

# PharMIG news

Issue 13 September 2003



## Chairperson's Review

2003 is already looking to be one to remember for a number of reasons. First of all there is the weather – can you remember such a summer where not only was the temperature high but was high on consecutive days, long may it continue. But what of PharMIG I hear you saying!

In 2003 Membership has already increased relative to the numbers published at the 2002 AGM and there is a target to have 100 Members by the end of the year – a target we remain confident of achieving.

With the changes in the office structure the Executive Committee have re-looked at the roles of the PharMIG Organising Committee. In the past the Committee Members had responsibility for not only putting together the technical programme for a PharMIG event but to also got involved in the organisation of the event. In today's industry with time being a valuable resource this has often proved difficult for Committee Members – and perhaps has also inhibited Members from putting themselves forward for election.

Primarily in response to this the PharMIG Committee will in future be re-structured to have up to four Technical Advisors who will have an important role in ensuring that PharMIG continues to identify and deliver events appropriate to you, the Members, but will not be required to spend their time in the planning etc.... This has been considered possible due to the resource available in the PharMIG office where the events organisation and management can be better focused. There will be more information available on the Committee re-structuring as we get closer to the AGM in Nov 2003. Perhaps you have thought of getting more involved with the PharMIG organisation in the past but felt that you were unable to commit significant time – with the re-structure perhaps you could reconsider? Call the office or contact me if you want to discuss further.

The European Union announced that 10 additional countries will become Members in 2004 – in the area of Pharmaceutical manufacture these countries will need to comply with EU requirements and regulations. Perhaps PharMIG could have a role in training – something to explore. Please do use the PharMIG Forum section on our website for your comments on this or anything else.

For those of you involved in Sterile Manufacture the up-date to Annex 1 of EU GMP will be something to remember. There is also the possibility that Annex 1 will be reviewed in full starting from the end of 2003 – a decision will be taken within the EMEA later on in the year. It is important that if this occurs that, as individuals and as PharMIG, we take an active role in reviewing and providing feedback once the text is made available for public comment. In this way "the web" is a real benefit to today's industry.

The PharMIG Action Groups continue to work well under the direction of Natasha but I am aware that a number of them are looking for new Members due to current ones moving jobs and careers. I would like to add to Natasha's comments and thank everyone, particularly those leaving the groups, for their hard work and dedication. However, with these changes there is a need to add new team Members to enable the Action Groups to continue and maintain momentum – contact Natasha if you are interested. I know she will always be pleased to hear from you.

Lastly, you will be receiving the conference brochure in the not too distant future and I am sure you will agree that this years programme has something for everyone – have you got the dates in your diary yet – 18th & 19th Nov 2003? I know I have and I look forward to seeing you all there.

Until the next time,

**Sharon Johnson, Chairperson, PharMIG.**

## in news issue 13...

Editors Note/IBA Sterigenics Site Visit  
Date for your Diary  
Notice of AGM  
PharMIG Conference

Page 2  
Page 3  
Page 4  
Page 5

PharMIG Conference continued Page 6  
PharMIG Action Group Page 7  
Monitoring - What, Where & How Often? Pages 8 -12  
Surviving a Microbiological Audit Page 13  
Personal Profile of: Poly Hajjipieris Pages 14 & 15  
PharMIG Diary Dates Page 16

# Editors Note



**Paul Lovegrove-Saville**  
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Dear reader, what a magnificent summer we are having, sunshine, sunshine and more sunshine. Doesn't it make you feel that it's great to be alive?

If you haven't taken a look at the web page recently I suggest you log on because its looking really good. There is lots of information, diary dates, the forum page where you can get answers to questions, an archive of newsletters and much,

much more. Find it at <http://pharmig.org.uk> . If you would like to contribute to the web or newsletter drop me a line at the address given above.

Have you seen the proposed revisions to Annex 1 of the EC Guide to Good Manufacturing Practice? This has been changed to state "When monitoring the concentration of particles in clean room areas Class A or B **continuous measurement** of particles should be guaranteed in principle". It also states that, for routine testing, the total sample volume at each point should **not be less than 1m<sup>3</sup>** at least for Grades A and B, preferably also in Grade C. For areas at rest and for Grade A during operation, they are expected to be completely free from 5µm particles. As it is impossible to demonstrate the absence of particles with any statistical significance the limits are set to one particle/m<sup>3</sup>. During clean room qualification it should be shown that the areas can be maintained within the defined limits.

I imagine that this will give some sites something to think about. Have a look at:

[http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2002/nov/Proposal\\_Revision\\_Annex1.pdf](http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2002/nov/Proposal_Revision_Annex1.pdf)

Also, don't forget to use the PharMIG Forum page to voice your concerns/opinions.

## IBA Sterigenics Site Visit

Article written by: **Robert Holt – JohnsonDiversey**

A one-day seminar was held by Sterigenics in Alfreton, Derbyshire during July for companies from the Pharmaceutical Industry. Representatives from Boots, 3M and JohnsonDiversey were amongst the companies attending the day. Sterigenics specialise in providing innovative solutions on all aspects of sterilisation worldwide. Sterigenics have 50 sites based in 12 countries around the world and offer sterilisation methods including ethylene oxide, gamma irradiation and E-beam / X-ray. The Alfreton site offers ethylene oxide sterilisation for use on medical devices and other pharmaceutical components.

Ethylene Oxide has been used as a sterilisation technique for over 60 years and is compatible with a wide-range of plastics and materials without affecting the integrity of the product.

The day comprised of presentations outlining the use and applications of ethylene oxide as an effective means of sterilisation followed by an in-depth tour of the site. The complexities of the process were highlighted together with the stringent controls required to ensure customers products are sterilised. The company promote the use of biological indicators as a control method during the sterilisation process. To support their commitment to improving sterilisation processes for the Pharmaceutical Industry, Sterigenics are continually investing in the site to stay at the forefront of sterilisation technology. The one-day seminar was extremely informative for those who attended and Sterigenics provided an invaluable insight into the world of ethylene oxide sterilisation.

