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THE CLEANROOM

# MONITOR

## The Scottish Society for Contamination Control

June 2005


Issue 53

 FUTURE TRENDS

 GLOVES

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### CLEANROOM TECHNOLOGY - A BRIGHT FUTURE AHEAD

**Where are we going? What are the trends and where are the areas for development? From his stance as an internationally recognised contamination control expert, Dr Hans Schicht offers a thought-provoking view on pages 2-4.**

# CLEANROOM TECHNOLOGY - A BRIGHT FUTURE

**The strong influence of high technologies on the development of cleanroom technology looks set to continue in the next few years. An increasing number of applications demand it and industrial nations can no longer imagine everyday life without it.**

Cleanroom technology is a key element of modern process technology. It is used in microelectronics and its applications, the pharmaceutical industry, biotechnology and the manufacture of medical devices, space travel and an area in which the future has already begun, micro- and nanosystem technology.

However high technologies develop in the future, they will continue to be characterised by certain key features:

- \* the technical use of exotic physical and biological phenomena
- \* the central role of increasingly fine structures down to molecular and atomic dimensions
- \* the creation and use of materials and process media of the highest purity and
- \* the increasing and increasingly broad-based utilisation of the potential of biotechnology.

If such challenges are to be met, cleanroom technology will be indispensable to production. Its role is to control contamination from both inanimate particles and micro-organisms and increasingly from gaseous foreign substances in the air.



## **No technological civilisation without cleanroom technology**

It would be wrong, however, to associate cleanroom technology only with the most advanced technologies. Increasingly, it is moving into new areas of application in established fields of industrial activity, such as the automotive industry, plastics processing, food production,

the bottling of beverages and the cosmetics industry, to name but a few. It is also essential for fundamental and applied research in natural sciences as well as in hospitals, where it finds applications in surgery, orthopaedics and intensive care.

The global market for products manufactured under cleanroom conditions is already worth far more than 1000 billion euros a year. Even now, in a period of economic stagnation, it is growing at an impressive rate. It is no exaggeration to say that our internationally integrated technological civilisation and its exceedingly diverse characteristics would be inconceivable without cleanroom technology. In spite of this wide impact, cleanroom technology remains a niche activity with a total market volume estimated by McIlvaine<sup>1</sup>, the well-known market researcher, at not more than USD 11 billion. This sum comprises all aspects of cleanroom technology: installations, system components, spare parts, consumables, garments, services etc.

The steady growth in sales of products manufactured under cleanroom conditions does not necessarily mean steady growth in investment in cleanrooms and clean workspaces. On the contrary, the different applications of cleanroom technology vary greatly in this respect.

There are three different investment characteristics to be distinguished:

- \* Investment behaviour that is distinctly cyclic.
- \* New product categories requiring massive initial investments for production and showing an investment dynamic that either grinds to a halt or is at least substantially diminished when the market becomes saturated.
- \* Areas of application characterised by steady market growth over a long period and therefore by a steady expansion of capacity.

Those who want to play a leading role in shaping the market for new product categories must have the courage to expand their capacity enormously. One product class currently demonstrating this kind of market breakthrough is the flat panel display, i.e. the flat displays for laptops and fixed computer workstations, liquid crystal displays and the like. This market is growing by USD 100 billion a year and should reach a volume of USD 500 billion this year. This requires large-scale investment. Unlike small semiconductors, flat screens are large products so it is not unusual for them to be manufactured in a production area measuring several hectares with air purity requirements that are certainly comparable to those of a semiconductor plant.

## **Cleanroom technology and life sciences**

Investment activity in the second largest area of application for cleanroom technology, the life science industries, is fundamentally different. The life science industries encompass all areas of activity that are concerned with life and health in some way. Leading sectors of the life science

## CLEANROOM TECHNOLOGY - A BRIGHT FUTURE



industries include the pharmaceutical industry, and the branch of biotechnology that is geared towards it, and the manufacture of medical devices.

The life science industries are associated particularly with the ageing population and the elderly, who above all need their products. 75% of all medicinal products are used by people over 65 years of age. And as age distribution throughout the world moves towards higher life expectancy, the course for continuous growth in demand and therefore continuity in investment behaviour is set.

