



## The Scottish Society for Contamination Control

March 2005

Issue 52

 RISK ASSESSMENT

 CLEANROOM  
TESTING COURSE

 NEC BIRMINGHAM

 COURSE PASSES

 STERILE SERVICES

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The greatest contamination risk to a product in a cleanroom comes from people. They are normally the sole source of microbial contamination, and can be the major source of particle contamination depending on the relative contribution of particles from machinery. There is good practice and bad practice and the photo shows an example of bad practice. The risk to products from contamination can be overcome by good cleanroom design and good cleanroom operational practices. However, to achieve the lowest contamination of the product, it is necessary to ensure that the sources of contamination are correctly controlled and monitored. A technique that has been applied for many years in engineering and other disciplines, and is now being adopted for the control of contamination, is 'Risk Management'. An important part of Risk Management is 'Risk Assessment' where the degree of risk from sources of contamination can be assessed and minimised. Tim Eaton and Bill Whyte have contributed a paper on this topic. See pages 2-7 & 10.

This paper is part of a Risk Management of Contamination system for cleanrooms and in co-operation with the Parenteral Society, S2C2 are soon to publish a monograph on this powerful contamination control technique.

# Microbial Risk Assessments for Pharmaceutical Products

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**W Whyte** University of Glasgow, Scotland, UK

## Summary

By using fundamental equations that model the dispersion, transfer and deposition of microbial contamination, the assessment of microbial risk to manufactured products in pharmaceutical cleanrooms can be comprehensively undertaken. The example given here is for microbial contamination during aseptic pharmaceutical manufacturing but the technique can be used for particles and microbial contamination in other manufacturing areas.

A general assessment of the transfer of contamination from all of the sources within the cleanroom suite can firstly be completed followed by an assessment of contamination within critical production areas. Such assessments will help to direct resources at the most appropriate areas or activities of the manufacturing operation in order to reduce microbial risk. These methods can be used at the preliminary design stage of a cleanroom manufacturing operation or, retrospectively, similarly applied to an established manufacturing operation.

## 1. Introduction

For an aseptic manufacturing operation, the correct identification of the areas of greatest microbial risk is fundamental, if effective improvements to the product contamination rate or security of the manufacturing process are required. To provide the most accurate assessment of microbial risk, the basic models of microbial contamination and the associated variables should be determined and utilised in the assessment process. Although a number of established risk management systems, such as Failure Mode and Effect Analysis (FMEA)<sup>1</sup> have been utilised for microbial contamination applications, such systems do not utilise the variables associated with the basic models of microbial contamination as part of the risk assessment process. Consequently, the assessment process utilised by such systems will not derive the most accurate microbial risk assessments. The fundamental mechanism of microbial contamination relates to the concentration of microbes on, or in, a contaminated source, and the likelihood of their dispersion, transfer, and deposition onto a product, either over a period of time or as the frequency of a contaminating incident. This has been previously developed<sup>2</sup> and can be expressed in Equation 1.

$$\text{No. of microbes deposited on a product} = C \times S \times P_d \times P_a \times A \times T \quad \text{Equation 1}$$

where,

**C** = concentration of microbial contamination on, or in, a source (number/cm<sup>2</sup> for surface, number/cm<sup>3</sup> for air);

**S** = the quantity of surface material, or air, that is dispersed, from a source in a given time (cm<sup>2</sup> /s for surface, cm<sup>3</sup> /s for air dispersion); this can also be expressed as the quantity dispersed per frequency of occurrence;

**P<sub>d</sub>** = proportion of micro-organisms dispersed from a source that are transferred to the area adjacent to the product;

**P<sub>a</sub>** = proportion of micro-organisms in the adjacent area that are deposited per unit area of the product (/cm<sup>2</sup>);

