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European Journal of Parenteral & Pharmaceutical Sciences

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New regulations and new guidance always sparks a number of responses depending on the quality assurance ethos and strategy of the particular site or company. The senior management team of all sites have a role to actively participate in the generation of new industry guidance rather than wait until it is “imposed”. Nothing changes without a reason for change. Nothing is implemented without considerable time spent in consultation within industry and between all the relevant competent authorities (CAs).

One way of “achieving” compliance is consciously not implementing the change in current good manufacturing and distribution practice (GMDP) with the view that if it was important, an observation or citation would be given in the next CA inspection. This observation would force a change in processes and procedures via inspection corrective and preventive actions. If the non-compliance was not picked up in the CA inspection, it is inferred that the area was adequately managed, the guidance/regulatory change was not important to the CA and all was satisfactory at the site. What is forgotten in this process is that any audit is a snapshot and that not all areas will be covered. It is the responsibility of the site to be compliant in all aspects and not the responsibility of the CA to audit all aspects – this is impossible.

Another way is giving lip service to new GMDP requirements with a gap/risk assessment, with the endpoint defined prior to exercise taking place resulting in minimal compliance. This will also lead to an observation, but it is less likely to be major/critical as the site had at least done something.

The final “avoidance” approach is to wait until other sites have complied and had successful regulatory audits, and copy their approach.

All these approaches are a cynical and irresponsible approach to compliance = a reactive compliance rather than a proactive approach. These approaches constitute “kicking the can down the road”, and, with an ever changing legislative landscape, can lead to shortfalls of compliance in a number of areas, resulting in greater CA focus and potentially more frequent inspections. This scenario is worsened where new legislation requires specific ‘chunky’ pieces of work to be carried out, as these may take some time, and we all know that there have been a few of these in recent years.

Pharmaceutical quality systems (PQSs) have compliance at their core. Avoidance of compliance via weak risk assessment, via a “how do we avoid this” approach and via conscious or ignorant non-compliance invalidates the PQS and is contrary to basic GMDP.

GMDP is dynamic and will change as dosage forms and technology develops. Industry is given many opportunities to drive GMDP improvements. Societies, such as the PHSS and the Pharmaceutical Quality Group, have working groups that interact very closely with the CA to ensure that industry, hospitals and research are well represented in feedback and discussion groups. All changes and new regulations are sent for comment via websites and via professional bodies. There are thus ample opportunities to comment on upcoming guidance. It is the responsibility of individuals and companies to respond to the requests for feedback. As with other aspects of life, it is “put up or shut up”. You are asked for your say, and if there is no feedback then there is implicit approval. There is nothing more tedious than complaints about something that is implemented in the absence of requested feedback and involvement.

It still amazes me that so many sites spend more time, money and effort in compliance avoidance than they do in attaining compliance. If they took part in the guidance generation as requested, then the basis for the changes would be better understood and the time-wasting “pushback” would be more positively directed towards achieving compliance.

We are lucky in that industrial or relevant experience is part of the entry criteria for Medicines and Healthcare Products Regulatory Agency inspectors. This gives them a pragmatic approach
both to the guidance and the application of guidance. Each inspector will visit many sites and have seen the spectrum of compliance on each area of GMDP. It is both pre- and post-inspection knowledge that goes into new or updated guidance.

The only honest approach to compliance with new or updated guidance is as follows.

- To be part of the new guidance generation via professional bodies or as an individual respondent in a timely manner with complete responses when requested.
- To fully understand the reasons behind the change. If not clear, then find out the basis of the change.
- To proactively examine the changes and to apply to your site(s) using a risk management process specific to your site(s) and product(s).
- To approach this within a continuous improvement process rather than “if it isn’t broken, why fix it” approach.
- To implement in a timely manner.
- This process is an intrinsic part of continuing professional development for any qualified person certifying a product.

Any other approach is non-compliant and, depending on the changes, presents a threat to both your GMDP licences and to the patient.

Kay O’Hagan

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Give scientific measures in SI units, temperatures in degrees Celsius and, wherever possible, the generic rather than the proprietary names of drugs. Abbreviations and acronyms should be spelt out in full the first time they appear within the text and, if necessary, defined.

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Each paper should have up to six key words or phrases that characterise the contents of the paper. These will be used for indexing and data retrieval purposes.

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Indicate within the text where figures and tables should fall.

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Section 1. Introduction and scope includes a review of the challenges and requirements for bio-contamination control and cross contamination control with a holistic approach to monitoring and proactive investigations in response to increased risk from changes in bio-contamination profiles.

Section 2. Bio-contamination characterisation and risk profiling. Methodologies and strategies that profile bio-contamination through establishing control, in operations and holistic monitoring.

Section 3. Bio-contamination control principles and best practice guidance considering Quality by Design, different processes, control attributes, background environments and Barrier technologies.

Section 4. Bio-contamination monitoring including classical and Rapid Micro Methods (RMM).

Section 5. Bio-contamination Deviation management including considerations and guidance in completing investigations and undertaking corrective and preventative actions (CAPA).

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Calculation of airborne cleanliness and air supply rate for non-unidirectional airflow cleanrooms

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Equations have been recently derived by Whyte, Lenegan and Eaton for calculating the airborne concentration of particles and microbe-carrying particles in non-unidirectional airflow cleanrooms. These equations cover a variety of ventilation systems, and contain the variables of air supply rate, airborne dispersion rate of contamination from machinery and people, surface deposition of particles from the air, concentration of contamination in fresh make-up air, proportion of fresh air, and air filter efficiencies. The relative importance of these variables is investigated in this present research paper, with particular regard to the removal efficiency, location, and number of air filters. It was shown that air filters were important in ensuring low levels of contamination in cleanrooms but the types of filters specified in current cleanroom designs were very effective in ensuring a minimal contribution to the cleanroom's airborne contamination especially when a secondary filter is used in addition to a primary and terminal filter. The most important determinants of airborne contamination were the air supply rate and the dispersion rate of contamination within the cleanroom, with a lesser effect from deposition of airborne particles onto cleanroom surfaces. The information gathered confirmed the usefulness of the equation previously used by Whyte, Whyte, Eaton and Lenegan to calculate the air supply rate required for a specified concentration of airborne contamination.

Key words: Airborne particles, airborne micro-organisms, microbe-carrying particles, cleanrooms, cleanliness, air supply rate.

Introduction

When designing a cleanroom to achieve a required airborne cleanliness standard or grade, such as specified in ISO 14644-1 or the European Union Guidelines to Good Manufacturing Practice (EU GGMP), designers have difficulties deciding how much filtered air should be supplied to the cleanroom to achieve the correct airborne cleanliness requirement. Currently, this decision is based on experience and ‘rules of thumb’ and not normally by an analytical method. The consequence of this is that many cleanrooms have excessive air supply that is associated with high capital and running costs, and energy waste. Conversely, a low air supply may result in too high a concentration of contamination, and major remedial work to rectify the problem. It would be useful if an analytical method was available to assist in calculating the air supply rate, as well as making clear what variables affected the calculation, and their relative importance.

Prior to the start of manufacturing, personnel will enter an empty cleanroom that has a low airborne concentration of particles and microbe-carrying particles (MCPs). Personnel will then prepare for manufacturing and switch on machinery, and these activities will increase airborne contamination. When manufacturing starts and activity settles, the airborne contamination will fall a little to a fairly constant ‘steady-state’ condition, i.e. the operational condition. The airborne concentration in this condition determines the airborne contamination of products, and several researchers have derived equations to calculate it. However, further investigations are still required into the effect of different designs of ventilation systems, and the method of calculating the reduction in the airborne contamination by the settling of particles from the air onto cleanroom surfaces, i.e. surface deposition. These variables have been incorporated into equations recently derived by Whyte, Lenegan and Eaton.