In addition, a marked development is becoming widespread. In the past, cleanroom technology focused almost exclusively on sterile production but is now - admittedly often in a slightly less elaborate form - an increasingly common link in the chain of safety measures employed in active substance production in the chemical and biotechnology industries as well as in the manufacture of non-sterile pharmaceutical forms. As part of this development, the expansion of cleanroom technology into the production of individual formulations and small-scale quantities of medicinal products in hospital pharmacies is also worthy of note.

### Future market prospects

In terms of emerging technologies from which new markets for cleanroom technology could develop, micro- and nanosystem technology, a technology that lies at the limits of microelectronics and micromechanics, seems particularly

promising. Some of the structures with which it is concerned are so small that quantum effects overlap traditional physics. This area is expected to reveal completely new phenomena from which completely new products, applications and markets should develop. As indicators of what is to come, miniaturised sensors and microsurgical instruments are already on the market and could trigger the breakthrough of minimally invasive surgery, a promising way towards new surgical procedures and the reduction of the length of time patients spend in hospital. Products in this category include, for example, micro-electromechanical systems, MEMS. McIlvaine expects cleanroom demand for the manufacture of such systems to grow by 45% a year. Thanks to the extensive range of possible applications, micro- and nanosystem technology is an area in which it may take a long time to reach market saturation or a cyclic pattern of market behaviour.

### User requirements

In terms of the direction in which user requirements are moving, microelectronics is and remains the driving force. The change from silicon wafers with a diameter of 200 mm and feature size of 0.17  $\mu\text{m}$  to wafers with a diameter of 300 mm and feature sizes of 0.13 or 0.1  $\mu\text{m}$  is fully underway and most of the wafer fabs under construction today are equipped for this new level of technology. Feature sizes of 0.065  $\mu\text{m}$  are expected to follow sooner or later and we may even see a 400 mm wafer in this decade.

As for what this means for cleanroom technology, the particles have had their day. They are simply not allowed to interfere with these extensive, finely structured elements. Molecular contamination is becoming the number one risk factor. Monomolecular oxide layers forming on the structures or structure contamination by, for example, ppb (parts per billion) concentrations of airborne boron molecules are becoming key risks in the semiconductor industry. All that remains is to move production processes to an inert gas atmosphere or straight into high vacuum. In this context, the widespread adoption of minienvironments and SMIF technology (standardised mechanical interface format) is unstoppable.

Isolator technology is the pharmaceutical industry's equivalent to the minienvironment and has been in the spotlight for several years. Its use in pharmaceutical production has grown enormously in the last few years, not only numerically but also in terms of geographical spread.

# CLEANROOM TECHNOLOGY - A BRIGHT FUTURE

After a long period in which Europe remained unchallenged at the top, 2000 was the first year in which more isolator-protected production lines were installed in North America than in Europe. Whether or not isolator technology becomes established throughout the world probably depends largely on the ability of the manufacturers of filling machines to reduce substantially the susceptibility of the production process to stoppages. As long as manual intervention in the process remains comparatively frequent, the sterility assurance of aseptic filling will be limited.

As shown recently by Ljungqvist and Reinmüller<sup>2</sup>, even those who dress and behave in compliance with cleanroom regulations are very effective at spreading micro-organisms. If, however, human intervention in the production process were to be eliminated as far as possible through extensive automation and other technical improvements, the triumphal procession of the isolator could be unstoppable.

Well-known experts in this field are convinced that by 2010 isolator technology will be a fully established feature of new plants. If human interference in the process were to be rendered completely unnecessary, aseptic production would be much closer to achieving the aim of completely eliminating the microbiological contamination spread by air and through contact. So will we soon be able to upgrade our assessment of aseptic production to that of a genuinely sterile process?

## International cleanroom technology standards

Development in the area of standards and regulations in the coming years is easier to predict than that of investment. This is linked to the fact that activity in this area is much less hectic. For a decade, work on cleanroom technology standards has been defined by the shift from national to international level. It is controlled by the ISO (International Organisation for Standardization) with active support from the CEN (the European Committee for Standardization "Comité Européen de Normalisation"), which now has 28 member nations, a figure that looks set to rise further in the next few years.