**A** = area of surface onto which microbes are deposit (cm<sup>2</sup>);

**T** = time, during which transfers occur(s); this can also be expressed as frequency of occurrence.

The Failure Mode Effect and Criticality Analysis (FMECA)<sup>1</sup> method of risk assessment is based upon the definition of risk indicated in Equation 2. This is generally accepted as the most appropriate definition of risk and is widely used. If the criticality associated with microbial contamination is considered to be the number of microbes deposited onto the product, then the criticality risk assessment Equation 2 is the same as the fundamental Equation 1, and the FMECA approach to risk assessment is fully supported.

$$\text{Risk} = \text{criticality of the occurrence} \times \text{frequency of occurrence} \quad \text{Equation 2}$$

The fundamental mechanism of microbial contamination expressed in Equation 1 can be utilised to assess the microbial risks to product associated with a cleanroom manufacturing operation. This is best approached by firstly considering all of the general hazards to the cleanroom environment and then considering the specific hazards associated with the manufacturing operations within the critical areas of the cleanroom. This can be best understood by considering the cleanroom manufacturing operation illustrated in Figure 1.

This is an automated aseptic vial filling line located in a EU grade A (Class 100) vertical unidirectional airflow workstation. The background to the filling workstation is a turbulently ventilated EU grade C (Class 10,000) area. These two areas are segregated by

a full length glass partition and the operation is controlled from the background area. Access to the grade A area, to address any line running issues, is achieved by opening the glass partition. Vials are fed to the point-of-fill through a hot-air depyrogenation tunnel. Product solution, stored in a sterilised holding tank, is fed to the filling machine through sterilising grade filters and filled into the vials. Lyophilisation stoppers, manually transferred into the filling area, are partially seated onto the vials, which are accumulated into a mobile isolator and then transferred into a sterilised freeze dryer. On completion of drying, the stoppers are fully seated onto the vials before removal from the freeze dryer for capping and crimping.

