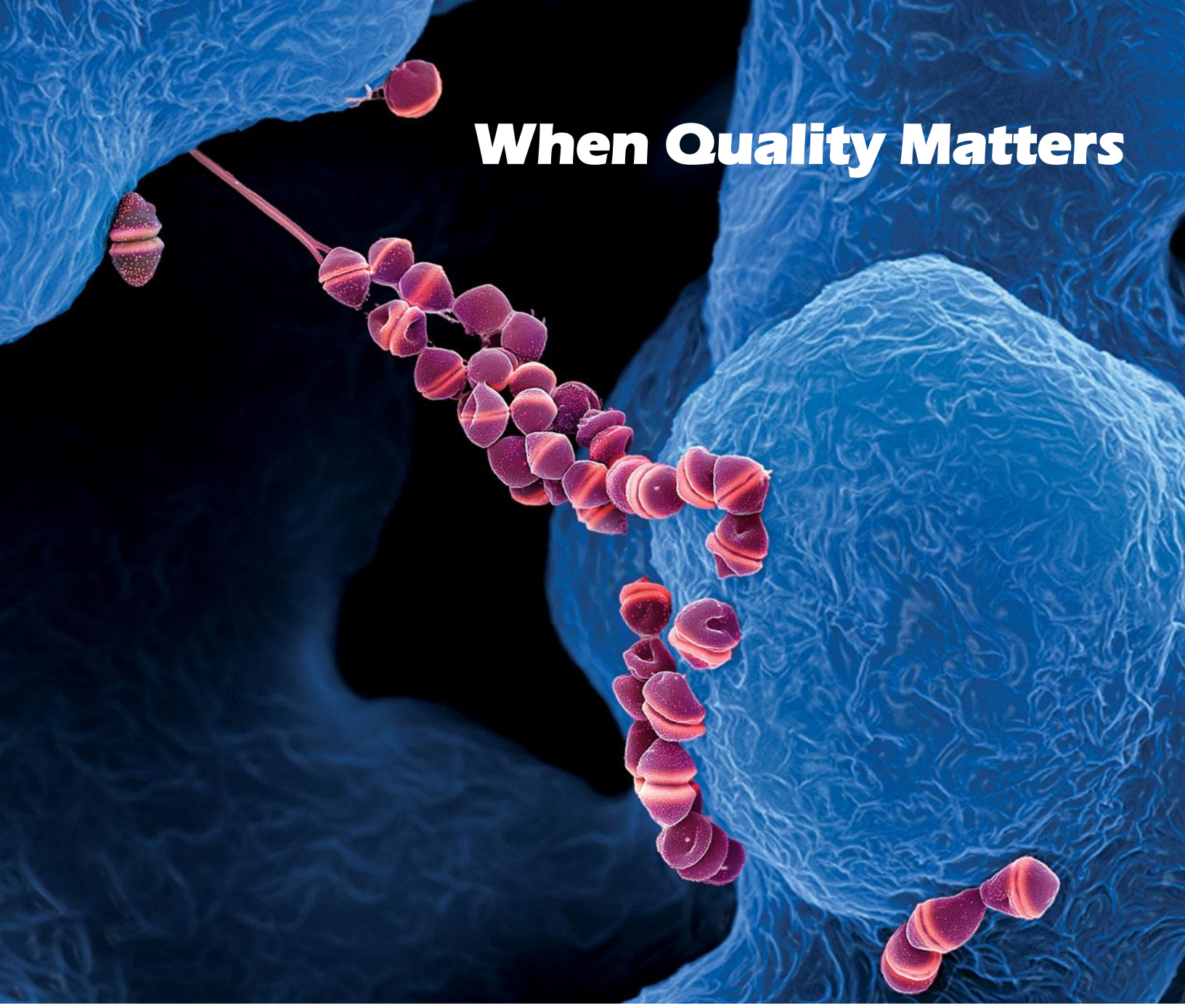


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# Microbial Air Samplers: Selection Criteria in Biopharma Manufacturing

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# Selection Criteria for Microbial Samplers

Microbial air samplers are widely used in the biopharmaceutical applications for aseptic monitoring to ensure manufacturing clean areas are in compliance with ISO, FDA, and GMP regulations.

Biopharma manufacturing regulated by the FDA or EU GMP is rife with risks associated with poor quality monitoring practices, as well as employing environmental monitoring equipment that is poorly designed and thus ill-suited for the task of monitoring in biopharma industrial manufacturing plants.