**JohnsonDiversey**  
Clean is just the beginning



**JohnsonDiversey,  
manufacturers and suppliers of  
detergents and disinfectants,  
are proud to support PharMIG**

# Date for your diary

## Practical Training on Cleaning & Disinfection

Tuesday 23rd & Wednesday 24th September 2003. The University of Bath, Claverton Down, Bath

### PROGRAMME Tuesday 23rd September 2003

09.30 – 10.00	<b>Registration &amp; Tea / Coffee</b>	14.45 – 15.15	<b>Tea / Coffee</b>
10.00 – 10.15	<b>Welcome &amp; Introduction</b> Dr Rosamund Baird	15.15 – 17.30	<b>Practical Demonstrations &amp; Laboratory Work:</b> Environmental monitoring Monitoring disinfectant concentrations Testing of skin disinfectants – EN1499 and EN1500 Filter integrity testing Microbiological aspects of disinfectant validation Rosamund Baird, John Barker, Rachel Blount, Lorna Simpson, Kim Morwood, Stuart Morgan, Stuart Rolfe
10.15 – 11.15	<b>Disinfection Theory</b> Dr Anthony Smith		
11.15 – 12.30	<b>Disinfection in Practise – Sterile &amp; Non-Sterile Areas</b> Rachel Blount		
12.30 – 13.30	<b>Lunch</b>		
13.30 – 14.15	<b>CIP – Review of Accepted Practice and Current Standards</b> Andrew Provan		
14.15 – 14.45	<b>Disinfectant Challenges in Hospitals and Home</b> Dr John Barker	17.30 – 17.45	<b>Discussion</b>
		18.45	<b>Reception drinks followed by Dinner</b>

### PROGRAMME Wednesday 24th September 2003

09.00 – 10.00	<b>Disinfection Challenges of Water Systems</b> Dr Annette Ellison	15.00 – 15.45	<b>Interactive Audit Workshop</b> Dr Robert Johnson
10.00 – 11.00	<b>Role of Monitoring in Contamination Control</b> David Wilson	15.45 – 16.00	<b>Tea / Coffee</b>
11.15- 11.30	<b>Tea / Coffee</b>	16.00 – 16.15	<b>Final Discussion and Depart</b>
11.30 – 13.00	<b>Case studies:</b> Small working groups will discuss cleaning related issues and report back on a suitable course of action Rachel Blount, Dr Rosamund Baird, Andy Martin	Fee:	£800 Members £925 Non Members
13.00 – 14.00	<b>Lunch</b>	Contact:	Please note: Fees include one nights accommodation and dinner on Tuesday 23rd September. Maxine Moorey on 01920 871 999 or email: <a href="mailto:info@pharmig.org.uk">info@pharmig.org.uk</a> for more details.
14.00 - 15.00	<b>The Importance of Cleaning Validation to the Pharmaceutical Industry</b> Dr Ansley Crockford		



Supporting PharMIG and the  
Pharmaceutical Industry

# Notice is hereby given of the 3rd Annual General Meeting (AGM) of PharMIG Ltd

The AGM will be held between 1700 and 1800 on Tuesday 18th November 2003 at the Stratford Manor Hotel, Stratford-upon-Avon.

Please note that the AGM is open to all fully paid up PharMIG Members of 2003 including Commercial/Allied companies.

The AGM will consist of four sections:

- (i) Reports from present Chairperson (Sharon Johnson), Treasurer (Bob Johnson), Secretary (Mary-Anne Weatherhead)
- (ii) Election of Committee
  - Anyone wishing to be nominated for any available Committee positions should make their intention clear in this section of the AGM. If you are unable to attend then please make your intention to stand for a position in writing. Nomination forms will be posted to all Members in October and will also be available on the website.
  - All nominations must be proposed and seconded by an existing PharMIG Member. This may be either at the AGM or prior to the meeting in writing.
- (iii) Open floor for Members to air views / questions about how PharMIG is performing and operating
- (iv) Any other business

In accordance with the Articles of Association, PharMIG is managed by an Organising Committee comprising of: Honorary Officers or Executive Committee and the Committee.

## The Executive Committee positions are as follows:

- Chairman
- Treasurer
- Executive Secretary
- Company Secretary
- Business Development Director

All the above positions are not electable at the AGM and are invited by the Board of Directors. These positions do have voting rights at the AGM.

## The Committee is comprised of:

### Vice Chair

- To support / deputise for the Chair. (This does not imply that the Vice Chair automatically succeeds to the position of Chair, but can put themselves forward to be voted in)
- Chairs Committee meetings in the absence of the Chair
- Helps to ensure the Group remains focused and meets their objectives
- Helps to ensure the Group remains focused to the needs of the Members

### Action Group-Cordinator

- Co-ordinate all Action Groups
- Ensure Action Groups have necessary resources made available to them
- Bring any issues raised by Action Groups to the Committee for discussion
- Help Action Groups to issue monographs with the help from the Committee
- Ensure Action Groups remain on track and focused

### Communications Co-ordinator

- Gather articles for the quarterly newsletter by: inviting delegates attending meetings to write up their findings, inviting people / companies to put forward a non-commercial article on relevant topic areas; incorporating pertinent surveys conducted by various Action Groups as and when they become available
- Provide own editorial comments for each newsletter
- Proof reading of all articles
- Help monitor the PharMIG website – providing additional articles for specific posting on the site and to help answer any questions raised on the forum page (along with all other Committee Members)

### Up to 4 Technical Advisors\*

- Help identify key topic areas that PharMIG should be addressing in the form of meetings / site visits / training courses etc
- Help in providing background research to ensure that chosen topic areas are viable
- Help in providing names of potential speakers
- To act as consultants and sounding boards to ideas generated that could help further promote PharMIG and aid its growth
- To act as ambassadors for PharMIG – ‘spreading the word’ of its existence and its goals and objectives
- To highlight what other meetings are being held by external companies and to review whether PharMIG should be holding similar ones
- To act as scientific editors for PharMIG articles as and when required

*Note: PharMIG has recently changed the structure of its Committee to reflect the current business requirements for individuals as well as those for PharMIG. This should ensure that individuals standing for Committee positions can meet the requirements of the role without compromising their full-time working positions.*

\*The Executive Committee are planning to appoint up to 4 Technical Advisors for 2003 – 2005 although there is flexibility (in the Articles of Association) to appoint up to 9 if required.