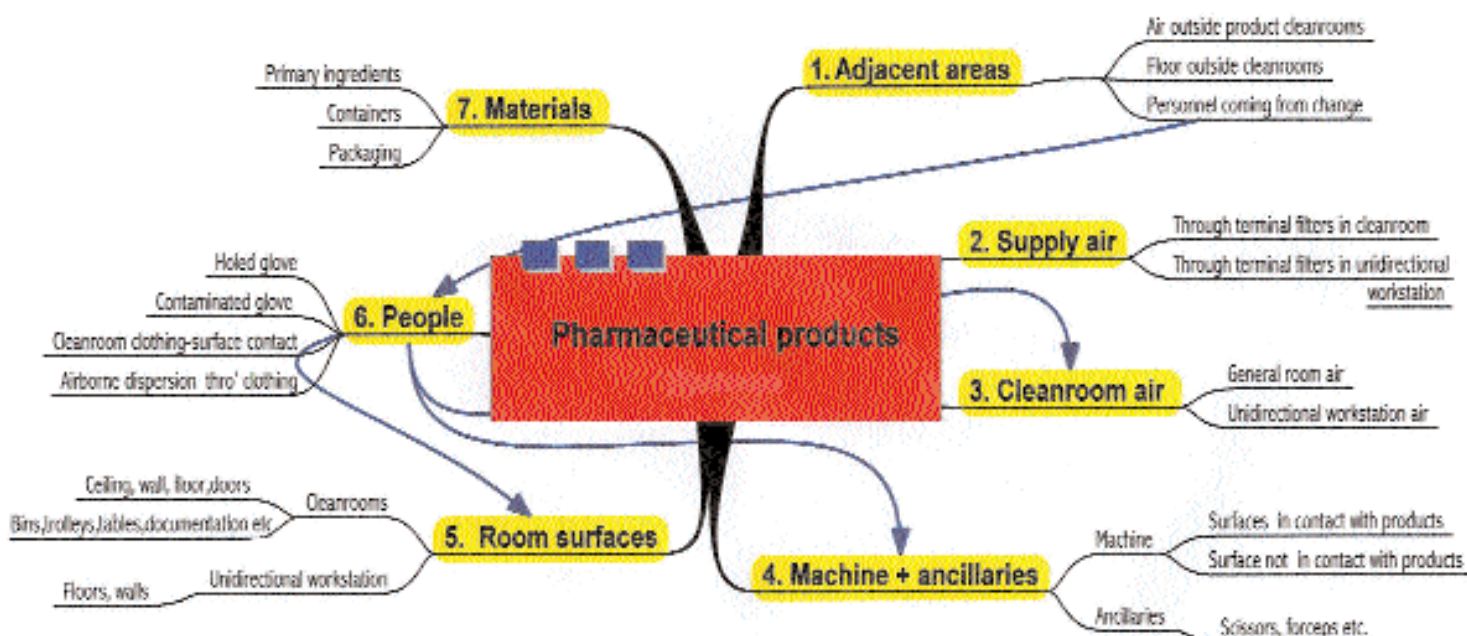
**Figure 1 Aseptic Filling cleanroom**



## 2. General Cleanroom Risk Assessments

If all of the general sources of microbial contamination to the cleanroom can be identified, the fundamental Equation 1 can be utilised to assess the level of hazard associated with each identified source. The identification and grouping of such sources of microbial contamination has been proposed by Whyte<sup>3</sup> and this approach can be utilised and tailored to a specific cleanroom operation. Indicated in Figure 2 is an example of the general sources of microbial contamination associated with the cleanroom shown in Figure 1.

**Figure 2 General cleanroom microbial sources**



Unfortunately, numerical values for all of the variables in Equation 1 are unlikely to be available and so absolute assessment of the identified sources is not possible. Some numerical data relating to the concentration of microbes associated with each source may be available but numerical information relating to the dispersion, transfer and deposition of micro-organisms is not. Similarly, the time duration, or frequency, of microbial contamination in a cleanroom, can be continuous (from cleanroom air for example) or unknown (by personnel accidentally contacting the product for example).

Consequently, for a general cleanroom risk assessment, the variable of time is not used and a simplified version of the equation using risk factors for the unattainable variables, indicated in Equation 3, should be utilised.

$$\text{Risk from microbial contamination (risk rating)} = A \times B \times C \times D \quad \text{Equation 3}$$

where,

A = microbial contamination on, or in, a source;

B = ease of dispersion and transfer;

C = proximity of source from critical area;

D = effectiveness of control method.

The risk rating of each source is determined by assigning scores to risk factors A to D. Given in Table 1 is an example of such scores that can be used. Any additional circumstances, for example, the direction of any air flow for factor C, would need to be carefully considered during the assessment exercise to ensure accurate scores have been assigned.

**Table 1 Scores for risk factors used for assessing hazards**

<b>Risk factor (A)</b> Amount of microbial contamination on, or in, a source	<b>Risk factor (B)</b> Ease of dispersion, or transfer, of micro-organisms	<b>Risk factor (C)</b> Proximity (location) of source from critical area	<b>Risk factor (D)</b> Effectiveness of control method
0 = nil	0 = nil	0 = remote	0 = full barrier control
0.5 = very low	0.5 = very low	0.5 = in outside corridor, air lock	0.5 = very good control
1 = low	1 = low	1 = periphery of cleanroom	1 = good control
1.5 = medium	1.5 = medium	1.5 = general area of cleanroom	1.5 = some control
2 = high	2 = high	2 = critical area	2 = no control

The highest scored risks for the cleanroom operation considered are given in Table 2. Also indicated are the control measures utilised. The designation of a higher risk score does not necessarily mean that it has a high risk to the product, but within a list of possible hazards it is likely to be one with a higher degree of risk. These hazards may then be further considered with a view to reducing their risk by reducing the risk scores of one or more of factors A to D.

The list of sources, and their risk ratings, can then be used in subsequent parts of a risk management analysis (such as HACCP<sup>3</sup>), to determine whether adequate control methods are used, and if the risks or their control methods are adequately monitored. In the case of the contamination source associated with holed gloves, this would require further information relating to the glove manufacturer's acceptable quality limit (AQL) with regard to holing and some determination of the robustness of the gloves during use. A thorough review of the finger dab method, used to monitor the double gloving control measure, should also be completed. This would include a review of the microbial media and the associated incubation temperature and times and the validation work. A review of several months monitoring data (where available) should also be completed to confirm the effectiveness of the control measure.