With seven already definitive titles supplemented by three draft standards, the experts now have an internationally recognised family of cleanroom technology standards and draft standards at their disposal. This already covers the important issues that need to be considered when planning, building, commissioning, testing and operating cleanrooms and their infrastructure. It will be updated, supplemented and developed on a regular basis in future.

## International compliance

Unfortunately, a breakthrough towards global harmonisation of the GMP (Good Manufacturing Practice) compendia of pharmaceutical regulatory authorities, comparable with that of ISO standardisation of cleanroom technology, is still wishful thinking. National or regional GMP guidelines dominate the scene and act as technical barriers to trade. In principle, it would be conceivable for the following three

institutional bodies to devise a global GMP guideline:

- \* The International Organisation for Standardization whose ISO 9000 family of standards on quality systems in general and ISO 13485, an extension of this for medical devices, have been accepted all over the world.
- \* The Pharmaceutical Inspection Convention, PIC, and its renowned body, the Pharmaceutical Inspection Co-operation Scheme, PIC/S, and
- \* The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH.

To all appearances, the regulatory authorities appear rather lukewarm towards ISO's quality system philosophies, although the other two bodies, in which the rule of inspectors remains unchallenged, also have their problems:

- \* Unfortunately, the USA is not part of the PIC.
- \* The ICH, which is supported by the European Union, Japan and the USA, continues to exclude the rest of the world.

So will an international GMP guideline have to remain wishful thinking?

## Where does it go from here?

The aforementioned trends and developments are undoubtedly only the tip of the iceberg. One thing is certain: the future of cleanroom technology will continue to be characterised by interesting challenges and opportunities.

## References:

- 1 The McIlvaine Company, based in Illinois, USA, is a market research company who function as a source for contamination control information by providing market reports, sales leads and directories.
- 2 Ljungqvist B and Reinmüller B. Modern cleanroom clothing systems: people as a contamination source. *PDA Journal of Pharmaceutical Science and Technology* **57** (2003) 2, 114-125.

This article is an abridged and updated version of a presentation first given at the Richter Building System Forum, Munich/Germany on 17.01.03 and first published in *GIT ReinRaumTechnik (GIT Cleanroom Technology)* **5** (2003) 2, p. 10-17. For further information or a bibliography contact either the author or S2C2 at [www.s2C2.co.uk](http://www.s2C2.co.uk).

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## CLEANROOM GLOVES

People's hands have millions of skin particles and bacteria on them, as well as surface oils and salts. To prevent this being transferred onto contamination sensitive products, gloves should be worn.

### Selection

There are 2 types of gloves associated with cleanroom. Knitted or woven gloves are used for lower classes, i.e. ISO Class 7 (Class 10,000) and poorer areas, as well as undergloves.

Barrier gloves, which have a continuous thin membrane covering the whole hand are used in the majority of cleanrooms.

There are a number of problems associated with cleanroom gloves.

Their surface may not be sufficiently free of contamination as they are not usually manufactured in a cleanroom. This means (a) they require further cleaning before being used (b) should be selected with regard to their surface contamination and, depending on the type of use, be free of particles, oils, chemicals or microorganisms.

They may be required to prevent dangerous chemicals, usually acids or solvents, attacking the operator's hands. Thicker and stronger gloves are required.

Other properties that may need to be considered are chemical resistance and compatibility, electrostatic discharge properties, surface ion contribution when wet, contact transfer, barrier integrity, permeability to liquids, heat resistance and outgassing.

Some operator's skin is allergic to the material that gloves are made from. Accelerators in latex, nitrile and neoprene gloves, and the protein in latex, can cause skin irritations. Hypoallergenic gloves, or inner fabric liners, should be worn to minimise this effect.

### Manufacturing process

Gloves are generally manufactured by dipping a 'former', the shape of a hand, into molten or liquid glove material. Formers are usually made of porcelain or stainless steel. The former is removed from the molten or liquid material and a layer of material allowed to set to form a glove. The glove is then stripped from the former.