## PharMIG Conference

### 'The Diverse Microbiologist'

18th & 19th November, Stratford Manor Hotel

**PROGRAMME Tuesday 18th November 2003**

Chairperson **Mrs Sharon Johnson<sup>c</sup>** PharMIG Chairperson

09.30 – 10.00	<b>Registration and Tea/Coffee</b>		
10.00 – 10.15	<b>Chairperson's Welcome &amp; Introduction</b>		
10.15 – 11.15	<b>Key Note Lecture</b> Regulatory inspections and how they impact microbiology <ul style="list-style-type: none"> <li>• Active Pharmaceutical Ingredients - the current situation</li> <li>• Expectations for medicinal products</li> <li>• Current inspection issues</li> </ul> <b>Mr Richard Andrews - MHRA</b>		<ul style="list-style-type: none"> <li>• Contamination control &amp; testing regimes</li> <li>• Regulatory aspects</li> <li>• Facilities (product protection and containment)</li> </ul> <b>Mr Paul Lovegrove-Saville<sup>c</sup> - GlaxoSmithKline</b>
11.15 – 12.00	<b>Microbiological Aspects of Manufacturing Control of APIs</b> <ul style="list-style-type: none"> <li>• Source &amp; control of contamination</li> <li>• Selective pressure in the manufacturing process</li> <li>• What is the impact on sampling regimes for APIs</li> </ul> <b>Mrs Kay O'Hagan – Bovis Lend Lease</b>	15.00 – 15.30	<b>EXHIBITION with Tea and Coffee</b>
12.00– 13.30	<b>EXHIBITION with finger buffet lunch</b>	15.30 – 16.10	<b>Practical Case Studies in Microbiological Failure Investigations</b> <ul style="list-style-type: none"> <li>• What is a Process Deviation? What is a Process?</li> <li>• Essential principles for dealing with Process Deviations and Failure Investigations</li> <li>• Investigating an environmental contamination problem - Case Study</li> <li>• Investigating problems with water systems - Case Study</li> <li>• Investigating sterility test failures - Case Study</li> </ul> <b>Dr Trevor Deeks – Fluor Ltd</b>
13.30 – 14.15	<b>Regulatory Issues for Non-Monographed Raw Materials</b> <ul style="list-style-type: none"> <li>• Quality assurance in the absence of a Pharmacopoeial monograph</li> <li>• How to define the quality required of the raw material</li> <li>• How to ensure that the material is of the quality defined</li> <li>• Where to find help</li> </ul> <b>Mrs Marie Rabouhans - Consultant</b> (Former Scientific Editor-in-Chief, British Pharmacopoeia)	16.10 – 16.40	<b>Microbial Risk Assessments for Aseptically Prepared Products</b> <ul style="list-style-type: none"> <li>• Modified HACCP approach to risk management</li> <li>• Risk assessments for general cleanroom areas</li> <li>• Risk assessments for critical areas</li> </ul> <b>Mr Tim Eaton - AstraZeneca</b>
14.15 – 15.00	<b>Contamination Control of Biopharmaceutical Products – Problems and Solutions!</b> <ul style="list-style-type: none"> <li>• Introduction to Biopharmaceutical processing (cell banking to purification)</li> </ul>	16.40 – 17.00	<b>Panel Discussion and Close of Day One</b>
		17.00 – 18.00	<b>AGM</b> (Members only)
		19.00 – 20.00	<b>Pre-dinner Reception</b> in the EXHIBITION AREA
		20.00 'till late	<b>Conference Dinner &amp; Dance</b> (smart dress required)

**PROGRAMME Wednesday 19th November 2003**

continued over...

09.00 – 09.15	<b>Chairperson's Remarks</b>		
09.15 – 10.00	<b>Water Use in Biopharmaceutical Processing</b> <ul style="list-style-type: none"> <li>• Regulatory requirements</li> <li>• Water Quality in biopharm</li> <li>• Water in relation to contamination control</li> <li>• Water in processing</li> </ul> <b>Mr Mike Breese</b> (formerly Genzyme Ltd)		<ul style="list-style-type: none"> <li>• Why Europe must respond – a role for PharMIG?</li> </ul> <b>Dr Paul Newby - GlaxoSmithKline</b>
		15.30 – 16.00	<b>Panel Discussion</b>
		16.00 – 16.15	<b>Summary and Close of Conference</b>
		16.15 – 16.30	<b>Tea/Coffee and departure</b>
10.00 – 11.00	<b>Open Discussions</b> Sessions 1,2,3 & 4 running concurrently		<sup>c</sup> Committee Member of PharMIG <sup>*</sup> Honorary Member of PharMIG <sup>^</sup> Action Group Member
11.15 – 11.45	<b>EXHIBITION with tea &amp; coffee</b>		<b>OPEN DISCUSSION SESSIONS</b>
11.45 – 12.45	<b>Open Discussions</b> Sessions 1,2,3 & 4 running concurrently		<b>WEDNESDAY 19TH NOVEMBER</b>
12.45 – 14.00	<b>EXHIBITION &amp; Buffet Lunch</b>	Session 1	<b>Water Activity</b> FACILITATOR : <b>Mr Richard Benton<sup>A</sup></b>
14.00 – 14.45	<b>Electronic Records and Signatures in the Microbiology Laboratory</b> <ul style="list-style-type: none"> <li>• Overview of USA and EU Legislation.</li> <li>• What Systems Need to Comply?</li> <li>• Ensuring Compliance: A Risk Based Approach</li> </ul> <b>Mr Barry Cook (Formerly GSK)</b> <b>Mr Andrew Clark</b> <b>Simon Carves Ltd</b>	Session 2	<b>Process Validation – the Practical Issues</b> FACILITATOR : <b>Mr Neil Rose<sup>*</sup></b>
		Session 3	<b>Method Validation – the Practical Issues</b> FACILITATOR : <b>TBC</b>
		Session 4	<b>Microbiological Aspects of Manufacturing Control of APIs</b> FACILITATOR : <b>Mrs Kay O'Hagan</b>
14.45 – 15.30	<b>Why Process Analytical Technology (PAT) needs Rapid Microbiological Methods</b> <ul style="list-style-type: none"> <li>• What is Process Analytical Technology?</li> <li>• What PAT is in relation to Rapid Methods</li> <li>• Why microbiology is central to PAT objectives</li> </ul>	Fee:	£600 Members £800 Non Members
		Contact:	Maxine Moorey on 01920 871 999 or email: <a href="mailto:info@pharmig.org.uk">info@pharmig.org.uk</a> for more details.



