

Annex 1 Proposed Changes and Particle Monitoring

EU GMP Annex 1 is under review. Comments on the proposed corrections must be with EMEA by 30 April 2006.

(http://pharmacos.eudra.org/F2/p_harmacos/gmp_doc.htm)

There is a revised classification table which allows a particle limit at $\geq 5.0\mu\text{m}$ of $20/\text{m}^3$ for both Grade A and B at rest and Grade A in operation to be considered. Does this mean a limit of $20/\text{m}^3 \geq 5.0\mu\text{m}$ will be universally used? False counts on modern particle counters at $5\mu\text{m}$ are normally real counts, they are not valid in

terms of the process because they are caused by contaminated sample tubing/particle counter sensor assemblies. $5\mu\text{m}$ particles fall out of the airflow in the sample tube and become reintroduced at a later time. If the new cleanroom classification table is adopted, the particle limits that companies use will depend on how the Annex is interpreted by the inspection authorities. Companies may be able to demonstrate using historical particle count data to help them

assess which limit should be adopted. One possible rationale could be: Regular $5\mu\text{m}$ counts, during the filling process run for example, would suggest process related problems. Occasional $5\mu\text{m}$ counts at random intervals may be related to false counts due to an unknown source, therefore a $20/\text{m}^3 \geq 5.0\mu\text{m}$ limit could be considered. The draft Annex says "...consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated". emphasis on a monitoring system as a diagnostic tool (early indication of a failure) is mentioned.

The proposed Annex 1 corrections do make a clear point of mentioning that it is not necessary for an automated particle monitoring system to take the same sample volumes as that taken for formal classification of cleanrooms.

Proposed EU GMP ANNEX 1 Classification Table.				
Grade	At Rest		In Operation	
	$0.5\mu\text{M}$	$5\mu\text{M}$	$0.5\mu\text{M}$	$5\mu\text{M}$
A	3,500	1*	3,500	1*
B	3,500	1*	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	Not defined	Not defined

*The maximum permitted number of particles at $\geq 5.0\mu\text{m}$ is established at $1/\text{m}^3$ but for reasons related to false counts associated with electronic noise, stray light, etc. a limit of $20/\text{m}^3$ could be considered.

Cherwell Laboratories Re-Validate New Facilities Using Lighthouse Solair 3100+ Particle Counter

Cherwell Laboratories, the UK based manufacturer of the Redipor® range of prepared media, re-commissioned their ISO 6 & 7 clean room manufacturing facility recently.

As a manufacturer of prepared media, emphasis is placed on microbial monitoring and Cherwell has an extensive daily monitoring regime. Scheduled assessment of particle counts also form part of the company's environmental monitoring and revalidation program.

To minimize any disruption to production, Cherwell required a

quick, easy to use particle counter to complete a program of over 60 samples throughout the suite. The 1cfm Solair 3100+ was recommended for use by operators inexperienced in particle counting. The unit was very portable and the intuitive colour touch screen allowed sample parameters to be easily set up and stored. The requirements of ISO14698 formed the basis of the sampling regime. The operating software proved very helpful in determining the number of samples required per room and the size per sample.

Cherwell's facility includes aseptic filling lines and an assessment of these areas was also included in the program. These critical areas, including laminar flow cabinet and ISO 5 filling areas were monitored using the isokinetic sampling probe and tripod.

Cherwell Laboratories & FMS are continuing to work together on specific projects that involve both microbial and particle monitoring solutions.

For details on Redipor® contact:
www.cherwell-habs.co.uk

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Solair 3100+ Particle Counter

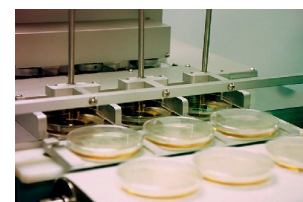


Plate pouring at Cherwell Laboratories new facility

Bassaire Engineers Review Solair 3100+



Zoom feature facility on the Solair 3100+



Bassaire Laminar Flow Workstation

With over fifty years experience in the design, supply and maintenance of clean air products and cleanrooms, Bassaire engineers routinely use the Solair 3100+ particle counters for validation and commissioning work.

The performance of any containment facility is critical to the quality and yield of the product, and in many situations, the safety of staff the end user. Particle count information is essential to provide verification that the facility is performing correctly. Bassaire engineers use Lighthouse Solair 3100+ particle counters supplied by FMS and provided the following

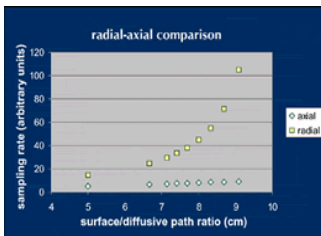
feedback on the practicalities of using the Solair.

