post event investigation' — you already have the answer!
- Air —> Inlet —> Capture. That's it! No false positives, no false negatives and results are colony forming units — **CFU** not 'events'.
- **Fully validated** by UKHSA (PHE) which is the globally recognized laboratory. We share the full validation test reports.
- **Trusted** by AstraZeneca, Novo Nordisk, Ecolab, Lilly and more.

SOLUTIONS

MODULAR DESIGN, CHOOSE YOUR OWN SOLUTION

- The CAMS 9cm range is based on a **modular design** approach. This makes it possible to have multiple product configurations that exactly meet the end user's specific needs throughout the plant.
- All CAMS products are based on the Slit-to-Agar method and are therefore all covered by the same **ISO14698 & EN17141 validation**. This makes end user validation and training much easier.
- Being a modular design, CAMS solutions are scalable like no other on the market. From single point monitoring to limitless numbers of monitoring points, CAMS has a solution.
- Our user friendly large touch screen display is used across the product range reducing the amount of training required.
- Every CAMS device has an Ethernet port and can be fully controlled using **MODBUS**, allowing fast and seamless integration into software systems and isolators.



FOR ISOLATORS

ISO-90 Hero

The **ISO-90 Hero** is a revolutionary product where overall system space is at a premium. The **Hero** monitoring head has a pump built-in and requires no other hardware if integrated into an isolator HMI system.

- Built-in pump
- Precision flow control
- Ethernet
- MODBUS
- 24V D.C Power

For applications where small numbers of monitoring heads are required, or where making changes to the isolator HMI software is not practical, CAMS also provide a mini controller that can control multiple heads.



ISO-CON-MHC

Multi-head controller

Control up to 4 Hero heads with this controller. This is an extremely easy way to install a multi head monitoring system with the absolute minimum of engineering input.





Clean Air Monitoring Solutions



COMPLETE EM SYSTEM

REAL-TIME VIABLE AND NON-VIABLE
ENVIRONMENTAL MONITORING



**VIABLE AND
NON-VIABLE**

Complete environmental
monitoring in one system



REAL-TIME DATA

Continuous monitoring
for greater control



GMP READY

Designed for
Annex 1 compliance



SCALABLE

From single zones
to full facility networks



INTEGRATED CONTROL

Particle counters,
samplers and software



ImpactAir®-90

PORTABLE CLEANROOM
VIABLE PARTICLE MONITOR

Accurate, reliable and easy to use
viable air monitoring for
cleanroom environments.

MONITOR

COMPLY

PROTECT



9cm
agar plates

Industry standard
media plates



Fully validated
for EN17141 & Annex 1

Proven performance
in regulated environments



Mains powered
desktop portable

Flexible monitoring
where you need it



HEPA filtered
exhaust

Protects people
and the environment

SOLUTIONS

ISO-CON - REMOTE PUMP SYSTEMS

Upgrade from sampling to an Annex 1 compliant monitoring solution with this drop-in system. Remove the existing systems and swap the head to a CAMS monitoring head while using the existing pipework as a conduit for the new control cable and hose.

CAMS has a range of ISO-CON Pump & Flow controllers to suit

different applications for cleanroom or technical area deployment



The 'technical area' versions of the ISO-CON (IFC/CFC) have built-in **VHP/H₂O₂** control features designed to allow sterilisation of the air flow path up to the pump unit.

A small pump and valve arrangement automatically draws the VHP gas up to the unit and to an exhaust port.



CLEAN AIR MONITORING SOLUTIONS

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