**Supporting 2003 PharMIG Conference**

# PharMIG Action Group

*"Far and away the best prize that life offers is the chance to work hard at work worth doing."*

*Theodore Roosevelt*

The PharMIG Action Groups work hard to produce information that will be of benefit to you, the pharmaceutical microbiologist. They have to produce this excellent work whilst still working in full time demanding jobs. So, I would like to take this opportunity to say thank you to all of you who have contributed both past and present to the Action Groups. Not only by actively taking part with the Groups, but by taking the time to respond to various questionnaires sent out and attending their seminars.

The Non-Sterile Monitoring Group are coming together to begin the preparations for a monograph. They are keen to recruit new Members to help with this document. It will give you the opportunity to provide input into the strategies of non-sterile monitoring and allow your published work to be shared with others within the industry. If you would like to join this Group please see the details below.

The Bacterial Endotoxin Group continues to work with the Parenteral Society to produce a joint monograph, the first drafts being ready to be reviewed soon.

Trudy and her team on the Disinfectant Action Group have completed their sections for their monograph and it is now out for final review. They have had some encouraging feedback from their paper and we can look forward to its publication. The Group's next venture is to look into producing a video to help with disinfection and cleaning practices and this will be in collaboration with disinfectant manufacturers.

The Steam Sterilisation Group has new Members joining. The Group have also issued questionnaires early this year and have had many responses back. Thanks again to those who have responded. If you have not received a copy of the questionnaire please contact the PharMIG Administrator on 01920 871 999.



The Water Activity Action Group is actively seeking new Members.

The current Action Groups are still as productive as ever but also dynamic, with Members moving on to pastures new within the industry or, in a completely new direction. PharMIG wishes you all the best of luck in your new ventures.

The Action Groups are constantly evolving and continually accept new Members. If you would like to know more information about the Action Groups or would like to participate in one then please contact myself on [natasha.sc.gibbs@gsk.com](mailto:natasha.sc.gibbs@gsk.com).

Wishing you all continued prosperity in the demanding field of Pharmaceutical Microbiology.

**Natasha Gibbs**  
*Action Group Co-ordinator.*



**Supporting 2003 PharMIG Conference.**

# Monitoring - what, where and how often?

Article written by: **Tim Sandle - BPL**

## 1. Introduction

This article examines some of the physical and environmental monitoring requirements for cleanrooms. The paper details a possible approach that a pharmaceutical manufacturer may adopt for the monitoring of cleanrooms. It does not follow any one standard directly but makes reference to several. The intention is to provide the basis for constructing a rationale for cleanroom monitoring (although the manufacturer should ensure that any approach adopted is in line with their respective licensing or regulatory authority).

An HVAC (Heating, Ventilation and Air-Conditioning) system requires a series of on-going checks in order to achieve a level of assurance in the system. An HVAC system is designed to:

- a) Control airborne particulates
- b) Have sufficient airflow and air changes
- c) Maintain appropriate positive pressure differences
- d) To operate with the appropriate temperature, humidity and lighting
- e) Have a low level of microbial contamination, appropriate to the operations

The monitoring is designed to provide information in support of the Grade or Class assigned to the cleanroom (be it to ISO 14644, USP <1116> or to EU GMP).

There are two aspects to monitoring:

- a) As a formal classification on an annual / six-monthly basis
- b) As a series of on-going checks to show the reliability of the system ('routine monitoring')

## 2. Formal classification

Formal classification (or commissioning) is made up by a series of tests selected by the manufacturer (although there is a great deal of guidance provided in different standards). There is an expectation that re-classification is performed at set intervals in a defined occupancy state. ISO14644-2 sets out a guide to the testing required.

The principles of classification / re-classification are to show that:

- a) Air supplied into the cleanroom is of a sufficient quantity to dilute or remove contamination generated in the room

- b) Air within the cleanroom moves from a clean to a less clean area (i.e. from a higher grade to a lower grade).
- c) Air supplied into the cleanroom is of a sufficient quality so it will not add to contamination within the room
- d) Air movement within the cleanroom should ensure that there is no area within the room with high areas of contamination

(Reference: Whyte, 2001: p116).

These principles are demonstrated by performing of a number of tests:

### 2.1 Particle count classification

Particle count classification is designed to show that the cleanroom, in the required state, conforms to the Grade / Class assigned to it. The Grade assigned will depend upon the operation and this will be up to the manufacturer to determine.

Where a cleanroom contains a fixed laminar airflow, this is subject to an independent classification.

There are different approaches to classification. The recent harmonised approach is ISO 14644 (of which parts 1, 2 and 4 have been published). However it is up to the manufacturer (in discussion with its regulatory authority) whether it chooses to adopt ISO 14644. If the standard is adopted the manufacturer must comply with regulatory guidelines first (such as EU GMP). The standard, however, provides a clear cut, approach which an organisation may decide is the most straightforward approach to take.

There are three states for cleanroom classification:

- a) As built
- b) At rest ('static state')
- c) In operation ('dynamic state')

As built applies to the testing of a cleanroom immediately prior to hand over. Monitoring in one of the other two occupancy states is then performed as part of the regular classification activity.

The manufacturer may choose to perform classification in the static or dynamic occupancy state. The recommendation is towards the dynamic state as more meaningful data can be obtained. However the choice may depend upon the nature of the operation and if some

cleanrooms are little used it can be difficult to always achieve the dynamic state and in such cases it may be advisable to select the static state.

It is important, however, to define what is meant by the static state and there are differences between USP and EU GMP definitions with respect to whether equipment is running or not.

Before commencing particle classification, two key elements require examination:

- a) Sample locations
- b) Sample volumes

a) The approach for determining sampling locations for the classification of a cleanroom is contained within ISO 14644 (part 1), which is similar to the now withdrawn standard FS 209E. The formula is:

$$N_L = \sqrt{A}$$

Where:

$N_L$  is the minimum number of sampling locations (rounded up to the nearest whole number)

A is the area of the cleanroom / clean zone in square metres

By calculating the square root of A the number of sampling locations required is determined. These should be marked on a map of the cleanroom and placed at an approximate equal distance apart (taking into account fixed equipment) by using a grid.