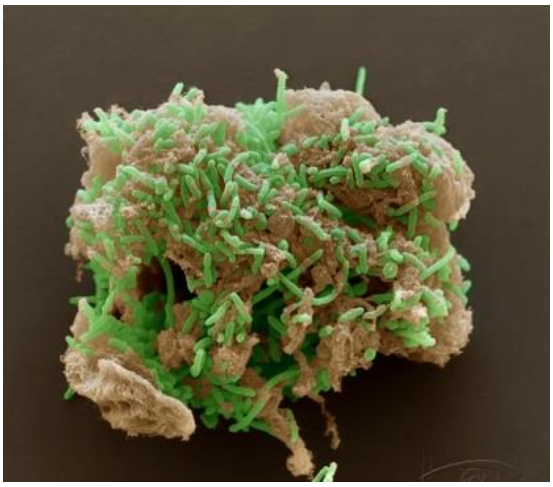
These risks include those to public safety, as well as substantial financial implications resulting from deviation reports and investigations, product recall, or scrap.

The best source for guidance in selecting an appropriate microbial sampler is ISO 14698-1. However, this source is also lacking key common sense criteria. Some of these criteria can be augmented by ISO 21501-4 and ISO 14644.

## 1. Stainless Steel Enclosure

Any qualified microbiologist can confirm that plastics pose an increase in the risk of biocontamination for several reasons.

First, plastics (and to a lesser degree aluminum) carry a static charge that attracts particles of all sizes. Plastics are essentially particle magnets. Moreover, *particle carrying microbes* will attach to plastics very easily. Thus, use of plastic enclosures will increase the risk of biocontamination.



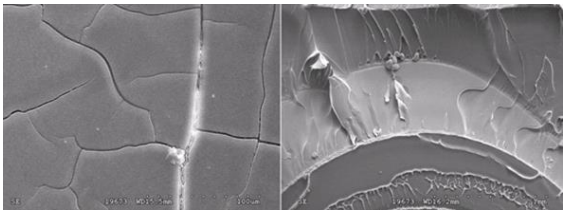
Second, plastics are soft materials that will scratch, scuff, and crack. When this occurs, a massive volume of particles are released into the environment adding to the particle burden of the cleanroom.

When scuffed, microfibers and abrasions are created (see below) making cleaning virtually impossible.

Scrubbing or aggressive cleaning will cause damaged surfaces and micro-fibers to break loose. Further, this damage creates hiding places for bacteria and other contaminants.

Finally, plastics are also susceptible to biodegradation when exposed to bacteria, enzymes, moisture, UV light, and wind. This is exacerbated by aggressive cleaning fluids used in biopharma production. As plastics biodegrade, they will slowly release inert particles into the environment, adding to the particle burden of the cleanroom.

As plastics biodegrade, micro-fractures (see below) will be created, which makes sanitation and disinfection difficult.



Polished stainless steel, like that used on Climet particle counters, is significantly more rugged, has a neutral static charge, and provides the highest level of resistance to particle and microbial attachment.

Perhaps most important, stainless steel is easy to clean and sanitize, which is an important factor in selecting a microbial sampler.

## 2. Validated Flow Rate with Alarm

Microbial samplers are calibrated, typically on an annual basis. More frequent calibration may be required in biopharma manufacturing due to a user's risk assessment.

The calibration of a microbial sampler is largely limited to a validation of the instrument's flow rate; correct flow ensures physical and biological efficiencies are maintained.

If the instrument is found out-of-tolerance during its interval calibration, a deviation report and investigation are required. The cost of the investigation among biopharma manufactures is $5,000 to $12,000 on average per incident, and often well exceeds the initial purchase price of the microbial sampler itself. [1]

Moreover, if product or API is scrapped as a result a deviation investigation, costs could skyrocket.

For this reason, a microbial sampler must have a validated flow control system that regulates flow and ensures the instrument stays within its calibration tolerance.

Also, if the instrument falls out of calibration, a **flow alarm** is necessary to mitigate or eliminate the risk of incurring the cost (and hassle) of a very expensive deviation report and investigation.

In a study conducted in 2015, Climet's Out-of-Tolerance interval calibration rate was **0% (a perfect score)**, substantially outperforming all other competitors. For more detail of the study, please contact Climet's sales team and request a copy of our Quality Assurance Report for our microbial samplers.

In short, Quality Managers would not consider using an aerosol particle counter that did not address sample volume uncertainty, which is a violation of ISO 21501-4. Why then would one use a microbial sampler that violates this same principle especially when a flow deviation can affect collection efficiency?

## 3. HEPA Filtered Exhaust

Blowers, fans, or impellers are used in microbial air samplers to draw air into the instrument. Mechanical friction from these devices will create inert particles, potentially on a massive scale.

[1] Climet microbial samplers have an interval calibration out-of-tolerance rate of less than 1%.