"...The simple lines of the stainless steel case means that it is very easy to clean, before entering a cleanroom. The Solair is light, compact and easy to configure for different classifications of rooms and cabinets. Long battery life, with quick and easy recharging, ensure that the units are always ready for use during the validation process. The touch screen displays are clear and easy to follow. The additional zoom feature means that the display is clearly visible from a distance, making it possible to view the information e.g. outside the cleanroom. When

working in a critical area, an initial time delay can be configured to provide time for the operator to move away, before the counts start. Reporting is simple and the internal printer provides hardcopy evidence instantly. Significant time savings can also be achieved by using the Solair's optional temperature and relative humidity probe to collect data during the particle counting process. We feel that this is an all round easy unit to set up and operate; we also get a good back up and technical service from FMS."

For further details of Bassaire's products and services: www.bassaire.co.uk

FMS distribute Radiello Diffusive Sampling System



For a traditional axial symmetry sampler the uptake rate increases linearly with the ratio of diffusive surface vs. diffusive path length, while for the radial symmetry sampler, the corresponding increase is exponential. This means that, let the diffusive surface vs. diffusive path length ratio be 8:1, for the axial sampler the uptake rate value is 8 (regardless of dimensions) while for the radial one it is 45.



RADIELLO Personal Monitoring

www.fmonsys.com
www.radiello.com

FMS is now distributing the **Radiello diffusive sampling system**. Diffusive sampling eliminates the need for heavy/encumbering pumping systems, it does not have power supply problems, nor does it require supervision, it is noiseless, inflammable and does not represent an explosion hazard. Testing can be performed by anybody, anywhere with very low costs. Furthermore, it is not subject to the breakthrough problem, which can be serious when active pumping is performed.

Why has diffusive sampling not been so extensively adopted up to now? This is due to the fact that the traditional axial symmetry sampler had poor sensitivity and reproducibility because of the limits set by its geometry. These limitations have been overcome by **Radiello**.

By virtue of radial symmetry, uptake rate is: **High**, it does not vary linearly but exponentially with the ratio diffusive surface vs. diffusive path length. With the same

dimensions, radiello's uptake rate is at least 3times higher than for any axial diffusive sampler.

Constant, due to the high adsorbing capacity of the adsorbing cartridge.

Reproducible, by virtue of the stiffness of the diffusive wall and cartridge and of the close tolerances characterizing all the components of **radiello**.

Invariable with air speed, due to the tortuosity of the diffusive path inside the microporous diffusive cylindrical surface.

Precisely measured, it is not calculated but experimentally measured in a controlled atmosphere chamber with or without interferents.

Furthermore **radiello**:

- is able to work properly even in bad weather conditions due to the water-repellent diffusive body
- has blank values lower than 3 times the instrumental noise due to the complex conditioning procedures of the bulk adsorbing (or chemiadsorbing) materials and to the repeated quality controls along the whole

production

- has low detection limits and high adsorbing capacities these allow exposure time from 15 minutes to 30 days and measure concentrations from 1 ppb to over 1000 ppm
- offers high precision and accuracy over a wide range of exposure values
- allows thermal desorption and GC-MS analysis without interferents
- is suited to the sampling of a vast range of gaseous pollutants
- is tough and chemically inert, being made of polycarbonate, microporous polyethylene and stainless steel
- is indefinitely reusable in all of its components apart from the adsorbing cartridge.

Radiello comes from the efforts of one of the main European scientific research institutions that produces it directly by high technology equipment and continuously submits it to severe tests and performs research and development in its laboratory in Padova, Italy.

Microflow Air Sampling in Composting Facilities

Centralised composting processes cause the release of micro-organisms into the surrounding atmosphere. Conditions currently being set in waste management licences specify that facility operators must sample for these micro-organisms around the site.

Some micro-organisms associated with compost production are recognised allergens. Examples include, thermophilic actinomycetes and *Aspergillus fumigatus*, both have been implicated in occupation lung diseases such as Farmers Lung, where gross exposure, typically greater than tens of millions of spores per m³ of air, have triggered the immune response.

One characteristic of the *Aspergillus fumigatus* biological cycle is its capacity to generate large numbers of spores. In rare instances these spores can cause severe or even fatal infections. Two such case studies have been reported associated with composting.

Actinomycetes are also found, they are filamentous Gram-positive bacteria that are commonly found coupled with soil and plant materials. Thermophilic actinomycetes, with a growth temperature range of 30 to 60°C, thrive in

wet compost that has begun the self-heating process. They are also recognised respiratory allergens. Actinomycetes produce thousands of very small spores (1-3µm diameter) which easily become airborne in large numbers when heavily colonised material is disturbed. Their size means that they can potentially penetrate deep into human lungs.

Not only is there a moral obligation to monitor compost sites, but it is a requirement of PAS100. The recommended method is fixed point sampling taken at various locations judged to be representative of work activities on site. However, there are conflicting views to the range spores can travel. Some argue that a 200m radius of the site should be monitored whilst there is some evidence that spores can be found up to 250m away. Fixed point sampling ensures the airborne particles are deposited directly onto agar plates. This has the advantage of direct inoculation of the agar on which the biological agent grows, however, they are susceptible to overloading and sampling periods are short for full "loading" of the plate, ranging from approximately 30 minutes for background samples to as short as one minute in highly contaminated environments.

The Microflow 90 air sampler is highly recommended for this application, as it has variable sampling speeds and volumes.