To allow the gloves to be removed from the former without damage, a release agent is normally employed on the former's surface. When removed, the release agent will contaminate the outside of the glove.

Release agents are a problem in cleanrooms. For this reason cleanroom gloves differ from domestic ones in that the release agent is kept to a minimum.



Gloves are also washed with a view to removing the release agent and any other additives added to the dipping medium. An example of this is magnesium silicate as a release agent in latex gloves made for domestic use. If the magnesium silicate is replaced with calcium carbonate, this powder can be removed from the surface by a mild acid wash. Another way of dealing with the release agent is during stripping. When the gloves are stripped from the former they are 'inside-out'. They may then be turned 'outside-out' to offset the release agent problem.

Glove formulations used in manufacturing non-cleanroom gloves can contain about 15 additives, and a number of these can cause contamination in cleanrooms. Cleanroom gloves may differ from those used domestically by minimising, or not using, some of these chemicals.

When stripped from the formers, latex gloves are 'sticky'. To correct this, latex gloves are washed in a chlorine bath. The free chlorine combines chemically with the latex chemical bonds and leads to a 'case-hardening' of the surface of the glove. This prevents them sticking to each other and the washing also helps to clean the gloves.

### Types

#### Polyvinyl chloride (PVC) or 'Vinyl'

These plastic gloves are popular in electronic cleanrooms. This type of glove cannot be satisfactorily sterilised and are therefore not used in bioclean rooms. They are available in normal and long-sleeve length and should preferably be long enough to cover the cuff of the garment sleeve. Consideration should be made of the fact that plasticisers make up almost 50% of a vinyl glove. Plasticisers come from the same group of chemicals used to test the integrity of air filters, i.e. phthalates. This material is necessary to make the glove pliable and also has the advantage of giving the gloves some antistatic properties. However, it can also cause contamination problems from outgassing and contact transfer onto surfaces.

#### Latex

This is the type used by surgeons, and the 'particle-free' type is used in cleanrooms. Latex gloves can be produced 'powder-free' and those gloves that are washed further by use of filtered, deionised water are often used in ISO Class 4 (Class 10) or ISO Class 3 (Class 1) cleanrooms.

They have good chemical resistance, giving protection against most weak acids and bases, and alcohols, as well as having a fairly good resistance against aldehydes and ketones. They are slightly more expensive to buy than the

## GLOVES continued

PVC type but are cheaper than any other polymer. They can be sterilised. Because of their elasticity the glove can securely incorporate the cuff of a garment under the sleeve.

### Other Polymer

Polythene gloves are used in cleanrooms and have the advantage of being free of oils and additives as well as resistance to puncturing. They are not resistant to aliphatic solvents. The main drawback of this glove type is that they are constructed from float sheets and the seams are welded. Manual dexterity is reduced with these gloves.

Neoprene and nitrile gloves are chemically similar to latex gloves but have the advantage of having a better resistance to solvents than latex gloves but are more expensive.

Polyurethane gloves are strong, very thin, quite inflexible and expensive. They may be manufactured with microporous material for better comfort, or with carbon in the formulation which makes them conductive.

PVA gloves are resistant to strong acids and solvents but not water in which they are soluble. They are expensive.

Gore-Tex gloves have welded seams and are hypoallergenic. They are breathable because of their porous membrane. They are expensive.

Special gloves are used in cleanrooms for heat resistance or insulation and usually made from polymers of silicone or Kevlar. Other polymers, such as butyl rubber, are occasionally used to make gloves for cleanrooms.

### Testing of Gloves

Information on the properties of gloves and methods used to test gloves is given in the Institute of Environmental Sciences Recommended Practice RP CC0055. Tests for surface cleanliness include the measurement of particles, non-volatile residues and ions.

Particle counting involves submerging a sample in a quantity of particle-free water and shaking on an orbital shaker for a given time. The water from the sample is then analysed for particles, either by use of a liquid particle counter or microscopically.

Measurement of the non-volatile residue involves submerging a sample in a suitable solvent, at a given temperature, for a given period of time. The sample is removed and the weight of the residue from the evaporated solvent measured. Ionic content is measured by submerging in deionised water for a period of time then measuring the ion content of the water.