Practical information on the values of the equation variables are required so that the equations can be used to design actual cleanrooms and these are discussed in this paper. Also investigated are the relative importance of the
equation variables, and the possibility of simplifying the equations by disregarding unimportant variables.

There is also a need for a method to calculate the air volume supply rate in non-unidirectional airflow (non-UDAF) cleanrooms to ensure the maximum airborne contaminations specified in ISO 14644-1\(^1\) and the EU GGMP\(^2\) are not exceeded. This can be done by rewriting the equations that are used to calculate the airborne concentration of contamination so that the air supply rate can be obtained. The authors of this paper have published information on such a method\(^9\) and the correctness of the approach was investigated.

**Equations used to calculate airborne cleanliness in a cleanroom**

Equations have been derived by Whyte, Lenegan and Eaton\(^4\) for calculating the airborne concentration of particles and MCPs in a cleanroom when the filtered air is supplied by a variety of designs of ventilation systems. These equations calculate the concentration in the steady-state condition, i.e. the operational state in non-UDAF cleanrooms and should not be used in UDAF systems where air cleanliness is dependent on the effectiveness of the UDAF, and not on dilution by air supply rate.

The deposition of particles and MCPs onto cleanroom surfaces has been investigated by Whyte, Agricola and Derks in a series of articles\(^{10-12}\), who suggest the following Equation 1 for calculating the particle deposition rate (PDR) onto cleanroom surfaces. This equation can be used to determine the reduction in the airborne concentration of contamination in a cleanroom owing to losses through surface deposition.

**Equation 1**

\[
PDR_{D} = C_{D} V_{D} A
\]

Where, \(PDR_{D}\) is the particle deposition rate onto surfaces, \(C_{D}\) is the airborne concentration of particles of a size equal to or greater than \(D\), \(V_{D}\) is the deposition velocity of these particles through air, and \(A\) is the area of particle deposition. If surface deposition in all of a cleanroom is considered, then \(A\) can be assumed to be equivalent to the floor area.

Air filters are normally discussed in terms of their removal efficiency, which is usually given as a percentage. In this article, the proportion of airborne contamination that penetrates the filters is also used. These parameters are related as follows.

Penetration proportion = 1 – (removal efficiency (%)/100)

A typical cleanroom ventilation system will recirculate air from the cleanroom, add fresh make-up air, modify the temperature and humidity, filter the air, and supply it into the cleanroom. The airborne concentration of contamination in the supply air is likely to differ according to the type of ventilation system utilised, and equations have been derived that allow the concentration to be calculated for three basic designs of ventilation systems (along with minor design modifications). The design of these ventilation systems and the derivation of the equations have been more fully described in a previous article\(^5\) and are only briefly described in this article.

The symbols used in the equations are as follows:

\(C = \) concentration of airborne contamination in a cleanroom (no./m\(^3\))

\(C_{F} = \) concentration of airborne contamination in fresh make-up air (no./m\(^3\))

\(C_{R} = \) concentration of airborne contamination in recirculated air (no./m\(^3\))

\(Q_{S} = \) total air volume supply rate to cleanroom (m\(^3\)/s)

\(Q_{F} = \) air volume supply rate of fresh make-up air (m\(^3\)/s)

\(Q_{R} = \) air volume recirculated from cleanroom (m\(^3\)/s)

\(\eta_{P} = \) removal efficiency of primary air filter

\(\eta_{S} = \) removal efficiency of secondary air filter

\(\eta_{T} = \) removal efficiency of terminal air filter

\(D_{M} = \) average dispersal rate of contamination from machinery (no./s)

\(D_{P} = \) average dispersal rate of contamination from personnel (no./s)

\(V_{D} = \) deposition velocity of particles through air of a size \(D\) (m/s)

\(A = \) area of deposition of particles (m\(^2\))

**Type 1: Standard recirculation loop**

Make-up air is normally mixed with recirculated air before any filtration occurs and the mixed air passes through a primary filter, a secondary filter (where installed) and a terminal filter (see Figure 1). However, if the make-up air and recirculated air are filtered by the same efficiency of primary filters before they are mixed, the same equations can be used. The airborne concentration in a cleanroom can be ascertained by a previously derived Equation 2.

**Equation 2**

\[
C = C_{D} Q_{S} (1 - \eta_{P}) (1 - \eta_{S}) (1 - \eta_{T}) + D_{P} + D_{M} \quad \frac{Q_{S} + V_{D} A - Q_{R} (1 - \eta_{P}) (1 - \eta_{S}) (1 - \eta_{T})}{Q_{S} + V_{D} A - Q_{R} (1 - \eta_{P}) (1 - \eta_{S}) (1 - \eta_{T})}
\]

If a secondary filter is not installed, Equation 3 should be used.

**Equation 3**

\[
C = C_{D} Q_{S} (1 - \eta_{P}) (1 - \eta_{S}) + D_{P} + D_{M} \quad \frac{C_{D} Q_{S} (1 - \eta_{P}) (1 - \eta_{S}) + D_{P} + D_{M}}{Q_{S} + V_{D} A - Q_{R} (1 - \eta_{P}) (1 - \eta_{S}) (1 - \eta_{T})}
\]

**Type 2: Fresh air filtered before mixing with recirculated air**

The make-up air is filtered by a primary filter, passes through an air conditioning plant, and then mixed with the recirculated air. The mixed air passes through a secondary filter (where installed), and through a terminal filter in the cleanroom ceiling. A variation of the design of this system is one where the air conditioning plant is located after the point of mixing of the fresh and recirculated air but the same quality of air passes through the same air filters. Equation 4 is applicable to both these designs.
CALCULATION OF AIRBORNE CLEANLINESS AND AIR SUPPLY RATE FOR NON-UNIDIRECTIONAL AIRFLOW CLEANROOMS

**Type 1: Standard Recirculation Loop**

- **AC =** air conditioning plant
- **D =** dispersion from machinery and personnel
- **Air filters**

Equation 4

\[ C = \frac{C_0 Q_o (1 - \eta_P) (1 - \eta_S) (1 - \eta_T) + D_P + D_M}{Q_S + V_o A - Q_R (1 - \eta_S) (1 - \eta_T)} \]

If a secondary filter is not installed, Equation 5 applies.

Equation 5

\[ C = \frac{C_0 Q_o (1 - \eta_P) (1 - \eta_S) + D_P + D_M}{Q_S + V_o A - Q_R (1 - \eta_T)} \]

**Type 3: Recirculated Air by-pass**

Where there is a large demand for clean air, but the air conditioning requirement is relatively small, a proportion of the recirculated air is designed to by-pass the air conditioning plant and flow directly to the terminal filter.

The make-up air will pass through all of the air filters, as will part of the recirculated air, but the other part of the recirculated air will only pass through the terminal filter. The concentration of airborne contamination in a cleanroom can be calculated by Equation 6.

Equation 6

\[ C = \frac{C_0 Q_o (1 - \eta_P) (1 - \eta_S) (1 - \eta_T) + D_P + D_M}{Q_S + V_o A - Q_R (1 - \eta_S) (1 - \eta_T) - Q_R y (1 - \eta_T)} \]

Where, \( x \) is the proportion of the recirculated air that goes through the air conditioning plant, and \( y \) is the proportion that enters directly into the supply air duct.