If the number of locations calculated is less than 10 an additional calculation step, on the date produced, to produce the 95% upper confidence level is required.

The samples should be taken either one metre up from the floor or at the working height of the activity in the room. For each location a sufficient volume of air should be sampled so that a minimum of 20 particles would be detected if the particle concentration of the 5.0 µm size was the limit for the designated class.

b) For sample volume it is important to ensure that the minimum required volume of air is taken. This is a volume of air large enough to count 20 particles of the largest particle size specified. The following formula is used:

$$V = \frac{20 \times 1000}{C}$$

Where:

V = Minimum single sample volume per location (in litres)

C = Class (Grade) limit for the cleanroom (expressed as number of particles per m<sup>3</sup>) for the largest particle size for the relevant class.

20 = The number of particles that could be counted if the particle concentration was at the class limit.

Recommended frequencies for reclassification are detailed in ISO 14644 (part 2). Frequencies are dependent upon the grade of the cleanroom (EU GMP Grade equivalents have been given):

Grade	Frequency of classification
A	Six-monthly*
B	Six-monthly*
C	Annually
D	Annually

\* Allowance is made for cleanrooms which have instrumentation that allows for more frequent monitoring (such as a facilities monitoring system) to classify less frequently (annually) provided that results remain within limits. A manufacturer may choose to incorporate this into its rationale.

## 2.2 Other physical parameters

### a) Air-velocity / supply.

Air-velocity for Grade A zones (a UDAFs in a Grade B cleanroom) should be measured to show a controlled air-velocity as part of a six-monthly re-classification using an anemometer. The EU GMP requirement is 0.45 metres / second (within +/- 20%) with the measurement taken at the working position. Air-velocity is important because the air movement needs to be sufficient to remove any potentially large particles before they settle onto a surface.

It is important to monitor that the correct supply of air is entering a cleanroom (this is measured using flow measuring hoods) and that air is moving in the right direction (unidirectional: horizontal or vertical as required).

### b) Air-changes

Each grade of cleanroom has a set number of air changes per hour, which must be met. Measurement of air-changes tests the re-circulation of filtered air and it is an important requirement in demonstrating that a cleanroom can remove any contamination that may be present. The guideline is for process areas is to have a minimum of 15 to 20 air-changes per hour (the FDA draft guidelines on Aseptic Filling, 2002, recommends a minimum of 20 air changes).

Air-changes are calculated using an equation that measures air flow and room volume. Grade B rooms are normally measured six-monthly and other grades annually.

Tests should also check air-movement within the cleanroom to show that there are no areas within a cleanroom where there is insufficient air movement and that contaminated air is not entering the cleanroom.

### c) Clean-up times

The clean-up time achieved by a cleanroom is linked to the particle classification and is often performed as part of the same validation exercise. Clean-up time is a measure of the time taken for a clean area to return to the static state appropriate for the grade after the cessation of a dynamic state activity (as measured by the number of air-borne particles). The EU GMP Guide defines this as a "short period" and states 15-20 minutes as a 'guidance value'

Clean-up time testing is often performed by filling an area with smoke, from a suitable generation device, and then measuring the time taken to achieve the static state level of particles.

#### **d) HEPA / ULPA filters – filter installation leak tests**

HEPA (High Efficiency Particulate Air) or ULPA (Ultra Low Penetration Air) filters are designed to control the number of particles (non-viable and microbial) entering a clean area and to straighten the air-flow. To check their effectiveness they are checked for leaks by challenging the filters with a particle generating substance (an aerosol challenge, for example Di-octyl phthalate [DOP] or Shell Ondino mineral oil) and measuring the efficiency of the filter.

There are different standards for filters depending upon the facility. One of the commonly used standards is BS EN 1822 (Part 1 and 2), for HEPA, where an efficiency rating of 99.97% for the filtration of 0.3mm particles is required (i.e. only 3 out of every 10,000 particles of a 0.3mm size could penetrate the filter). The equivalent efficiency for a ULPA filter is 99.999%.

The frequency of validation every six months and the filter installation leak test is designed to test both the filter itself and the filter housing.

### **3. Routine / on-going monitoring**

#### **3.1 Physical parameters**

##### **a) Airflow mapping**

Airflow mapping is not part of classification but it is an expectation that critical activities need to be studied in order to show that air turbulence does not interfere with critical processes and that air moves from a higher grade to a lower grade. This is in order to show that there is not a contamination risk. Such critical processes will include filling machines, laminar airflow devices and specific activities like the loading freeze-dryers.

Airflows are mapped using smoke generating devices. It is a good idea to capture smoke studies using video tape or a camera and to add to a report.

A manufacturer will need to develop a rationale for the frequency of such mapping. A biannual frequency is often selected. However more frequent studies should be performed following major changes to equipment.

##### **b) Positive pressure**

As part of maintaining the air quality in a cleanroom the pressure of a given room must be greater relative to a room of a lower grade. Generally this is a pressure differential of 10 - 15 Pascals (as described in EU GMP) or 5- 20 Pascals (as described in ISO14644-4). However certain special activities in a manufacturing area may require different pressure differentials (such as activities involving dust extraction), in such instances these should be explained in a rationale. Pressure differentials are

maintained through air-balancing techniques.

Pressure differentials are often measured on a daily basis either manually using manometers or by automated room sensors. Ideally some form of alarmed warning system should be in place.

##### **c) Temperature, relative humidity and lighting**

Cleanrooms will have set requirements for temperature, humidity and lighting which will be based on particular processes and user requirements.

Generally, for Grade B, the guideline for temperature is 18°C (+/- 3°C). This is important for operator comfort and to control the amount of perspiration, which could result in a decrease in the effectiveness of cleanroom garments (in terms of the garments ability to retain micro-organisms, refer to ISO 7730 for more details). For relative humidity the guideline is an RH of 30 to 65%.

Some organisations establish lighting requirements by lux ratings (the former BS 5295 stated 300 lux). Lighting should always be adequate to the task, uniform and anti-glare in order to allow staff to perform tasks effectively.

Some manufacturers will also include checks on heating and cooling systems; sound, vibration and energy conservation.