To test gloves for punctures or tears the used glove can be filled with water and checked for leaks or the glove can be blown up with air (by mouth is sufficient), closed at the cuff and squeezed. Any leaks can be found by passing the glove close to the cheek.

Punctured gloves allow contamination to pass out. It has been shown that the number of bacteria coming through a glove when it was punctured to give a 1mm hole, was 7000 from an unwashed hand and 2000 from a washed hand.

## GLOVES - SEMINAR

### Seminar "Selecting the Right Gloves" London and Edinburgh, March, 2005

Experts from Germany, Finland, Malaysia and the UK examined the scientific evidence on the use of natural rubber latex gloves and latex allergy. Sponsored by the Malaysian Rubber Export Promotion Council, the Tun Abdul Razak Research Centre (the Malaysian Rubber Board in the UK) and supported by the Association of British Healthcare Industries, the topics were related to how other European countries have tackled latex allergy issues in hospitals. This was by using only powder free and low allergen examination gloves and surgeons' gloves, and it looked at how these changes in glove selection policy have reduced the number of new cases of occupational asthma and dermatitis. They questioned whether a move to synthetic gloves will provide the answer to the allergy problem and explained how manufacturers have improved the quality of their gloves and how glove quality is monitored.

Dr Henning Allmers<sup>1</sup> described the German experience of successfully tackling the issue of latex protein allergy, through the change from powdered to powder-free latex gloves, from his perspective as Director of the Department of Occupational Medicine, and head of the Occupational Medicine Laboratory at the Department of Dermatology, Environmental Medicine and Health Sciences at the University of Osnabrück in Germany.

Dr Kristiina Turjanmaa<sup>2</sup>, Chief Physician of the Allergy Unit at the Department of Dermatology, Tampere University Hospital in Finland, explained how Finland had already adopted a different, but equally successful, approach by using gloves with a low allergen content and monitoring and publishing the allergen levels of gloves in the marketplace. She has worked on the latex allergy problem for many years.

### Information related to this seminar:

- [1] Natural rubber allergen content of latex gloves: a market surveillance study 2003. [www.nam.fi/english/publications](http://www.nam.fi/english/publications)  
A new survey will be published later in 2005.
- [2] Specific tests for identifying and quantifying individual latex allergens have been developed by the Finnish company FIT Biotech. [www.fitbiotech.com/fitkit\\_brochure.pdf](http://www.fitbiotech.com/fitkit_brochure.pdf)
- [3] Malaysian Rubber Export Promotion Council. [www.mrepc.com](http://www.mrepc.com)

### Footnotes:

<sup>1</sup> Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German healthcare workers. *J Allergy Clin Immunol* 2004; **114**: 347-351.

<sup>2</sup> Turjanmaa K, Reinikka-Railo H, Reunala T, Palosuo T. Continued decrease in natural rubber latex (NRL) allergen levels of medical gloves in nationwide market surveys in Finland and co-occurring decrease in NRL allergy in a large university hospital. (abstract) *J Allergy Clin Immunol* 2000, **104**: S373p.

## GLOVES - FORUM QUESTIONS AND ANSWERS

The following questions and answers taken from the Cleanroom Forum ([www.s2c2.org/dc/dcboard.php](http://www.s2c2.org/dc/dcboard.php)) illustrate various problems and possible solutions.

**Question No. 1:** Can powder-free latex gloves be used in class 100 cleanroom? Any issues in autoclaving it before using?[K]

**Answer:** You should ONLY use powderfree gloves in a Class 100 cleanroom, providing they are clean and are low in particles. There are many powderfree gloves on the market which are purported to be suitable for Class 100 use, but which are in fact loaded with particles to contaminate your cleanroom environment.

First rule is all gloves in a cleanroom must be powderfree.

Secondly, for Class 100 its generally accepted that the glove should have a particle count (particle size 0.5 micron and larger) of no more than 1,500 counts /cm<sup>2</sup>.

You should not autoclave any glove. They should be sterilized preferably by gamma irradiation...and will be presented as a pair pack pouch.[D]

**Question No. 2:** I'm looking for a general opinion on the preferred method of monitoring sterile gloves in sterile manufacturing areas i.e using the 'finger dab' method versus contact plate at knuckle joint.