If a secondary filter is not installed, Equation 7 is applicable.

Equation 7

\[ C = \frac{C_0 Q_o (1 - \eta_P) (1 - \eta_T) + D_P + D_M}{Q_S + V_o A - Q_R x (1 - \eta_P) (1 - \eta_T) - Q_R y (1 - \eta_T)} \]

**Simplified Equations**

If air filters in the ventilation system have a sufficiently high removal efficiency to ensure that no airborne contamination is supplied to the cleanroom, i.e. the removal efficiency (\( \eta \)) is 1, Equations 2 to 7 can all be simplified to the ‘dilution and deposition’ Equation 8.

Equation 8

\[ C = \frac{D_P + D_M}{Q_S + V_o A} \]

If the reduction in the airborne concentration of the cleanroom by surface deposition has no practical importance, then Equation 9, which is known as the ‘simple dilution’ equation, can be used.

Equation 9

\[ C = \frac{D_P + D_M}{Q_S} \]

**Constants and Variables for Use in the Equations**

To calculate the concentration of particles or MCPs in cleanroom air by means of the equations given in the previous section, the following information is required.

1. **The Air Volume Supply Rates of Fresh, Supply and Recirculated Air**
   - The air volume supply rates of fresh \( (Q_o) \), supply \( (Q_S) \) and recirculated air \( (Q_R) \) are obtained either from design data, or measurements made when the cleanroom is commissioned or tested.

2. **The Concentrations of Particles and MCPs in Fresh Make-up Air**
   - Compared to cleanroom air, the concentration of particles and MCPs in the outside fresh air is high. The outside...
concentration can be measured externally at the cleanroom’s site but if this is not possible, typical concentrations can be used. The authors have carried out sampling of outside air in rural and urban sites, when the weather was sunny, windy and rainy. All of the results were quite similar, and the highest results are given in Table 1. However, it is probable that even higher concentrations of particles and MCPs may be found. For use in this article (with a little rounding off), the particle concentrations were increased 10-fold, and the MCP concentrations doubled.

<table>
<thead>
<tr>
<th>Table 1. Concentrations of airborne contaminants found in outside air.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contaminant</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Particles ≥0.5 µm</td>
</tr>
<tr>
<td>Particles ≥5 µm</td>
</tr>
<tr>
<td>MCPs</td>
</tr>
</tbody>
</table>

3. The rate of particles emitted from machinery and equipment

MCPs are unlikely to be dispersed by machinery, and this possibility can generally be disregarded. Typical emission rates of particles have been reported⁹, and, generally speaking, they are lower than from personnel. Total emission rates from actual machines may be available from the manufacturer, or can be obtained experimentally by means of the method outlined in Annex B4 of ISO 14644-14¹³. This test method can be modified to include the particle emission from people operating the machinery to obtain the dispersion rate from all cleanroom sources.

4. Dispersion rate of particles and MCPs from cleanroom personnel

Information on the airborne dispersion rate of particles and MCPs from personnel exercising in a dispersion chamber (body box) has been reported by Whyte and his co-authors¹⁴–¹⁷, and by Reinmüller and Ljungqvist¹⁸–²⁰.

Cleanroom clothing should act as an air filter against particles dispersed from the skin and inner clothing of people, and designed to fully cover a person and ensure that a minimum amount of airborne particles is dispersed into the air. It should also be made from a fabric that disperses few particles. The effectiveness of different designs of cleanroom garments used in cleanrooms, better quality garments are available that give lower dispersion rates. Also, the results given in the second row of Table 2 were obtained from personnel who wore their normal clothing under cleanroom coveralls. Discussion with Reinmüller and Ljungqvist, along with our unpublished observations, shows that more effective garments used with cleanroom undergarments can lower the dispersion rates to those given in the third row of results in Table 2.

The results in Table 2 came from people exercising in a dispersal chamber, and this activity is likely to give a dispersion rate greater than found in a cleanroom. If an accurate estimate of the dispersion rate from the actual garments used in a cleanroom is required, then the rate from personnel working in a cleanroom can be measured in a cleanroom during simulated or actual manufacturing, and by use of the method suggested in Annex B4 of ISO 14644-14.

5. The deposition of particles and MCPs onto cleanroom surfaces

The PDR onto cleanroom surfaces can be calculated by means of Equation 3, which requires the deposition velocities through the air of different sizes of particles. Airborne particles are counted in cleanrooms as ‘cumulative’ counts, which includes all particles that are equal to, or greater than, a considered size. The deposition velocities of cumulative counts from a range of particle sizes are available¹¹ and a limited range of these values are given in Table 3. The deposition velocities given in Table 3 were obtained from observations in an ISO Class 8 cleanroom. For a range of particles between about ≥5 µm and ≥30 µm, the deposition velocities should be increased by about 1.7-fold when applied to an ISO Class 7 cleanroom, about 3-fold when applied to an ISO Class 6 cleanroom, and about 5-fold when applied to ISO Class 5. The same deposition velocity for small particles (≥0.3 µm or ≥0.5 µm) can be applied over a range of cleanroom classes.

Airborne MCPs are counted by microbial air samplers as a total number, and not as cumulative counts recorded by air particle counters. The deposition velocity that should be used with microbial counts is, therefore, the average

<table>
<thead>
<tr>
<th>Table 2. Average dispersion rate of particles and MCPs from people.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of cleanroom garments</strong></td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Normal indoor clothing with, or without, gowns (smocks) over them</td>
</tr>
<tr>
<td>Typical coveralls, hood and full length boots</td>
</tr>
<tr>
<td>Good quality coveralls, hood and full length boots</td>
</tr>
</tbody>
</table>
velocity of all airborne MCPs. MCPs rarely occur in cleanroom air in unicellular form, but are found on skin or clothing detritus dispersed from personnel, and have been shown to have an average equivalent particle diameter in air of occupied rooms of about 12 µm\textsuperscript{17,21}. A recent investigation\textsuperscript{22} has shown that the deposition velocity of MCPs is influenced, in a similar way to particles, by airborne conditions in a cleanroom, and the deposition velocity increases as the airborne concentration decreases. The deposition velocities of average MCP sizes have been shown to be about 1000 times greater than for the MPPS\textsuperscript{25}, where the average particle size has been shown to be about 0.2 µm and 0.5 µm\textsuperscript{2}\. The EN 1822:2009 classification system is used in this article. The MPPS varies according to the filter media, but in high-efficiency filters of the type used in cleanrooms, it is normally known. In this case, and although an underestimate, it is reasonable to assume the same removal efficiency as obtained from the MPPS. However, in the case of MCPs, where the average particle size has been shown to be about 12 µm\textsuperscript{17,22} and the removal efficiency of filters has been shown to be about 1000 times greater than for the MPPS\textsuperscript{23}, a 1000-fold increase in removal efficiency is assumed.

### Characteristics of cleanroom used as practical example

To investigate the changes in the concentration of particles ≥0.5 µm and MCPs in a cleanroom caused by changes in the variables in Equations 2 to 9, a cleanroom with the following characteristics is investigated.