Moreover, viable microorganisms may be entrained, and suctioned into the interior of the microbial sampler. If the viable microorganism attaches to an interior wall or other surface, it may be allowed to multiply into a substantial colony. When the instrument's blower is engaged, sections of the colony may be blown out through the exhaust adding to the biocontamination of the cleanroom.

According to ISO 14698-1:

> *The exhaust from the microbial sampler should not contaminate the environment being sampled or be reaspirated by the sampling device.*[2]

Therefore, the exhaust MUST be either externally removed from the cleanroom, or it must have an internal HEPA filter.

Once again, Quality Managers would typically disqualify an aerosol particle counter that did not have an internal HEPA filter. Why then would one select a microbial sampler that violated this same principle?

## 4. VHP Compatible

For reasons mentioned above, specifically, if a viable microorganism attaches to an interior wall or other surface, it may be allowed to multiply into a substantial colony.

The best way to completely sanitize environmental monitoring equipment, that is particle counters and microbial samplers, is with VHP.

## 5. Sensitivity down to 1µm

According to ISO 14698-1:

> *Impaction air samplers must allow the entrapment of viable particles down to approximately 1µm, and be low enough to ensure viability avoiding mechanical damage or the breakup of clumps of bacteria or micromycetes.*[3]

A good D50 cutoff is ≥ 50% physical collection efficiency at 1µm.

## 6. Biological and Physical Efficiency Validated to ISO 14698-1

The "Sampling Efficiency" equation provided in ISO 14698-1, Annex B.3 is merely a measure of how a microbial sampler's biological efficiency ***compares*** against a membrane or impingement sampler. In short, it is a COMPARISON EFFICIENCY, not a sampling efficiency.

Always insist upon reading the actual biological efficiency test report. Do not simply trust a marketing claim. You should know what instrument the microbial sampler (device under test) was compared against. And, why was the comparison instrument chosen as the reference standard? Moreover, you should have an idea of the comparison device's physical collection efficiency at 1µm, which should be > 50%.

[2] ISO 14698-1, Section A.3.2

[3] ISO 14698-1, Section A.3.4.2

Beware, a microbial sampler tested against a poor performing alternative will always yield excellent results.

Climet believes the comparison test required under ISO 14698-1 ***must be a challenge***. Climet chose to test the biological efficiency of our microbial sampler against the SKC BioSampler, which is a glass impingement sampler that according to the **American Association for Aerosol Research** (2000); and later confirmed by the **U.S. Army Research, Development, and Engineering Command** (2011) has, "***close to 100% for 1µm or larger particles***."

Also beware, manufacturers who claim 100% or more "collection or sampling efficiency" without reference to a comparison or reference device should be considered suspect as the science simply does not support these conclusions.

Quite simply, viable particles become stressed both during aerosolization and impaction. As physical collection efficiency nears 100%, the increase in flow rate and impaction velocity causes a significant decline in biological recovery rates.[4]

## 7. Multi-functionality

Biopharma manufacturing may employ the use of isolators or biosafety cabinets (BSC), as well as the use of high pressure gases.

Placement and removal of a microbial sampler in a BSC or isolator, as well as the sampler's exhaust, significantly disrupts laminar flow, increasing the risk of biocontamination.

When the microbial sampler has a plastic enclosure, the risks of biocontamination are multiplicative as plastics pose a significant risk.

In micro-environments such as isolators or BSC's, best practices are to accomplish aseptic monitoring with autoclavable tubing and a remote sample head (See below).


The microbial sampler should also have the ability to monitor high pressure gases where applicable, which is accomplished through the use of a High Pressure Diffuser (see below).

[4] "Impact Stress on Microbiological Recovery on an Agar Surface." Applied and Environmental Microbiology, 1995.

Climet's microbial sampler has an optional adapter head that connects to a High Pressure Diffuser (shown above). The diffuser, tubing, and adapter are all autoclavable.


## 8. Display

The display of a microbial sampler should be large enough to display the delay, battery status, Site ID, and the sample volume without having to flip between screens.


## 9. Size and Weight

In biopharma manufacturing size and weight of a microbial sampler are important, but not to the exclusion of the aforementioned criteria.

"Weight" and "quality" typically have a direct relationship. For example, we can reduce the weight of an instrument by eliminating the stainless steel enclosure and replacing with plastic. We can also reduce weight by eliminating the HEPA filter, and removing circuitry that regulates air flow, alarms, etc. However, this reduction in weight would result in a substantial reduction in quality and assurance required by parenteral, enteral, and topical biopharma production or similar applications.

Both microbial samplers and particle counters, according to pharmaceutical best practices, are transported on carts, and not typically hand carried from location-to-location. Therefore, the criteria for size and weight are generally mitigated.

If a microbial sampler is carried between locations, it should intuitively be lighter in weight when compared to an aerosol particle counter (less than 14 lbs.).