**Table 2 Calculation of the risk rating for highest identified sources**

Contamination Source	Risk factor (A)	Risk factor (B)	Risk factor (C)	Risk factor (D) (control method used)	Risk Score
<b>PEOPLE - During interventions</b> Transfer to product via gloves with holes	2	2	2	0.5 (two pairs of gloves)	4
Transfer to product via gloves with secondary contamination	1	2	2	1 (disinfection)	4
Airborne transfer of micro-organisms from personnel working in unidirectional walk-in area	1	2	2	0.5 (garments, sweeping action of unidirectional air)	2
Surface transfer to product from cleanroom clothing	1	2	2	1 (garments, aseptic disciplines)	4
<b>NON MACHINE SURFACES - Unidirectional air area</b> Walls, floors	1	1.5	2	1 (disinfection)	2.25

### 3. Critical area risk assessments

The two routes of microbial contamination, either by contact with a contaminated surface or by deposition from the air, are considered separately as part of the assessment within the critical product areas. Assessments for both of these routes of contamination are derived from the fundamental mechanism of microbial contamination indicated in Equation 1.

#### 3.1 Contact contamination

A derived simplified equation to model surface contact contamination is indicated in Equation 4.

**Number of micro-organisms deposited by surface contact over a given time (no.) = concentration of microbes on contaminating surface (no./cm<sup>2</sup>) x transfer coefficient x area of product that is contacted (cm<sup>2</sup>) x frequency of contact**  
**Equation 4**

The 'transfer coefficient' is the proportion of micro-organisms on a contaminating surface (such as a glove) that are transferred to the product.

For the cleanroom manufacturing operation illustrated in Figure 1, which is typical of most such cleanroom manufacturing, the activities can be separated as follows:

1. Transfers of contact parts, components, product into the critical area;
2. Setting-up of contact parts, production machinery
3. Normal production activities
4. Interventions into the critical area to address production issues.

The overall risk to the product by surface contact can be assessed by adding the risk from each of these activities, as shown in Equation 5.

**Risk by surface contact = risk from critical transfers + risk from setting up + risk during normal production + risk during interventions**  
**Equation 5**

The overall number of micro-organisms deposited by surface contact could be determined by applying Equation 4 to each of the activities of Equation 5. Unfortunately, not all of the variables in Equation 4 are known and so a solution must be sought with the use of risk factors for the unattainable variables. The first variable is microbial contamination of the contacting surfaces but because many surfaces will either not be sampled or would be found to be sterile if monitored, it cannot be utilised. Similarly, there is unlikely to be any information regarding the transfer coefficient, although this variable can be considered later and utilised to

increase the accuracy of the risk assessment method. The next variable is the area of the product that is contacted and as this is likely to remain constant, there is no advantage in including it for this assessment (if this variable changes for different operations of the process, then it should be incorporated to improve the risk analysis). The variable of time, or frequency, which was not used previously in the general risk assessment, can now be used as it is likely to be available or can be determined. Time can be expressed either as the time the product is exposed to contamination, or the frequency of a contamination incident. Utilising these assumptions, a simple risk equation that combines the surface contact contamination from the four stages of manufacture is given in Equation 6.

$$\text{Risk by surface contact} = \alpha [\text{no. of critical transfers}] + \beta [\text{setting up complexity}] + \chi [\text{body involvement x complexity of critical area x no. of manipulations}] + \delta [\text{no. of interventions}] \quad \text{Equation 6}$$

where  $\alpha$ ,  $\beta$ ,  $\chi$  and  $\delta$  are weighting coefficients

The normal production variable now however comprises of three risk descriptors. As these are multiplied together, this combined risk score will be much greater than any of the other three stages and will therefore need to be divided by 3. Additionally, some stages e.g. interventions are more likely to contribute more surface contamination than the other stages. These imbalances in the risk equation can be corrected by assigning weighting coefficients. These were shown in Equation 6 as  $\alpha$ ,  $\beta$ ,  $\chi$  and  $\delta$ , and examples of values that can be assigned are shown in Equation 7. These values can be considered to be representative of the transfer coefficient variable.