1. The cleanroom is non-UDAF with a floor area of 10 m \(\times\) 10 m and height of 3 m, i.e. 300 m\(^3\) in volume. It is supplied with 3.33 m\(^3\)/s of high-efficiency particulate air-filtered air, which is equivalent to 40 air changes per hour. Of the room air supply, 10% is fresh make-up air. When a Type 3 ventilation system is studied, half the recirculated air by-passes the air conditioning plant.
2. Two people work in the cleanroom and wear cleanroom clothing that consists of a one-piece, woven-polyester coverall with hood and over-boots. The total dispersion rate for two people is assumed to be 34,000/s for airborne particles ≥0.5 µm, and 6/s for MCPs.
3. A filling machine in the cleanroom disperses 500 particles ≥0.5 µm/s.
4. The concentration of particles ≥0.5 µm in the outside fresh air is assumed to be 10\(^6\)/m\(^3\) and 100/m\(^3\) for MCPs.
5. The deposition velocity of particles ≥0.5 µm was assumed to be 0.006 cm/s (0.00006 m/s). The deposition velocity of MCPs depends on the airborne conditions in the cleanroom and it was necessary to carry out several iterations of the calculation of the airborne concentration in the cleanroom to determine an appropriate deposition velocity. This was finalised at 1.5 cm/s (0.015 m/s).
6. Using the EN 1822 classification, the primary filters were E10 bag filters with a removal efficiency of 0.85. The secondary filters (when installed) were H13 with a removal efficiency of 0.9995, and terminal filters were H14 with a removal efficiency of 0.99995. Other removal efficiencies were also investigated. The removal efficiency against MCPs was assumed to be 1000 times greater.

#### Calculation of airborne concentration from different ventilation systems

Using the cleanroom properties given in the “Characteristics of cleanroom used as practical example” section, Equations 2 to 7 were used to calculate the concentration of airborne contamination in a cleanroom when air is supplied by the three different types of ventilation systems, and with and without an installed secondary filter. The results are given in Table 5, where it can be seen that the type of ventilation system made no practical difference to the airborne concentration in cleanrooms, although the omission of a secondary filter gave a slight increase in the particle concentration. It was also determined that the airborne concentration of MCPs did not vary according to the type of ventilation system, or from the addition of a secondary filter.

#### Effect of equation variables on airborne concentrations in cleanrooms

The importance of the equation variables was found by calculating the different airborne particle concentrations in a cleanroom when the variables were changed. Equation 2 was used, which applies to the commonly used Type 1 ventilation system.

The concentration of airborne particles ≥0.5 µm in the cleanroom whose characteristics are described in the

### Table 3. Deposition velocities of a range of cumulative particle diameters.

<table>
<thead>
<tr>
<th>Cumulative particle diameter</th>
<th>≥0.3 µm</th>
<th>≥0.5 µm</th>
<th>≥5 µm</th>
<th>≥10 µm</th>
<th>≥25 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deposition velocity (cm/s)</td>
<td>0.003</td>
<td>0.006</td>
<td>0.3</td>
<td>0.9</td>
<td>4.2</td>
</tr>
</tbody>
</table>

### Table 4. Deposition velocities for different airborne concentrations of MCPs.

<table>
<thead>
<tr>
<th>Concentration of MCPs/m(^3)</th>
<th>0.1</th>
<th>0.5</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deposition velocity (cm/s)</td>
<td>3.55</td>
<td>2.04</td>
<td>1.61</td>
<td>0.92</td>
<td>0.73</td>
<td>0.42</td>
<td>0.33</td>
</tr>
</tbody>
</table>
The reference value of 10,342/m³ and the results shown in their values were 10 times lower or higher, was divided by air of the total supply air were investigated. proportions of 0.01 to 1 of the fresh make-up were interconnected and could not be individually constant. As the air volumes of fresh and recirculated air calculated when the rest of the variables were kept its standard value, and the cleanroom concentrations then given a value 10 times less, and 10 times greater, than the cleanroom's airborne concentration differs from that found in the standard set of characteristics.

A similar study was also carried out into the effect of the equation variables on the cleanroom’s MCP concentration, and this gave similar values to those obtained from particles. Changes in the dispersion rates were in direct proportion to the airborne concentration in the cleanroom, although the changes in air volume did not have as great an effect as the particles (presumably owing to the effect of particle deposition). The effect of both the deposition velocity and floor area gave a 0.26-fold decrease in MCP airborne concentration. The other variables gave no change to the airborne concentration. The particle concentrations for each variable when their values were 10 times lower or higher, was divided by the reference value of 10,342/m³ and the results shown in Table 6. These results are the number of times the cleanroom’s airborne concentration differs from that found in the standard set of characteristics.

Table 6 shows that the most important variables are the air supply rate and dispersion rates from personnel and machinery, and a 10 times change of both these variables gives an almost directly proportional change in the airborne concentration of particles ≥0.5 µm in the cleanroom. The floor area and deposition velocity gave a small change in the airborne concentration. The change in the removal efficiency of each filter made no difference, but a 10-fold change in efficiency was small in comparison to the range of filter removal efficiencies that are available. Filter efficiencies were, therefore, studied in more depth, and reported in the next section.

A similar study was also carried out into the effect of the equation variables on the cleanroom’s MCP concentration, and this gave similar values to those obtained from particles. Changes in the dispersion rates were in direct proportion to the airborne concentration in the cleanroom, although the changes in air volume did not have as great an effect as the particles (presumably owing to the effect of particle deposition). The effect of both the deposition velocity and floor area was greater than particles ≥0.5 µm, e.g. a 10-fold increase in both deposition velocity and floor area gave a 0.26-fold decrease in MCP airborne concentration, and a 10-fold increase gave a 1.4-fold decrease in MCP airborne concentration. The other variables gave no change to the airborne concentration.

**Effect of filters and different ventilation systems on airborne concentrations**

The effect of the number of air filters installed, their placement and removal efficiency was investigated using the three types of ventilation systems. Using Equations 2, 4 and 6, the airborne concentrations of particles ≥0.5 µm in a cleanroom were calculated for combinations of the three filter efficiencies. The combinations of the filter removal efficiency that are investigated are given in the top part of Table 7, and progressively increase from zero removal efficiency in the left side of the table, to total removal efficiency in the right-hand side. Also investigated was the use, or not, of a secondary filter, with these results given in alternate rows in the bottom part of the table. It was assumed that the filtration system, i.e. filter, gasket and frame, had no leaks.

The concentration of airborne particles ≥0.5 µm in a cleanroom that had no air filters installed was 9.8 x 10^7/m³, and the importance of air filters is clearly shown by the concentration dropping to 10,342/m³ when the removal efficiency of the filters was 1. This demonstrates that effective air filters can be responsible for reducing the cleanroom’s airborne concentration of particles ≥0.5 µm by about 99.98%.

It can be seen in Table 7 that when the filter efficiencies of the secondary and terminal filters are 0.9995/0.99995 (H13/H14), the concentration of particles ≥0.5 µm in a cleanroom supplied by any of the three ventilation systems reaches a minimum of 10,342/m³, and any further increase in the filter’s removal efficiency gives no further reduction in the airborne concentration. Use of a less-efficient filter combination of 0.995/0.9995 (E12/H13) gives an increase of 3 to 6 particles/m³, which is of no practical significance. However, to test for leaks, the filter system is challenged with a test aerosol of a size similar to the MPPS, and any penetration greater than 0.01% of particles through the filter is considered a leak. Therefore, to easily find a leak, without it being obscured by the normal passage of particles through undamaged filter media, the overall efficiency of filter should be equal or greater than 99.99%, i.e. a H14 filter.