Surely the 'finger dab' method would be a more reliable method for assessing bioburden on operators' hands? [E]

**Answer:** Since it is the fingers of an operator that touch everything (and eventually they do touch just about everything), the fingers are a very good indicator of what is going on. In the facility that I am at, finger tips, as well as the sleeve cuffs of the operators are monitored daily using contact (RODAC) plates. [R]

**Question No. 3:** I have a problem with gloves when we wear them for about 5 minutes. They roll up a bit so the skin comes free. Has someone a solution for this problem? [G]

**Answer 1:** A practical solution is to use cleanroom tape around the cuffs, OR take a 'ball' of glove at your wrist and tape that up to cause the cuff to actually be a little smaller. [M]

**Answer 2:** Taping as suggested, which may well work, is not really recognized as good protocol. Wearing the correct length glove, of the right material for the specific task, and ensuring that the sleeve length of the cleanroom coverall is of the correct length usually overcomes the problem you have encountered.

I have seen this problem many times and it's usually because the coverall sleeve length is too short and the glove being used is a 240mm glove and not a 300mm cleanroom glove. It's generally accepted that cleanroom gloves should always be at least 300mm in length. [D]

**Answer 3:** I would recommend a Vinyl or Tyvek sleeve. [R]

**Question 4:** Why will the surface color of some nitrile gloves change to yellow in partial position such as wrist, palm finger, after reserving the used used nitrile gloves for several days?

**Answer:** Nitrile gloves usually change color on wearing because of copper contained in sweat secreted by wearers. Some wearers will see a color change within a few minutes of donning, some hardly at all. Sometimes it takes a while for the discoloration to develop. There are formulations of nitrile glove which can avoid this discoloration, but this totally depends on your glove manufacturer.

**Question 5:** If I work in this environment of Class 100 and it is necessary to wear the nitrile glove, how do we decide the frequency of changing the nitrile glove? [K]

**Answer:** In a Class 100 (now internationally called ISO Class 5) you should change gloves every time a cleanroom worker leaves the environment, i.e. for a tea break, lunch, bathroom break etc. Before re-entering the cleanroom new gloves should be donned and also a new facemask. The old ones should be discarded and thrown out. Typically it would be 4-5 changes per shift per worker. [D]

**Question 6:**

Can anybody here give me some information about which detergent is suitable for sterilizing during the process of cleaning the used nitrile gloves in ISO 5 cleanroom? I would be pleased about any possible information related to these detergents. Our company is a supplier to laundry including garments, recycled gloves and packtray in ISO 5 cleanroom so these sterile detergents you provide possibly must be able to be used in cleanroom and can not damage to ESD performance of recycled gloves. [K]

**Answer 1:**

Gloves and other consumables are usually gamma-irradiated rather than washed before use.

I'm not sure if you are re-using these items... If you are then I would say you shouldn't. The insides of these things are bacterial breeding grounds!! [NB]

**Answer 2:**

This is absolutely correct. It's a disgusting and very unsafe practice. I have seen this recycling of disposable gloves practice in several areas in Asia, including China, and it's quite unacceptable.... [D]



# NON-VIABLE PARTICLE MONITORING TO MEET cGMP REQUIREMENTS

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## Introduction

Several changes have occurred within the last year that have brought an elevated review of practices with regard to non-viable particulate monitoring, specifically the new Food & Drug Administration's (FDA) Guideline on Aseptic Manufacture, September 2004 and the revision of the EU GMP Annex 1, September 2003. In both of these documents, the focus on proving control over the manufacturing environment has been increased.

This paper aims to identify the common factors in both the FDA and EU guidelines and how pharmaceutical manufacturers can review current practices within these changes.

## Legislative Limits

There are three current standards for cleanrooms applicable to pharmaceutical manufacturing: ISO14644-1, for room certification, and the above FDA and EU guidelines on monitoring. The table below identifies where the three standards overlap. The table has been simplified due to the FDA's recent adoption of a metric (and ISO) room classification.