$$\text{Risk by surface contact} = 1 [\text{no. of critical transfers}] + 1.5 [\text{setting up complexity}] + 2 [(\text{body involvement x complexity of critical area x no. of manipulations})/3] + 2 [\text{no. of interventions}] \quad \text{Equation 7}$$

It is now necessary to allocate risk scores to each risk factor in Equation 7. Indicated in Table 3 are such allocations for each of the manufacturing operations.

**Table 3 Risk factors and scores used to assess contamination contact surface risks**

Manufacturing Activity	Risk factor	Risk score 0 = nil	Risk score 1 = low	Risk score 2 = medium	Risk score 3 = high
<b>Transfers into the Critical Areas</b>	Number of critical transfers	None	No more than 10	No more than 30	More than 30
<b>Setting up Production Machinery</b>	Setting up complexity	No set up activities	Not complex. Time to set up no more than 10 min	More complex. Time to set up no more than 30 min	Complex. Time to set up more than 30 min
<b>Normal Production</b>	Body involvement	None	Hands	Hands and arms	Body
	Complexity of critical area	Not Applicable	Simple	Some complexity	Complex
	Number of manipulations	None	No more than 5% of time	No more than 50% of time	More than 50% of time
<b>Interventions</b>	Number of interventions	None	No more than 5	No more than 10	More than 10

For the cleanroom manufacture shown in Figure 1, the manufacturing parameters, risk scores and calculated overall risk ratings for the activities associated with each manufacturing operation are indicated in Table 4. From this it can be seen that the filling and stoppering stage had the highest risk score. To reduce the risk of contact contamination during manufacture, the operations of this stage would be the most appropriate to consider and were addressed in the following manner:

1. *The number of critical transfers:* The vial stoppers were supplied in bags of 500. With a single batch size of up to 25,000 units, up to 50 critical transfers were required. As the stopper feed bowl had adequate capacity, the stoppers were supplied in bags of 1000, reducing the number of transfers by a factor of 50%.

2. *Filling machine set up complexity and time*: The control of filling volume was achieved via a time-pressure system with a high level of automated control. However, this required a complex aseptic assembly of machine parts that took on average 35 minutes to complete. Modifications to the pipe work were undertaken, whilst maintaining its cleaning and sterilisation functionality. The resultant assembly operation utilised less parts, was less complex, and had an average assembly time of 9 minutes.

3. *The number of interventions*: Stopper-to-stopper adhesion, a consequence of the sterilisation process, resulted in feed bowl blockage, which then required manual removal with sterilised forceps. Modifications to the feed bowl, to automatically reject adhered stoppers, reduced the average number of interventions from 38 to 4.

The above modifications reduced the risk rating of the filling and stoppering stage from 13.5 to 5.5.

**Table 4 Risk scores and risk ratings for contact surface risk for all manufacturing stages**

Manufacturing Operation	Transfers into the Critical Areas (A)	Setting up Production Machinery (B)	Normal Production Number of manipulations (% total time) (C1)	Normal Production Body involvement (C2)	Normal Production Complexity of critical area (C3)	Interventions (D)	Risk Rating*
Vial washing and sterilisation	None score=0	None score=0	1% score=1	None score=0	Simple score=1	1 score=1	2.0
Solution storage	3 score=1	5 min score=1	1% score=1	None score=0	Simple score=1	None score=0	2.5
Filling and stopper placement	50 score=3	35 min score=3	3% score=1	None score=0	Simple score=1	38 score=3	13.5
Freeze drying and capping	150 score=3	5 min score=1	One manipulation score=0.5	None score=0	Simple score=1	None score=0	4.5

\*Risk rating = [A] + 1.5 [B] + 2[(C1 x C2 x C3)/3] + 2 [D]

### 3.2 Airborne contamination

A derived simplified equation to model airborne deposition onto a product contamination is indicated in Equation 8 and has been shown to predict airborne contamination over a wide range of conditions during pharmaceutical production <sup>4</sup>.