It can be seen in Table 7 that Type 1 and Type 2

<table>
<thead>
<tr>
<th>Type of airborne contamination</th>
<th>Type 1: standard</th>
<th>Type 1: no secondary</th>
<th>Type 2: filtered fresh air</th>
<th>Type 2: no secondary</th>
<th>Type 3: recirculation by-pass</th>
<th>Type 3: no secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particles ≥0.5 µm/m³</td>
<td>10,342</td>
<td>10,417</td>
<td>10,342</td>
<td>10,417</td>
<td>10,342</td>
<td>10,417</td>
</tr>
<tr>
<td>MCPs/m³</td>
<td>1.24</td>
<td>1.24</td>
<td>1.24</td>
<td>1.24</td>
<td>1.24</td>
<td>1.24</td>
</tr>
</tbody>
</table>

**Table 5.** Airborne contamination concentrations obtained from various types of ventilation systems.

**Table 6.** Effect on the cleanroom’s airborne concentration caused by 10-fold changes to the equation variables.
Calculation of airborne cleanliness and air supply rate for non-unidirectional airflow cleanrooms

Calculation of airborne concentration by the simpler equations

The airborne concentrations in the cleanroom example were also calculated by use of the ‘deposition and dilution’ Equation 8, and the ‘simple dilution’ Equation 9. These results were compared to those obtained from Equation 3, which includes all the variables that influence airborne concentration. The filters investigated were a typical primary/secondary/terminal filter combination of E10/H13/H14, with removal efficiencies of 0.85/0.995/0.99995. The results in Table 8 show that variations between the concentrations of particles ≥0.5 µm calculated by each of these three approaches are of little practical importance. However, the ‘simple dilution’ Equation 8 gave a concentration that was a little higher and caused by lack of removal by surface deposition. Equation 9 took into account the deposition, and gave results identical to the equation with all variables included.

Calculating the required air supply rates for a required airborne concentration of contamination in non-UDAF cleanrooms

Previous sections of this article contain equations for calculating the airborne concentration likely to be found in non-UDAF cleanrooms. However, it is also important to be able to ascertain the air supply rate for a required maximum concentration of airborne contamination, such as specified in ISO 14644-1 or the EU GGMP.²

It has been shown in this article that the main variables that affect the airborne concentration in non-UDAF cleanrooms are the air supply rate and the total rate of dispersion of contamination in the cleanroom. Air filters have a large effect, but this is negligible if the filters have high removal efficiencies that are typical of filters used in current cleanroom designs. If the other equation variables, including surface deposition, are considered to have no practical influence, the previously discussed ‘simple

### Table 7. Airborne concentration of particles ≥0.5 µm in a cleanroom with respect to filter efficiencies and type of air ventilation system.

<table>
<thead>
<tr>
<th>Filter type</th>
<th>Filter efficiency according to EN 1822</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>0</td>
</tr>
<tr>
<td>Secondary</td>
<td>0.85/0.95/0.995</td>
</tr>
<tr>
<td>Final</td>
<td>0.95/0.995/0.9995</td>
</tr>
</tbody>
</table>

### Table 8. Comparison of airborne concentration calculated by different types of equations.

<table>
<thead>
<tr>
<th>Type of airborne contamination</th>
<th>Type 1: standard recirculation loop equation</th>
<th>Simple dilution equation</th>
<th>Simple dilution and deposition equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particles ≥0.5 µm/m³</td>
<td>10,342</td>
<td>10,360</td>
<td>10,342</td>
</tr>
<tr>
<td>MCPs/m³</td>
<td>1.24</td>
<td>1.80</td>
<td>1.24</td>
</tr>
</tbody>
</table>
Concentration (number/m$^3$). Where, Equation 10 calculate the air supply rate.

**Equation 10**

$$Q_S = \frac{D_T}{C}$$

Where, $Q_S =$ total air supply volume rate (m$^3$/s), $D_T =$ total average particle dispersion rate from both personnel and machinery/s, and $C =$ required airborne particle concentration (number/m$^3$).

If the cleanroom design requires consideration of large particle sizes or MCPs then, to take account of surface deposition, the dilution and deposition Equation 11 should be used.

**Equation 11**

$$C = \frac{D_T}{Q} - V_pA$$

The calculation of the air supply rate by means of Equation 10 or 11 is based on the average dispersion rates from personnel. Therefore, when airborne particle concentrations are measured in an actual cleanroom, the average concentration of the air samples will be the same as the concentration calculated by Equations 10 or 11. This may be acceptable, but many cleanrooms users will expect the airborne concentration not to exceed a maximum value, such as required in the class limits of ISO 14644-1.

It is a scientific impossibility that all counts from air samples will never exceed a specified value, as the counts will conform to a statistical distribution where large counts will occasionally be found. However, it is possible to calculate an air supply volume that limits the occurrence of large counts to a specified, and low, frequency. This air supply is influenced by the spread (variation) of counts found in the cleanroom and, the greater the spread, the greater the air supply required to ensure the counts do not exceed the required concentration. The spread of the counts can be described by a coefficient of variation ($CV$) shown in Equation 12.

**Equation 12**

$$CV = \frac{\sigma}{\mu}$$

Where, $\sigma$ is the standard deviation of the counts and $\mu$ is the mean of the counts.

Airborne sampling in cleanrooms by Whyte, Eaton and Lenegan$^9$ has shown that $C_r$ can vary from about 0.5 to 2, with 1 being a common value. In addition, the Poisson distribution is often considered to represent the distribution of counts in a cleanroom and, as this distribution has a standard deviation equal to the count mean, this confirms the reasonableness of using a $CV$ equal to 1.

The required air supply is also dependent on the percentage of counts that the cleanroom user requires to be below the specified concentration. Shown in Table 9 is the number of times ($N_r$) the air supply should be increased above that calculated by Equation 11 when $C_r$ is 1 and the percentage of counts below the specified concentration is either 95% or 99%.

If the air supplied to a non-unidirectional cleanroom does not perfectly mix with cleanroom air, there will be locations that receive less clean air than the average, and the airborne concentration of contamination will be higher than average. Extra air is required to compensate for these higher concentrations, and the air change effectiveness (ACE) index can be used to calculate the extra amount. A method of measurement and calculation of the ACE index ($\varepsilon$) is described in the American National Standards Institute/American Society of Heating and Air-Conditioning Engineers (ANSI/ASHRAE) standard 129-1999 (RA 2002)$^{26}$. However, this method is best adopted for use in a cleanroom$^{27}$, and if the recovery rate is measured at a critical location by means of the method given in ISO 14644-3 then, as the recovery rate is the same as the air change rate, the ACE index can be calculated from Equation 13.

**Equation 13**

$$\varepsilon = \frac{\text{Air change rate measured at a critical location}}{\text{Average air change rate in cleanroom}}$$

If air mixing in the cleanroom is perfect, the ACE index will be 1 but if the test location receives more clean air than average (and hence the airborne concentration of contamination will be lower than average), the ACE index will be higher than 1. Locations that receive less clean air will have an ACE index lower than 1. When the ACE index is less than the room average i.e. $<1$, the air change rate may have to be increased to achieve the specified airborne concentration.

A method of obtaining the ACE index in non-UDAUF cleanrooms has been previously described$^{27}$, and it was shown that when effective air diffusers were fitted in non-UDAUF cleanrooms, and the air extracts were at low level, ACE indexes close to 1 were common, and unlikely to be less than 0.7$^{27,28}$. An ACE index of 0.7 can, therefore, be used to compensate for poor air mixing. However, in cleanrooms where good mixing is not obtained by effective air diffusers and low level extract, lower ACE

<table>
<thead>
<tr>
<th>Table 9. Increase in air supply rates.</th>
<th>Percentage of counts below the particle limit</th>
<th>Ratio of standard deviation to mean ($CV$)</th>
<th>Number of times increase in air supply rate ($N_r$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>1</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>99%</td>
<td>1</td>
<td>3.5</td>
<td></td>
</tr>
</tbody>
</table>
values may be found and higher air supply rates are required to compensate.