ISO14644-1		ROOM FUNCTION		FDA GUIDE	EU ANNEX 1	
Class	Limit			Operational	Operational	At Rest
5	3,520	Sterile Critical	(A)	3,520	3,500	3,500
7	352,000	Sterile Background	(B)	352,000	350,000	3,500
8	3,520,000	Support / Preparation	(C)	3,520,000	3,500,000	350,000
N/A		Support	(D)	N/A	N/A	3,500,000

NOTE: All Data is for  $0.5 \mu\text{m}/\text{m}^3$ . Although the EU imposes limits for 5.0 microns, they are not presented above.

It can be seen that the harmonization on metric limits makes the requirement overlap more apparent where the critical areas need to be maintained around  $3500/\text{m}^3$  at  $0.5 \mu\text{m}$ .

The use of  $0.5 \mu\text{m}$  data is useful to prove control over a cleanroom; statistically it is important to have a dynamic number. If we were to try to control the cleanroom using the  $5.0 \mu\text{m}$  data, we are faced with very few and sporadic events which are difficult for SPC purposes. Based upon the  $0.5 \mu\text{m}$  information, we are best able to define operational limits to 'normal' activities. The greatest issue with cleanroom control and statistics, however, is the source of contamination. People, when present, can significantly increase counts, and when absent, low counts will skew the statistics. However, it is this data that is used to define the maintenance of a room's contamination control with respect to particles, from all sources.

Control of the  $5.0 \mu\text{m}$  data to meet compliance with the EU regulations can prove to be a logistical hurdle; the regulations state that a  $\text{m}^3$  of sample be taken for Class A, B and preferred for C rooms. However, this is for portable, routine testing and where an automated monitoring system is installed a different approach needs to be adopted.

## Requirements for Sampling

The guidelines and the ISO standards both identify that the measurements must be done using a laser based light scattering optical particle counter. The basic principle is that, as particles from any source are passed through the optical chamber of a particle counter, they are sized and counted in real-time, giving immediate information relating to contaminant levels.

The first point of proving room cleanliness is the performance of certification following the ISO14644-1 standards. The standard specifically identifies where samples are taken, what volume should be used to take such samples, and how the data is treated to prove compliance to the standard - a very specific set of instructions. Once the room has been tested, it can be used for its prescribed purpose and room monitoring can now begin to prove maintenance of room standard. Both standards identify the difference in approach required to monitor the environment for critical areas and to support clean areas.

## NON-VIABLE PARTICLE MONITORING TO MEET cGMP REQUIREMENTS

### Critical Areas

There is agreement from both standards on how these areas should be monitored. The EU Annex 1 says, "A continuous measurement system should be used for monitoring the concentration of particles in the grade A zone, and is recommended in the surrounding grade B areas". The FDA says, "Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters".

To satisfy the FDA and the EU, it is important to review the implementation of an automated measurement system. This gives more frequent data and therefore a greater ability to prove control in the most critical areas. It is also less invasive than a portable particle counter, which can be difficult to use to sample the environment without disruption to personnel, process, or both.

Treatment of data from the continuous sampling needs to be reviewed. Where once a single page of data existed, now several pages per sensor will be normal. The primary requirement is that one can prove control over the environment; the log of events showing compliance during batch production is therefore key information. This is supported using tabular, graphical, and statistical analysis as required.

### Support Clean Areas

This is still the domain of the portable particle counter. Routine testing can be performed at regular intervals; these intervals are based upon risk assessment and essentially follow the PDA guidelines on best practices. For compliance to EU regulations, a m<sup>3</sup> of sample needs to be taken in Grade B and is preferred in Grade C areas. This increase over old values is because this is a 'snap-shot' of conditions at a single reference point in time, and therefore to improve confidence in the data a volume expectation is used. There is currently no volume requirement for the FDA routine sampling and so the ISO14644 guide would be the best reference. For most cleanrooms, this would be at least one minute at each location.

For further information and details of changes to particle counting and GMP, please contact Particle Measuring Systems.