##### **d) Compressed Air / Gasses**

Compressed air and gas lines in a cleanroom should be qualified for physical requirements, such as moisture, and microbial levels (often <1 cfu / m<sup>3</sup>), and a routine monitoring programme constructed.

##### **e) Surfaces**

Regular checks on the general construction of the cleanroom should be performed, such as, inspection of the surfaces and walls for cracks and defects.

### **3.2 An environmental monitoring programme**

#### **3.2.1 Viable monitoring**

One of the key on-going checks on a cleanroom is microbiological ('viable') environmental monitoring. Such monitoring shows the number of micro-organisms present that can be recovered using the given sampling technique, culture media and incubation conditions applied, at a set point in time. Techniques include:

- Air samples (using either active, volumetric samplers or passive settle plates)
- Surface samples (using RODAC plates or swabs)
- Personnel samples (finger plates; contact plates of gowns)

The main aim of microbiological monitoring is to allow the monitoring of trends over time. Individual results (whether of a high count or a low count) are rarely significant. Results are measured against recommended (or more

ideally: user defined based on a statistical review of the data) warning (or alert) and action levels. In addition some trending of the micro-organisms recovered should be performed.

When action levels are breached or adverse trends are detected the user should define appropriate measures to be taken in out-of-limits (OOL ) procedures.

Microbiological monitoring should be performed in the dynamic state because this represents the 'worst case' scenario (i.e. the cleanroom with people present and performing processing). Given a large facility a rationale needs to be constructed to determine:

- a) Where monitoring takes place
- b) How often monitoring is performed
- c) Appropriate corrective and preventative actions for action level excursions

As a rule, sterile filling activities are monitored during each fill. Whether this is continuous monitoring or at defined intervals will depend upon the user. The level of monitoring must be sufficient to allow an assessment to be made during product release. For the monitoring of other activities in lower grade cleanrooms different approaches are needed.

This can be established by using a risk assessment tool. There are several techniques available including HACCP (from the food industry) and FTA or FMEA (from the engineering industry). Various 'Total Quality' approaches also offer useful analytical tools.

Such approaches share a similarity in that they involve:

- Constructing diagrams of work flows
- Pin-pointing areas of greatest risk
- Examining potential sources of contamination
- Deciding on the most appropriate sample methods
- Helping to establish alert and action levels
- Taking into account changes to the work process / seasonal activities

By using such tools different approaches for different cleanrooms can be established. This may involve:

- Monitoring in areas which have a more 'dirty' activity taking place in an adjacent room
- Varying the frequencies for surface monitoring compared to viable air monitoring
- Examination of the movement of people (corridors and changing rooms are often routes of the spread of contamination and a monitoring programme may focus more heavily on these areas)
- Routes of transfer / in-coming goods
- Component preparation
- Having higher frequencies of monitoring for areas at ambient temperature with high amounts of water compared to cold rooms

- Intensifying monitoring towards final formulation / purification / secondary packaging / product filling
- A monitoring programme designed to test the effectiveness of cleaning regimes
- More frequent monitoring for open, compared to closed, processes
- Areas of potential contamination, for example door handles

One approach may be to establish a 'criticality factor' where different rooms, with different activities, can be rated. Therefore one room where product purification takes place, would be given a higher criticality factor and be monitored weekly, whereas a wash-up area, would be given a lower criticality factor, and be monitored monthly.

### 3.2.2 Monitoring for non-viable contaminants

On-going particle monitoring examines the quantity of airborne particles in the air for particle sizes 5.0mm and 0.5mm using specialised particle counters. For USP conformance monitoring for the 0.5mm size, in the dynamic state, is recommended, whereas both sizes are required for EU GMP and most manufacturers will monitor for both sizes of particles. Although monitoring determines the level of non-viable particles such monitoring gives a level of assurance regarding the presence of micro-organisms. A high level of particles may imply corresponding levels of micro-organisms (although this has never been determined, Ljungqvist and Reinmuller 1996, consider the relationship to be 105 particles: 1 micro-organism).

Aside from the classification requirements in either the static or dynamic state (as previously outlined) some level of 'routine' monitoring in the dynamic state is required. For sites with an Aseptic Filling Suite the common approach is for continued monitoring throughout the filling activity for the Grade A filling zone and the Grade B cleanroom or Grade A isolator (and this is likely to become part of the next revision to the EU GMP Guide). Furthermore rooms associated with the fill, such as, areas where product vials are located and the loading of freeze-dryers are also monitored. Monitoring should also note events like shift changes and filling line interventions.

For Grade C and D areas things can be more problematic. Given a large facility with many different operations being performed the organisation will need to select those activities considered critical to its operations for dynamic state monitoring and construct a rationale around it. This maybe by:

- Listing areas and operations which will not be monitored (such as operations which are known to generate a high level of particles, such as, centrifugation. Some work maybe needed to show that any particles in the room are generated from certain items of equipment, and probably are not microbial. This could be by determining the level of particles in the cleanroom without people and equipment

running; then with the equipment running and without people; and then with people and equipment running, and comparing the differences).

- Focusing on downstream operations like purification, final formulation and primary packaging (component preparation)
- Determining a frequency for such monitoring (one approach is to start off frequently and then justify decreasing to monthly on examination of satisfactory data).

The location for such monitoring could be determined from:

- The results of the particle count classification study, if one location was 'worst case'
- By means of examining the process flow and selecting representative tests of the operation
- By means of risk assessment. For example, does the operation in question impinge on a neighbouring cleanroom (perhaps one of a different grade)? In such an example a particle counter may be required to be placed in the adjacent area.

#### 4. Conclusion

This article has set out some of the requirements and recommendations for re-classification and routine monitoring of cleanrooms. Some of these are defined in different standards; other recommendations need to be considered by the user and supported in a rationale. For routine monitoring there is less guidance and the programme is for the organisation to develop.

For organisations with a large number of cleanrooms a degree of rationalisation is required and to be considered alongside cost and available resource.

The key approach to such rationalisation is through some form of criticality risk assessment. By focusing upon critical areas, mapping process flows and adopting a risk assessment approach an organisation can build both a programme that demonstrates that its cleanrooms are in control and a defensible case to present to the regulatory authority.