If clean air devices are located in a non-UDAF cleanroom, they will reduce the airborne concentration of contamination in the cleanroom and hence the supply air rate requirement. Not all of the air from a clean air device mixes well with cleanroom air and the ventilation effectiveness coefficient ($\beta$) gives the proportion of the supply air ($Q_D$) coming from a clean air device that efficiently mixes with cleanroom air. Examples of values of $\beta$ that have been reported are as follows.

- If a large unidirectional workstation is used, in which its intake air is drawn from the cleanroom and the supply air returns to the device’s intake through the cleanroom, $\beta$ may be about 0.5.
- If a large unidirectional airflow workstation is supplied with air from the main mechanical ventilation plant and its air exhaust is extracted through low level extracts around the cleanroom, $\beta$ may be about 0.2.
- If the clean air devices are small and their supply air mixes well with room air before being drawn back into the device’s intake, then a $\beta$ of about 0.8 can be use.

The effect of (a) the additional dilution effect from clean air devices, (b) the ACE, and (c) an increase in air supply to ensure that measurements in the cleanroom will rarely exceed the specified concentration, can all be accounted for by Equation 14.

**Equation 14**

\[
Q_S = \frac{D_T \times N_S}{0.7 \times C} - \beta Q_D
\]

The surface deposition of particles has been shown to have little practical effect in reducing the airborne concentration of small particles such as ≥0.5 µm, but if the particles are large or are MCPs, then for greater accuracy, the effect of surface deposition should be included, and Equation 15 used along with the appropriate deposition velocities given in Tables 3 and 4.

**Equation 15**

\[
Q_S = \frac{D_T \times N_S}{0.7 \times C} - \beta Q_D - V_D A
\]

A final requirement that may have to be considered is whether the air supply rate calculated by Equations 14 or 15 is sufficient to ensure that the ‘clean up’ requirements given in the EU GGMP, or a specified recovery rate or recovery time as described in ISO 14644-3 are likely to be achieved. This can be ascertained by a method described by Whyte, Lenegan and Eaton, who report that when the ventilation effectiveness is taken into consideration, an air change rate of 26/hour should be sufficient for an EU GGMP Grade B cleanroom to ensure the correct ‘clean up’ requirements, and 13/hour for a Grade C cleanroom. However, the article should be consulted for further information.

**Discussion**

Equations have been derived by various researchers to calculate the airborne concentration of particles in non-UDAF cleanrooms in the operational state but their equations usually apply to one type of ventilation system with a specific method of introducing fresh air into the recirculated air, and placement and number of air filters. However, a recent article written by Whyte, Lenegan and Eaton describes equations that deal with various ventilation systems, and these equations are studied in this article.

The variables that might influence the airborne concentration of contamination in non-UDAF cleanrooms are the air supply rate, airborne dispersion rate of contamination from machinery and people, surface deposition of particles from air, concentration of airborne contamination in fresh make-up air, proportion of fresh air, and the removal efficiency, location and number of air filters. Actual values of some of these variables have not been previously available, and it has not been possible to use these equations for designing actual cleanrooms, or to investigate the relative importance of the variables. However, the principle author of this article has been involved in investigations into the surface deposition of contaminants and the airborne dispersion rate of particles and MCPs, and the three authors of this article have investigated the concentration of particles and MCPs in outside air. Using this information, it is possible to calculate the airborne concentration likely to be found in actual cleanrooms, and the effect of the type of ventilation system and the equation variables.

The equations derived in a recent article were used to calculate a cleanroom’s airborne concentration of contamination when different ventilation systems are used, and it is shown in Table 5 that when air filters of the type typically installed in cleanrooms were used, the type of ventilation plant made no practical difference to the airborne concentration in the cleanroom, although the installation of a secondary filter in addition to a primary and terminal filter, gave a noticeable reduction.

The importance of the variables in the equations was investigated by increasing or decreasing each variable by 10-fold and calculating the effect on the airborne concentration of particles ≥0.5 µm in a cleanroom which used typical air filters. The most important variables were shown in Table 6 to be the airborne dispersion rates from machinery and people, and the air supply volume, both giving a change in concentration that was almost in direct proportion to the change in the value of the variable. An increase in the outside concentration of airborne contamination, and the proportion of fresh make-up air in the air supply did not influence the cleanroom’s concentration of contamination. The effect of surface deposition of particles ≥0.5 µm was small and could be ignored. However, if larger particles and MCPs have to be considered, the amount of deposition should be included, and Equation 12 used.

Air filters of the type typically used in cleanrooms could reduce the airborne concentration of particles ≥0.5 µm by 99.98% compared to an identical cleanroom
that did not use filters. It was shown in Table 7 that there was no improvement in the particle concentration by any combination of air filters more efficient than the typical secondary/terminal filter combination of H13/H14. It was also demonstrated that a H13/H13 or E12/H13 combination gave a similar concentration of contamination in the cleanroom. However, the requirement to achieve a leak penetration of less than 0.01% during a particle test challenge meant that a H14 terminal filter would be required to ensure that leaks could be found without a problem of background contamination coming through undamaged filter media.

This study confirmed the correctness of our previous approach to calculating the air supply to a non-UDAF cleanroom by means of the dilution Equation 11. However, to increase the accuracy of the calculation, the following should be included: (a) the additional air-cleaning effect of clean air devices, (b) an air change effectiveness index, and (c) an increase in the air supply to ensure that air samples taken in the cleanroom will rarely exceed the required concentration. To achieve this, Equation 13 should be used. When the concentration of larger particles and MCPs are calculated, the deposition effect should be included, and Equation 14 used. If the design of a cleanroom specifies a ‘clean-up’ requirement, or a similar recovery rate or recovery time, then the ability of the calculated air supply rate to achieve such requirements should be checked using the previously published information29.

References


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**Notes:**
- The references cited above provide a comprehensive overview of the topics related to cleanroom design, airflow, and contamination control. The references include studies on classification, particle control, and the effectiveness of cleanroom systems.
- The studies referenced here emphasize the importance of accurate airflow calculations, the role of cleanroom clothing in dispersion control, and the impact of particle deposition on product contamination.
- The references also cover the classification of cleanroom cleanliness levels and the performance testing of air filters and cleanroom garments.
- The work by Whyte, Eaton, and Lenegan is particularly notable for its contributions to the understanding of airborne particle behavior in cleanrooms and the development of equations for predicting airborne cleanliness.