**Number of airborne micro-organisms deposited onto the product in a given time (no.) = Deposition rate of microbe carrying particles (no./cm<sup>2</sup>.s) x area of product exposed (cm<sup>2</sup>) x time of exposure (s) Equation 8**

The variables required for this equation are readily available. The microbial deposition rate can be obtained from the counts on settle plates exposed adjacent to the product. The results from settle plates are commonly reported as the number of colony forming units (cfus) settling onto a settle plate of a given area exposed over a given period of time. To achieve an accurate simulation of contamination, settle plates must be positioned adjacent to the exposed product and open only when contamination occurs. Settle plate counts from cleanroom areas often give a series of zero results, with an occasional positive. This lack of sensitivity can be improved by using larger settle plates (15cm diameter), several 9 cm diameter plates during a period of high sampling intensity, or combining results obtained from routine sampling results, and averaging them over a one or two year period.

It is necessary to check that dehydration of the microbiological medium in the settle plates, caused by air movement, does not reduce the count. Experience shows that as long as the plate is well filled with agar medium, and its exposure in unidirectional airflow is not much in excess of four hours, the resultant count is not significantly affected <sup>5</sup>.

The surface area of the product exposed to airborne contamination is required. As it is known that gravitational settling mainly governs the deposition of microbe carrying particles during pharmaceutical manufacturing <sup>6, 7</sup>, only the horizontal area of the exposed product is required. This might be the area of the inner neck of a container, or the upwards-facing area of a solid product.

*Continued on page 10.*

## CLEANROOM TESTING COURSES



A one day course on Cleanroom Testing is being given at Glasgow University, Glasgow  
Wednesday, June 22, 2005 (Registration 8:30 - 9:00 am)

Course given by Bill Whyte includes hands-on demonstrations of equipment used to test a cleanroom.

**Cost:** per delegate including lunch and tea/coffee is

Members: £160 + VAT (£188.00) Non-members: £177 + VAT (£207.97)



While the above one day course is being held, the Cleanroom Testing and Certification Board (a body set up to run courses for people in the cleanroom industry) is concurrently running a certification course in Cleanroom Testing which runs over 3 days, i.e. June 21-23, 2005.

**Course Options:** If you wish to attend any of these courses in the future see below,

**Payment:** Credit card facilities are now available on the web at [www.s2c2.org/shop](http://www.s2c2.org/shop).

### If you want CTCB certification then it is the 3 day CTCB course

#### Registration

To attend the course, registration is essential as candidate suitability is assessed.

#### Eligibility

This course is for people who test cleanrooms either daily or regularly. There are 2 levels: professional or associate.

#### Cost

Registration is £110 + VAT. This covers the course and Question and Answer manuals. The course fee is £616 + VAT which includes a one day practical training course.

#### Examinations

Two - theory and practical.

#### Certification

On successfully passing both exams a certificate is awarded.

### If you do not want CTCB certification then it is the 1 day S2C2 course

#### Registration

Contact S2C2 office to obtain a course brochure and application form or use the application form on page 9.

#### Eligibility

This course is for anyone. For example, cleanroom *designers* who need to understand the standards and the tests to which their cleanroom is tested, *users* who have to understand what tests are required or *personnel* responsible for testing and monitoring cleanrooms.

#### Cost

Members: £160 + VAT (£188.00)  
Non-members are required to pay an additional £17 + VAT. See above for June 22, 2005.

#### Examinations

None.

#### Certification

A certificate of attendance is issued.