## FORUM TOPICS - PARTICLE MONITORING

**Question:** What is the latest on particle counting procedure for Grade B rooms? Does one still have to do a 1 cubic metre cumulative count for the room i.e 35 mins minimum for each room? [PG]

**Answer:** I'm afraid so; Annex 1 still requires the 1cu.m sample volume. [CP]

**Question:** I am facing a particle count problem in class 100-classification area. While performing a particle count test, the counter shows 10 - 15 readings within the acceptable range and only one reading shows increase in the count level. This repeats continuously. According to me, this may be a false count due to fan surge / air turbulence or there may be some another reason. Can any one help me in this regard by suggesting an appropriate solution? [BP]

**Answer 1:**

If the high count is consistanly in the same location, you probably have a problem with your cleanroom in that vicinity.

It may be an airhandler or FFU module has failed or tripped a breaker, or you have a leak in your filter. OR you may have something causing high particle counts in that area. If it is not always in the same location, it might be a personnel related issue....[R]

**Answer 2:**

We are facing the same problem here. We are continously getting high counts especially in the dynaminc condition in class 100. As we are using PMS to measure the particle in the class 100, we use the portable counter to verify against the PMS and both showed the same result. This showed that there is no deviation from the PMS.

We cleaned the impacted area and we managed to get better result. Our filling machine is within the barrier and under unidirectional HEPA filter. What will be the probable cause then? [MC]

**Answer 3:**

You need to really dive into the high counts and isolate the source.

90% of the time an experianced contamination contol engineer can find the source with a portable particle counter. But it requires looking at the installation. [R]

## CTCB CLEANROOM TESTING FOR TESTERS R3 NORDIC

Nordic R3 Association, together with the Scottish Society for Contamination Control and the Irish Society for Contamination Control, have started a group in order to get an international certification for validating and testing cleanrooms.

At the end of January 2005 the first certification took place at KTH (the Royal Technical University in Stockholm).

At the beginning of December there was a meeting of the members of the reference group to discuss the details of the planned certification. These are the tutors who will teach the practical part of the course and come with a great deal of industrial experience.

Present at this meeting were: Jesper Kure, Lennart Hagberg, Jan Tullgren, Nils-Johan Björklund, Lars Jansson, Berit Reinmüller and Bengt Ljungqvist.

Bengt Ljungqvist and Berit Reinmüller will lecture about the theoretical parts. Bengt Ljungqvist, together with Bill Whyte will be the final examiners of the participants. As it is the first time the course is to be held, the numbers will be limited.

The reference group teachers are:

Nils-Johan Björklund and Mats Björklund from CRC, Lars Jansson, Aerotechtelub, Jesper Kure, NovoNordisk Engineering, Tenho Rissanen and Jan Tullgren, Advisor.

It is planned that future courses will be once a year probably during the months of January or February.

Anyone who is interested can now attend the course which will be run within the Department of Skyddsventilation at KTH.



In the laboratory at KTH



Teachers and CTCB candidates

An examination is to be held and an international certificate will be issued upon successful completion. The certificates are at:

“Associate level”

“Professional level”

To get a certificate at the Professional level you must (1) pass the examination and (2) confirm that you have work experience in this field. Lastly, if there is an interest in having a course earlier than January 2006, this could be possible.

The course covers the following topics:

- \* Cleanroom air conditioning plants
- \* High efficiency filters
- \* Classification and testing standards
- \* Measuring air supply volumes
- \* Differential pressures
- \* Containment, visualisation and recovery methods
- \* Air filter integrity testing (installed filter leakage testing)
- \* Particle and microbial measurements
- \* Conduct in cleanrooms

For further information and questions contact:

Berit Reinmüller

email [berit.reinmuller@byv.kth.se](mailto:berit.reinmuller@byv.kth.se)

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Neil Stephenson (left) demonstrating equipment at the R3 Nordic CTCB course.

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**SALVAGING OF CLEANROOM EQUIPMENT**

The mothballed NEC semiconductor plant located at J3 off the M8 at Livingston is currently being dismantled. If anyone is interested in salvaging cleanroom equipment from this Class One cleanroom facility, contact Peter MacDonald, project manager for Masterton Demolition on 07887 541 732. As an example there is still a fully automated stocker system with wafer handling track, AHUs, FFUs UHP systems, scrubbers, etc still on site.

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