Workers on composting facilities are potentially exposed to considerably higher concentrations of bacteria, including Gram-negative bacteria, actinomycetes, fungi and their associated toxins than are likely to be present in background air away from bioaerosol sources, and that the microbial components of compost bioaerosols have a known potential to cause respiratory ill health.

Conclusion — Composting on a major scale is a relatively new and rapidly expanding industry in the UK. As yet there is little published evidence of serious/chronic disease in compost workers, although there is evidence of early ill health responses to bioaerosol exposure in compost workers, e.g., raised antibody levels and inflammatory mediators, and evidence of progressive allergic respiratory disease exists in industries such as other waste handling, agriculture and cotton mills, where similar exposure to bioaerosols may exist.

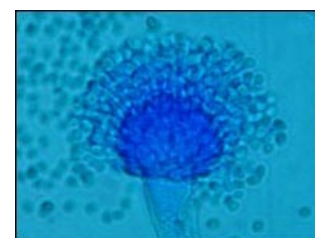
Chronic ill health may not yet have had time to develop.



The Microflow 90 Air Sampler — Perfect for setting volumes and sampling times



Typical growth pattern after sampling



Aspergillus fumigatus

Lighthouse Introduces the Latest in Liquid Particle Counting Technology

Water quality is an ever growing concern in today's industrial environment. In fact, millions of pounds a year are lost in the electronics, biotech, semiconductor, data storage, pharmaceutical, food production, and defence industries due to contamination.

Today, these and other industries must focus upon the detection of contaminants in

order to survive. Lighthouse introduces the latest in liquid particle counting technology with its **Remote LPC 0.2**.

Designed for continuous 24 hour a day, 7 day a week operation the Lighthouse Remote LPC 0.2 integrates easily into facility monitoring systems. With its 4 channels of continuous data, high sample flow rate (100 ml/min), small

foot print and low cost per point the Remote LPC 0.2 is the right choice for your online liquid particle monitoring needs.

The REMOTE LPC 0.2 integrates seamlessly with large facility monitoring/management systems and transfers 4 channels of simultaneous particle count data using RS-485 Modbus.



Designed and built by Lighthouse, a name you can trust.

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f acility
m onitoring
s ystems

The Science - The System

Facility Monitoring Systems Ltd (FMS) was established in 2000 and employs 19 members of staff. We draw on over 80 years experience to provide highly secure and robust monitoring systems tailored to exact customer requirements. Specialising in critical processes and storage monitoring systems, FMS has an existing customer base which includes:

- Pharmaceutical
- Blood Products
- Biotechnology
- Hospital, Pharmacy & Healthcare
- Industrial Clean Processes
- Microelectronics
- Water Industries
- Food and Drink
- Medical Devices
- Automotive
- Aerospace

As the UK distributor for 'Lighthouse Worldwide Solutions' particle counting equipment, whatever your monitoring requirements – Wired or Wireless – we can deliver the complete package, giving you confidence and peace of mind.

FMS offers full hardware and software training for your staff, local first line calibration, maintenance and software support, no third party calibration houses/companies are used.

Embryologist and Stem Cell Continuous Monitoring

Clean Modules, the experts in modular Clean Rooms, have constructed a major new Clean Room facility that complies with EU GMP for Sheffield Hallamshire hospital. We were delighted then, when Clean Modules Ltd selected FMS Ltd as the facility monitoring system provider for the Sheffield Assisted Conception Unit (ACU) and combined Stem Cell Laboratory.

The FMS monitoring system supplied is able to continuously monitor temperature, pressure and particle counts in real time. The immediate access to the data to generate printed reports enabling regulatory compliance to be quickly demonstrated, and aid in root cause investigations is an advantage. Conveniently, the FMS monitoring software enables full FDA 21 CFR part 11 compliance.

The forthcoming Tissue and Cell Directive and the possible requirement to carry out procedures in a Grade A environment were the main regulatory drivers when specifying the system.

Drawn from our experience in supplying continuous monitoring systems for similar facilities, such as the National Institute of Biological Standards and Control (NIBSC), and working closely with the Sheffield team and Clean Modules, a complete validated system that monitors all the critical process parameters was delivered.

Importantly, the system project lifecycle activities, the development of the monitoring software and associated validation documentation follow the latest Good Automated Manufacturing Practice (GAMP).

Incubators, fridges, Liquid

Nitrogen dewars are now continuously monitored for temperature. Room pressures and oxygen depletion data are also collected and alarmed in real time. The Grade A Laminar airflow cabinets have continuous particle counting data reported back to the FMS system every minute enable full compliance to EU GMP Annex 1 to be demonstrated.

The monitoring system installed by FMS helps to reduce pressure on staff, as the system provides immediate, real time alarms as soon as any parameter is out of range. The system is connected to the Hospital alarm system which initiates a call to the senior embryologist who can immediately investigate the excursion; the problem can then be quickly identified.

www.clean.modules.dial.pipex.com



FMS work station



Inside the facility



Comment:

We welcome contributions to this newsletter, if you have articles, comment or information to share, send it to us (addresses seen above) and we will endeavor to include it in a future issue.

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