#### For further information:

Mrs Kay Johnston, Administrator, James Watt Building, Glasgow University,  
Glasgow, G12 8QQ, Scotland  
Tel: 0141 330 3699 Fax: 0141 330 3501  
E-mail: [s2c2@mech.gla.ac.uk](mailto:s2c2@mech.gla.ac.uk)

[www.s2c2.co.uk](http://www.s2c2.co.uk) and click on 'CTCB' and then 'Cleanroom Testing'

## Cleanroom Testing Course, Glasgow University, June 22, 2005

Over the past few years S2C2 have run a successful course on how to test a cleanroom. Owing to the needs of the Cleanroom Testing and Certification course of S2C2, that course has now been expanded.

### Who Should Take This Course?

- Cleanroom designers who need to understand the standards to which their cleanroom is tested.
- Cleanroom users who have to understand what tests are required to ensure that their room continues to perform as required.
- Personnel responsible for testing and monitoring cleanrooms.

**Why?** As an introduction to new technology or to brush up knowledge and skills.

### MORNING - LECTURE

08.30 - 09.00 Registration  
 09.00 - 13.00 Lecture Course given by Bill Whyte

Topics include:

- The reasons for validating a cleanroom
- Validation philosophy • Validation standards
- How a cleanroom air conditioning plant works
- Cleanroom conduct • Microbiological measurements
- Air volumes and velocities
- Differential pressures • Air filter integrity test
- Infiltration of contamination into the cleanroom
- Particle measuring methods according to ISO 14644-1

### AFTERNOON - PRACTICAL

13.00 - 14.30 Lunch  
 14.30 - 16.30 Practical Demonstrations

In this session a 'Hands-on' demonstration of equipment used to test a cleanroom will include:

- Instruments for measuring air velocity, volume & pressure differential
- Filter integrity testing method
- Particle counting apparatus
- Bacterial counting apparatus
- Air movement visualisation methods

### COST

Price per delegate including lunch and tea/coffee is £188 (£160 + VAT)  
 Non-members will be required to pay an additional £19.98 (£17 + VAT)

### PAYMENT

- [1] Credit card: go to [www.s2c2.org/shop](http://www.s2c2.org/shop)  
 [2] Cheque for £ .....attached  
 Please make cheque payable to *Scottish Society for Contamination Control* and forward with this remittance form to  
 S2C2, James Watt Building,  
 University of Glasgow,  
 Glasgow G12 8QQ.

### CONTACT

Tel:0141 330 3699 Fax: 0141 330 3501  
 Email: [s2c2@mech.gla.ac.uk](mailto:s2c2@mech.gla.ac.uk)

## APPLICATION FORM

Please reserve places for the following people:

Name(s)	Company: Address:	Tel: Email:
Send invoice to (if different from above):		Purchase Order No.

The time the product is exposed to airborne microbial contamination is required. The total manufacturing time should not be used, but the average time a single product is exposed to the airborne environment. For example, the first product through a filling line may be exposed for only a few seconds, but the last one will be exposed for the total time of the process; the average exposure time is therefore 50 % of the total process time.

For the cleanroom manufacture indicated in Figure 1, the relevant manufacturing parameters and associated settle plate counts can be utilised to predict the number of micro-organisms deposited during the manufacturing operation.

Several settle plates (9 cm diameter, area 64 cm<sup>2</sup>) are exposed for four hours in the areas adjacent to the open vials. A review of 6 months of data indicated that of the 926 settle plate samples taken, 62 had at least one positive count. The average microbial count for this period was calculated to be 0.067.

The deposition rate of the micro-organisms can be calculated from the settle plate data i.e.

$$\begin{aligned}\text{Deposition rate (no./cm}^2\text{.hr)} &= \text{average count on settle plate} \div [\text{area of settle plate (cm}^2\text{) x time plate exposed (hr)}] \\ &= 0.067 \div [64 \times 4] = 2.62 \times 10^{-4}\end{aligned}$$

The vial has an inner neck area of 2 cm<sup>2</sup> and is open to contamination for an average of 6 minutes. The number of microbes that would contaminate the product by depositing through the neck area is calculated from Equation 4.

$$\begin{aligned}\text{No. of airborne microbes deposited into product in a given time} &= \text{deposition rate (no./cm}^2\text{.hr)} \times \text{exposed product surface area (cm}^2\text{) x time of product exposure (hr)} \\ &= 2.26 \times 10^{-4} \times 2 \times [6 \div 60] = 5.23 \times 10^{-5}\end{aligned}$$

It is a reasonable assumption that microbe carrying particles will be deposited randomly throughout the critical area <sup>6</sup> and therefore 5.23 vials in 100 000 will be contaminated.