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**Additional Information:**
- The references are formatted in APA style, which is commonly used in academic publications for citation.
- The page number 88 indicates that this text is from a publication that spans multiple pages, and the context suggests it may be part of a larger discussion on cleanroom design and operation.
QP Forum Conference

3rd November 2016
Llangoed Hall, Brecon, Wales, UK
£200 + VAT

Schedule

9.30am - 10.00am
Registration

10.00am - 10.15am
Welcome
Kay O’Hagan
Senior QP, Tecmac UK Ltd

10.15am - 11.15am
Supply chain - do you know yours
Gail Heavey
Director of Time Design51 Ltd
Alan Heavey
Consultant & Managing Director, Sterilization Solutions

11.15am - 11.30am Coffee

11.30am - 12.30pm
Current Challenges facing QPs
Certifying ATIMPs
Diane Hiscocks
Reneuron

12.30pm - 13.30pm
QP Certification API and Supply Chain Aspects
Di Morris
GSK Global auditor,
Ex-MHRA senior inspector

13.30pm - 14.15pm Lunch

14.15pm - 15.15pm
Changes and Best Practices in Cleanroom testing and monitoring
Tim Triggs
ATI

15.15pm - 16.15pm
New CT regulations and update on IMPs
Richard Funnell
Funnell Pharma Consultants Ltd

16.15pm - 16.30pm
Close
Kay O’Hagan
Senior QP, Tecmac UK Ltd
Assessing contamination control of pre-sterilised container tub transfers into an aseptic manufacturing filling isolator via a de-bagging/no-touch-transfer process step

Bengt Ljungqvist1, Berit Reinmüller1*, Corinna Maier2 and Ann-Catherine Roth2
1 Chalmers University of Technology, Goteborg, Sweden
2 Aseptic Processing Technologies & GMP Compliance, Franz Ziel GmbH, Billerbeck, Germany

Experimental contamination transfer challenge studies were designed to assess whether contamination control and sterility are maintained when using a no-touch-transfer (NTT) de-bagging tub transfer method to introduce pre-sterilised containers into a FlexPro50 aseptic manufacturing isolator/restricted-access barrier system filling line system. Importantly, the sterile tubs of product containers are enclosed in double steri-bags, and remain sterile through the supply chain to point of filling. Use of NTT means that any of the current automated bio-decontamination steps usually employed prior to material transfer into Grade A areas are rendered unnecessary; since the bag contents remain sterile and protected and can be transferred without exposing the Grade A aseptic processing zone to the outer bag. To support this rationale, two key contamination control studies were undertaken during processing of tub transfers with the NTT/de-bagging technology; 1) surface-to-surface transfer of human commensal microorganisms representing the challenge of ‘worst case’ operator handling, and 2) a structured approach evaluating the risk of airborne contamination as tubs move through the NTT process steps into the Grade A isolator environment by a particle challenge method (limitation of risks method). In these studies, the barrier–isolator environment remained robust to adverse particle movement, without microbial contamination transfer. In addition, the sterile tub outer surfaces were confirmed as maintaining sterility during the NTT process step. These results provide proof of concept of NTT technology.

Key words: Pre-sterilised containers, no-touch-transfer (NTT), de-bagging, aseptic manufacturing filling isolator, L-R method.

Introduction

There is a significant trend in the market towards biological products with more targeted delivery systems and improved efficacy which can be given in smaller doses and manufactured on a smaller scale1. Personalised medicines, advanced therapeutic medicinal products and investigational medicinal products have to be filled in controlled environments, but in much smaller batches at clinical trial phases and potentially in final production batches. Consequently, new product types are supported by new technology developments including increasing use of pre-sterilised single-use disposable systems for sterile product holding, and fluid pathways that transfer product to point of fill. Pre-sterilised product containers in different formats (syringes, vials and cartridges) are particularly useful for sterile medicinal products manufactured in small batches2. This increased use of pre-sterilised product containers has challenged established container tub transfer methods for entry into filling line isolators/restricted access barrier systems (RABS).

The industry response has been developments in process/scale compatible manufacturing technologies, and here we examine an important development in pre-sterilised container processing. Transferring tubs of pre-sterilised containers into the Grade A/ISO 5 filling zone traditionally necessitates bio-decontamination of the outside of the tub of containers at entry into the filling zone. Transfer of material must not compromise the stringent requirements for good manufacturing practice (GMP) EU controlled environment classification – Grade A/ISO 5–3.

Traditionally, pre-sterilised container manufacturers provided no assurance that the tub outer surfaces were sterile at manufacture and through the supply chain, so by default an
automated decontamination step at entry to filling lines was required; tub surface bio-decontamination steps were either eBeam, cold/low temperature plasma or vapourised hydrogen peroxide6–8.

Recent developments presented by pre-sterilised container manufacturers have provided the necessary assurance that outer tub surfaces are sterile at manufacture with assurance this sterility is maintained through the supply chain via use of tamper proof carton closing. Such assurance of sterility is a prerequisite to implementation of no-touch-transfer (NTT) process steps that further maintain the tub sterility in transfer to point of de-lidding (removal of tub Tyvek® cover) and filling/container closing9.

Currently, if specified, the outer tub surface bio-decontamination step, e.g. eBeam, requires the tub to be unpackaged from the protective steri-bag with consequent exposure to contamination in the surrounding environment or lower classification environments, so even if the tub outer surfaces were sterile, due to the in-process contamination risks, a tub outer surface decontamination step was required at entry to Grade A filling environments. If a tub surface bio-decontamination step is specified, it is acceptable to process pre-sterilised containers starting with a single steri-bag and without assurance the outer tub surfaces are sterile.

Considering alternative methodology, with the assurance that outer tub surfaces of pre-sterilised container tubs are also sterile, NTT technology can be applied that does not expose the tub to a lower environmental classification than Grade A through process steps of outer packaging removal and tub transfer into Grade A processing zones. The NTT de-bagging method requires double steri-bag packaging and removes the need for a post-delivery automated bio-decontamination process step by ensuring the sterile tubs and contents are transferred to the aseptic environment under controlled environmental conditions, including operator to process separation via RABS in the final steri-bag NTT/de-bagging step9,10.

Carefully controlled NTT techniques are used for double bags to remove the initial outer-bag at entry to either a Grade B cleanroom with a RABS-filling barrier system or at entry to a RABS–NTT system in a Grade C cleanroom where filling is completed in an isolator filling system. The RABS–NTT has a controlled environment to Grade B with a Grade A air supply at the transfer point of the sterile tub. It is recommended that a manual disinfection wipe step is used to reduce bioburden entering the Grade C cleanroom on the double-bagged tubs. At the final entry into the Grade A filling zones, the application of semi-automated or fully automated de-bagging/NTT technology, depending on the line filling speed, with sterile tub transfer under Grade A air supply conditions is applied, and thus the tub pre-sterilised containers are protected throughout a continuum from primary manufacture to filling (see Figure 1).

Every new technology requires experimental evidence to prove the concept and validate its use in a process operating with GMP3–5. Although a small number of US Food and Drug Administration/EU-approved facilities are using de-bagging technology, supportive data in the public

Figure 1. Pre-sterilised containers manufacturing, supply chain distribution and NTT process steps for transfer into Grade A processing zones for filling.
domain is required that sterile tubs (inside and out) which have the necessary assurance of sterility can be transferred together with sterile containers into Grade A/ISO 5 zones via the NTT process whilst sterility and environmental control is maintained.

The study objective was to verify that tubs of sterile containers which are protected by a steri-bag can enter the filling zone without contaminating the sterile tub outer surface or the filling zone when using a de-bagging NTT mechanism that does not employ an automated tub surface bio-decontamination step. This study simulates a worst case contamination scenario to fully interrogate the robustness of the NTT process. Human commensals representing the most likely contamination challenge through packaged tub handling, were deliberately inoculated onto the steri-bag outer and the bag cutting blade. To challenge the NTT–RABS environment, the tubs were singly wrapped in a steri-bag rather than doubly bagged so there was no NTT step at bag loading to the RABS that contained the final NTT mechanism at entry to the Grade A isolator. Furthermore, the surrounding cleanroom was Grade D, although Grade C is the recommendation for isolators filling sterile products.