#### 5. References

- a) PDA Technical Report No. 13 (revised): 'Fundamentals of an Environmental Monitoring Programme', September / October 2001
- b) USP#25 <1116>
- c) 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors' ('EU GMP Guide'), MCA, 2002
- d) 'Guidelines on Sterile Drug Products Produced by Aseptic Processing', FDA, 1987 (draft produced for review in 20021)
- e) BS EN ISO 14644 Parts 1, 2 and 4
- f) BS EN ISO 7730
- g) BS 5275 (withdrawn)
- h) Code of Federal Regulations, 1998, Title 21, Part 210, Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs – General, 210:3
- i) US Federal Standard 209E: Airborne Particulate Cleanliness Classes in Cleanrooms and Cleanzones (FS209E) [now withdrawn]
- j) BS EN 1822 Parts 1 and 2
- k) Whyte, W. (2001): 'Cleanroom Technology: Fundamentals of Design, Testing and Operation', Wiley, Chichester
- l) Ljungqvist, B. and Reinmuller, B. (1996): 'Some observations on Environmental Monitoring of Cleanrooms', European Journal of Parenteral Science, 1996, 1: 9 –13

# Hi everyone,

I hope you have been enjoying the amazing weather we have been experiencing recently. I have loved it!

Just thought I would keep you updated on PharMIG's plans over the next few months:

As usual you will find the various meetings and the Conference programme within the Newsletter, as well as the diary date section on the back page.

Due to frequent requests, we have re-examined aspects of 'advertising'. As a special inclusion for this issue of the Newsletter you will find various logos from our Commercial / Allied Members who are supporting the Conference this year. We are hoping to expand this further in our future Newsletters - opening it up to all our Member Companies.

The next plan is to create a new section on the website where recruitment agencies, and pharmaceutical companies in general, can place their vacancies and job specifications onto the site and have a link through to their own web page which you can then click through to if

required. This then gives you, our Members, the freedom to explore potential job opportunities without being bombarded by phone calls from recruiters etc. We would like to implement this over the next couple of months and would be interested in receiving your thoughts and feedback on the types of advertising that PharMIG are planning/expanding on.

Do you think this will help you in finding out more information about companies and their products linked to Microbiology? Will you find this a good resource in looking for employment? Do you think it is too much? What other services on the web and in our Newsletter would you like to see in the future?

Your comments would be gratefully received and I look forward to hearing from you in due course.

Maxie



# Surviving a Microbiological Audit

Article written by: Gavin Little - MedImmune Vaccines

The course was set at the Robinson College Executive Centre, Wyboston, Bedfordshire on the 24th April 2003.

The course was opened by Andy Martin; Pharmaceutical Training Centre Manager for Reading Scientific Services Limited (RSSL). As acting Chairperson for the day Andy formally introduced the other speakers and gave a brief overview of the course contents. The delegates were then asked to introduce themselves, describe their role within their own organisation and explain what they hoped to gain from the course.

The first session was hosted by Natasha Gibbs; Microbiological Co-ordinator for GlaxoSmithKline (GSK). Natasha guided the delegates through various aspects of a microbiological audit. The areas covered in this session included such topics as 'who are the auditors', 'what do you need to do before an audit', 'what is audited' and 'what happens following an audit'. This was a very useful guide to who the auditors are and the areas that they tend to focus on during an audit.

The second session of the morning was presented by Les Meader; Training Manager for Wyeth BioPharma. Les introduced the delegates to the psychology of an audit from the perspective of the auditor and from the people involved in an audit. This session covered areas such as 'essential behaviour skills', 'auditors questioning

techniques', 'how to relate to auditors' and how to answer questions if asked. This session also involved 'role play' which although was a light hearted affair introduced the participants to the kind of mind games auditors like to play!

The first afternoon session, following lunch, was presented by Andy Martin. Andy focused primarily on audit scenarios. This session had an open format in which the delegates could voice individual concerns about audits and the systems they have experienced in their working environments. The concerns were then discussed between all of the course participants with a view to resolving these issues. Areas covered during this session included environmental monitoring, documentation and the quality control of materials.

The final speaker was Paul Lovegrove-Saville; Manager of Microbial and Environmental Assurance with GSK. Paul presented an overview of the regulatory issues that befall many companies. This included a list of the most common auditor observations in the last two years and covered hot topic such as environmental monitoring, validation, training and record keeping.

The audit course was concluded with a final question and answer session hosted by Andy, Paul and Natasha, which wrapped up a very useful and instructive day.

## Date for your diary - Sterility Assurance in Practice

Revised date – Tuesday October 14th 2003 - **PROGRAMME**

09.30 – 10.00	<b>Registration and Tea / Coffee</b>	13.45 – 14.45	<b>Parametric Release Annex 17 –</b> a practical application
10.00 – 10.15	<b>Sterility Assurance System</b> An overview of the elements	14.45 – 15.00	<b>Tea / Coffee Break</b>
10.15 – 11.15	<b>Conducting a Risk Assessment of Sterility Assurance Systems – a roadmap</b> This session considers the individual elements of a generic sterility assurance system and will be interactive. It will provide you, the delegate, with an approach that can be readily applied in your facility	15.00 – 16.00	<b>Open Discussion Session</b> Do you have specific topics that you want addressed in this forum? If so, send you questions in advance to the PharMIG office or hand them in at registration on the day.
11.15 – 11.30	<b>Tea / Coffee Break</b>	16.00 – 16.15	<b>Summary and Close</b> Workshop leaders: Sharon Johnson, Baxter & Julian Kay, GlaxoSmithKline
11.30 – 12.30	<b>FDA Aseptic processing concept document –</b> what is the impact?	Fee:	£350 Members £400 Non Members
12.30 – 13.45	<b>LUNCH</b>	Contact:	Maxine Moorey on 01920 871 999 or email: info@pharmig.org.uk for more details.

# Personal Profile of: Poly Hajpieris

## Professional Background

I have an Honours Degree in Microbiology and Biochemistry from the University of London (Queen Mary College). Trying to get my first job was very difficult in 1981 as there was a recession. I really wanted to join the Pharmaceutical industry then but all my applications were unsuccessful.

My first job was at the London Hospital Medical College as a research assistant to Professor Williams looking at the frequency and type of b-Lactamases produced in Gram negative clinical isolates. After 6 months and my first research publication, I moved to St Stephens Hospital in Chelsea as Dr David Shanson's research assistant working on the effects of Probenicid on serum Amoxycillin levels in endocarditis patients (lots & lots of microbiological assays!).