This contamination rate of about 1 in 20 000 could be improved by reducing any of the variables in Equation 8. However, the vial size was fixed and the line running speed already optimised. The airborne deposition rate could however be reduced by minimising the airborne microbial concentration. Investigation of the settle plate data indicated that the plate located in close proximity to the stopper bowl feed bowl was the plate that routinely recorded microbial contamination. Further investigation indicated that the interventions performed by the operator to address the feed bowl blockage were likely to be introducing contamination into this area. In addition to the modifications previously implemented to reduce the incidence of feed bowl blockage (section 3.1), which greatly reduced the number of required interventions, a longer bespoke tool, to utilise for any remaining feed bowl interventions was introduced. The longer tool, sterilised for each manufacturing batch and retained on a sterile surface within the critical area, enabled the remaining blockages to be addressed without the need for the operator to work over exposed product and components. A review of the subsequent 12 months of settle plate data taken following the introduction of the tool indicated that of the 1781 settle plate samples taken, only 3 had at least one positive count. The average microbial count for this period was reduced to 0.0017 and consequently the calculated number of contaminated vials was reduced to 1.32 x 10<sup>-6</sup> i.e. approximately 1 in 1 000 000.

#### 4. Discussion

The microbial risk assessment methods outlined in this paper utilise the fundamental models of microbial contamination. Consequently, they facilitate the most accurate assessments of microbial risk to product and also support the established FMECA method of assessing risk.

These risk assessment methods have been developed to provide, firstly, a general assessment of contamination to the cleanroom areas. Secondly, a risk assessment method has been developed that focuses on the manufacturing process in the critical areas by examination of the surface contact and airborne deposition routes of contamination. Subsequently, manufacturing activities with the highest risk ratings can, if deemed unacceptable, be modified to reduce the microbial risk to the product.

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7. Whyte W. Sterility Assurance and models for assessing airborne bacterial contamination. *Journal of Parenteral Science and Technology* 1986; 40: 188-197.
8. Whyte W. Matheis W. Dean-Netcher M. and Edwards A. Airborne contamination during blow-fill-seal pharmaceutical production. *PDA Journal of Pharmaceutical Science and Technology* 1998; 52: 89-99.

## S2C2 COURSES 2005 & 2006

The two educational cleanroom courses organised by the S2C2 and presented by Bill Whyte at the NEC, Birmingham, February 2005 were well attended with 58 attending the Cleanroom Testing course on the first day and 77 attending the Cleanroom Technology course on the second day.

It is expected that these two courses will be repeated next year in much the same manner, i.e. at the NEC in February and will coincide with the 14th Annual Contamination Control and Cleanroom Products Exhibition.

## STERILE SERVICES

On 15th & 16th February Health Protection Scotland held a conference in Glasgow for the Sterile Services Department Consultative Group. During this Andrew Tweedie gave a presentation on Cleanroom Technology to the group.

The presentation covered: history, design, testing, operation, common problems, as well as the results of a 2004 study on environmental monitoring in SSD packing rooms.

## SEROLOGICALS PASSES



(L to R): Eileen McCracken, Robert Dorris, Sandra Crowhurst and Derek Robson, all from Serologicals, Kirkton Campus, Livingstone, successfully passed their Cleanroom Technology exam in October 2004.

## AT YOUR SERVICE

**HACH ULTRA ANALYTICS**

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 • Aerosols, Gases & Oxygen Analyzers  
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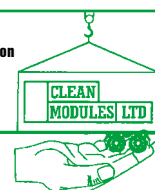
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