After 7 months I joined the NHS at St Paul's Hospital (a urology hospital closed in 1986 and merged with the Middlesex and UCL) as an MLSO. I received lots of Medical Microbiology training and loved every minute of it. However, the lack of career structure and poor pay made

me move on again to Imperial College (working in a private subsidiary of the University) conducting R&D in new biocatalysts for the food and healthcare industries.

Finally, I joined the Pharma industry in late '89 as Microbiology Section Head for Cilag Ltd (Johnson & Johnson). I then went on to Roche Products and GlaxoWellcome before working for PharMIG.

I was the first and only qualified microbiologist employed at Cilag and my broom cupboard turned micro lab was really cosy! I was trying to get to grips with Specifications, SOP's, audits, purified water systems, raw material & product testing and validation etc. etc., with nothing more than a very thin Orange Guide and BP. So, I thought I'd talk to the QA Manager about getting some Pharmaceutical Micro training and perhaps meeting another microbiologist from J&J. I was told there is no Pharmaceutical Microbiology training course I could do and as for meeting a fellow colleague from another site, suffice it to say, it was not an option, at this time.

## Family Background

Married to Peter for 23 years (I was a child bride at 10!) with two children Stefanos (6 years old) and Elena (14 months old). Stefanos is currently awaiting an Honorary Degree in Palaeontology from the Natural History Museum and Elena is studying dramatic art!

I am the eldest of three with a brother Mel and sister Helen. My parents emigrated to the UK in the early 50's when Cyprus was still a British colony and labour was desperately needed here. They still live here in North London.

Peter started at my school soon after the Turkish invasion of Cyprus in 1974. When I met him I disliked him terribly, but then took pity on him and we started secretly dating when I was 16 years old and got engaged just before I was 19 – ahh childhood sweethearts.



Helping all people live healthy lives

# The Poly Hajipieris that you didn't know about...



## What did you want to be when you were growing up?

I always wanted to be a Vet until I found out how many years it took to qualify! I'm also allergic to most furry creatures so that put an end to veterinary medicine. My parents wanted me to be a doctor but dissecting rats and humans was worlds apart so I studied microbiology convincing my parents that it is the microbiologists that tell the doctors what illnesses people have as the doctors don't have a clue!

## Did you like science at school?

I loved it! I had great science teachers: Mrs Roberts & Mr Broadribb for Biology, Mr Holt for Chemistry and Mr Beard for Physics. Gosh I can still remember their names! Although I passed Physics 'O' Level first time, Mr Beard didn't recommend I did the 'A' Level so I chose Environmental Studies with Biology and Chemistry.

## What is your earliest memory of a scientific experiment going wrong?

I was doing a titration in 'A' level Chemistry with a fellow school pal (and friend to this day) called Pandy. I cannot recall the detail but it ended up in serious dispute (because he wouldn't listen to me) with him calling me "a domineering woman" so the HCl and NaOH started flying around and then I was the one that got thrown out of the class! We had to stay behind after class and do the experiment again on our own.

## Do you have time for hobbies? If so, what are they?

Unless going out socialising can be classified as a hobby, my first real hobby in adulthood was PharMIG! I have no time for anything now I have two children – does sleep qualify?!

## When was your first trip abroad with work and where did you go?

Hey, you're talking to a microbiologist – you don't leave the lab unless you're going home!

## How many countries have you visited in both work and holiday trips?

I travelled to Scotland and France on business and six other countries for pleasure. I do love travelling and should have done more before the children arrived.

## What is your favourite country and why?

I never thought I'd say this but after a momentary ponder, I would say America (with Chile a real close second). Not for the culture but the geography – it has such diverse landscape and weather.

## What is your favourite drink?

Water, then milk then tea! Pete says it's the main reason he asked me out! Mild persuasion might see me with a glass of Champagne or Pina Colada!

## What is the most unusual meal you have eaten?

My Mum always used to cook black and white lambs liver when I was a kid. Once I had covered a bit more anatomy in biology I said to my Mum, "There is only one organ called the liver in our body so where does the white liver come from?" Ah, she said, that's the lung. Needless to say I've not eaten it since!

## Were you a teenage fashion freak?

Well I never dyed my hair orange or pink nor did I stick safety pins through my body, but I did follow fashion avidly. My parents had their own business making ladies clothes for top companies like Biba, Ossie Clark, Lulu, Quorum etc so I used to get a free sample of everything. I was also a key participant (against my Mum on the PTA) in getting school uniform abolished!

## Do you like music? What is your musical taste?

I love music. I can do without books, newspapers, TV, cinema etc but on a desert island I must have music! I played the piano badly as a child so started with a taste for classical music (Mozart is my fave) but soon fell in love with the Elvis, Beatles, Hollies, Supremes, Osmonds, Rod Stewart and lots more! I prefer the 60's and early 70's music and love contemporary jazz.

## What is your favourite participative and spectator sport?

My only participative sport is swimming with the kids and I love watching tennis and swimming.

## Have you met anyone famous?

Apart from David Begg and Paul Hargreaves I've met Princess Anne, Duchess of Kent, Peter Ustinov, David & Victoria Beckham.

## If you could change your career at this stage in your life what would you do next?

Be an astronaut – seriously! Always loved space and science fiction.

## PharMIG Diary Dates - Events Schedule 2003/2004

September 23rd & 24th

Practical Training on Cleaning & Disinfection - Bath  
2 Day Training Course

October 14th

Sterility Assurance in Practice (re-scheduled date & now being held at  
Robinson College Executive Centre, Wyboston)  
1 Day Meeting

November 18th & 19th

PharMIG 2003 Conference  
Stratford Manor Hotel, Stratford-upon-Avon  
2 Day Conference & Exhibition

December 9th

Rapid Microbiology Methods  
Robinson College Executive Centre, Wyboston  
1 Day Meeting

February 11th & 12th 2004

Engineering for Microbiologists  
2 Day Training Course

Full details will be mailed in due course. In the meantime if you have any questions regarding the event schedule please do not hesitate to contact

Maxine Moorey on (T) 01920 871 999 (Email) [info@pharmig.org.uk](mailto:info@pharmig.org.uk)