It was considered that if the process was robust to a worst case scenario, it would operate at acceptable risk reduction to potential contamination in a manufacturing facility working under GMP and using good aseptic technique. The focus points for environmental monitoring of the contamination transfer studies are shown in Figure 2, which is a diagrammatic representation of the NTT process.

The NTT process has been described previously by Drinkwater et al., but in brief the process comprises of the following steps. The pre-sterilised containers for transfer in the NTT process, e.g. nested filling containers in tubs are placed in membrane steri-bags (double bags) made of Tyvek® filter material. A number of bagged tubs are then placed in a perforated carton – all layers allow ethylene oxide (ETO) to pass through into the product containers to render the contents sterile. After this classical certified sterilisation step, the carton of sterile tubs of containers are then secured by a tamper-proof label-tape to provide assurance of maintained sterility through the supply chain.

On receipt at a manufacturing facility, the carton tamper-proof closures are checked for integrity and if valid the bagged tubs are removed and transferred within the facility to point of use following documented procedures. The still-enclosed bag contents are moved to a tub loading preparation area for material transfer via NTT.

During the final de-bagging step, the steri-bag is cut open by a semi-automatic blade cutting mechanism whilst clamped so that particles do not enter inside the bag onto the tub. The operator (or machine) then completes the NTT process and pushes the sterile tub into the Grade A area under Grade A air supply protection without touching the sterile tub (Figure 2).

The NTT concept relies on the fact the tubs are ETO sterilised together with double steri-bags and the process of NTT is only under Grade A airflow protection and the transfer zones are protected from contamination via outer bag surfaces using the NTT technology. In principle, no
decontamination step is required other than initial manual disinfection on tub packaging at transfer into a Grade C cleanroom if isolator technology is used in the filling process.

The experiments reported here were conducted in an isolator engineering facility with an isolator filling system housed in a Grade D cleanroom (Figure 3). Two potential routes of contamination were identified: 1) surface-to-surface microbiological contamination transfer, and 2) airborne contamination transfer that may be in the form of non-viable particulate or microbe carrying particles. To reproduce the most likely microbiological challenge, the microorganisms collected to inoculate surfaces were human commensals from finger touch.

To risk assess the possibility of airborne contamination during the process, the method for limitation of risks (the L-R method) was applied with its visualisation and challenge test. Airborne contamination transfer through the NTT tub transfer was evaluated by monitoring of particle concentration during the particle (smoke) challenge test to study if there was compromise to the controlled process environments. In these studies, the barrier technology remained robust to adverse particle movement during the NTT/de-bagging process.

Furthermore, zero colony forming units (CFU) were recorded via environmental monitoring in the Grade A filling area and on outer tub surfaces after the ‘worst case scenario’ purposeful inoculation of the steri-bags and NTT equipment. These results provide proof of concept of NTT technology and it is up to individual sites to qualify NTT for a given application.

**Materials and methods**

Contamination transfer challenge studies included analysis of potential airborne and surface contamination during the process of tub transfer via the de-bagging/NTT principles into a FlexProS0 de-lidding/filling machine (Groninger GmbH) inside a small batch isolator connected to a RABS enclosing the NTT mechanism with a surrounding Grade D cleanroom environment (F. Ziel GmbH), as shown in Figures 3, 4(a) and 4(b).

All environmental zone classifications were verified by classical environmental monitoring as EU Annex 1 GMP compliant before the tub transfer studies. The transfer tubes were pre-sterilised containers sealed with Tyvek® lids and were provided by an approved supplier, Nuovo Ompi Stevenato Group, Italy.

Tub transfer studies were completed with a single outer packaging bag as an experimental worst case scenario. In manufacturing process operations, double bagged sterile tubs are best practice. Single wrapped sterile tubs of nested containers used in the study were not disinfected on entry to the RABS Grade B NTT zone to provide an additional contamination challenge. Furthermore operator gowning in the Grade D Cleanroom was deliberately basic – an overall, shoe covers and no hair cover to contribute to the worst case challenge scenario.

Two key experiments were conducted: Experiment 1) a structural approach to physical risk assessment using particles from a smoke pencil as tracer and challenge and an optical particle sensor for detection, and Experiment 2) confirmation of absence of surface contamination transfer with NTT technology via classical microbiological environmental monitoring methods which comprised contact plates and swabs.

**Qualification of room and isolator environmental conditions**

Prequalification testing verified that the isolator interior complies with EU-GMP Grade A (ISO Class 5, the de-bagger unit (RABS) in front of isolator in-feed ‘mouse-hole’ complies with EU-GMP Grade B – with Grade A air supply at critical tub opening/transfer point.

Operator intervention into the de-bagging NTT zone is only possible via RABS gloves. Tub initial entry from the
Grade D Cleanroom into a preparation area with uni-directional airflow (UDF) protection in front of a tub entry ‘mouse-hole’ performs to EU-GMP Grade C compliance. These classifications were determined in advance of the tub transfer/contamination challenge studies by environmental monitoring methods as referenced in EU GMP Annex 13–5,11.

Experiment 1: L-R method
Experiment 1 utilised the application of the L-R method with its visualisation of air movements and its challenge test of the process environment. The L-R method provides a reliable procedure for assessing potential ‘microbe carrying particles’ as microbiological risks of airborne contamination in clean zones in a systematic way. It relies upon sensitive measurements of potentially non-visible particle movements and not simple visualisation of smoke movement. Particle challenge testing and calculation of the risk factor presents an effective way for measuring different types of risk in medicinal product manufacture and environmental monitoring12.

It can be used for tracing the dispersion routes of airborne contamination, for identification of risk situations, for evaluating risks connected to single process steps, for immediate evaluation of changes, and for assessment of potential risks. A modification of the L-R method can be used for evaluating the response of sampling locations in clean zones.

Figure 4. NTT equipment: pre-sterilised container transfer into filling system.
The illustrative technique of smoke studies provides a useful technique for visualising air movements and dispersal of contaminants. This technique requires that isothermal smoke is released continuously and almost momentum free using a diffuser. The smoke pattern can be recorded by means of still photography and video. Ljungqvist et al. demonstrated that smoke particles are typically so small that under normal turbulent conditions, they are dispersed in the same way as gases.

During the challenge test, the process simulation and operating conditions should preferably exaggerate the human interference and interventions in order to more rapidly identify potential risk situations. To assure the result, generally not less than three measurements of not less than 1 minute each should be performed for each intervention and at each representative location. The maximum concentration (number/ft³) value of each intervention and location, respectively, forms the base for risk factor calculations. The advantage with this approach is the uncomplicated, immediate registration of results using electronic discrete particle counters. The critical regions become contaminated only by non-viable particles, and this approach can be safely used in microbiological clean zones with no added risk of contamination.

In this study, the barrier technology was challenged with a smoke pencil during NTT to represent an airborne challenge (simulating total particulates into airborne microorganisms’ movements) and a particle counter was used to scan and map the particle movements.

The first step of risk assessment with the L-R method was a confirmation study that the de-bagger/NTT zone operates to Grade B with Grade A air supply and that the FlexPro 50 isolator modules meet Grade A (particles and microorganism levels) requirements. Figure 5 shows the testing environment and probe placement (P1–P8). The L-R method is performed in three steps:

1. Visualisation (by using the smoke technique) of the main air movements and identification of turbulent regions and critical vortices where contaminants can be accumulated or dispersed in an unpredictable way.
2. The particle challenge test, which identifies potential risk situations. It involves placing the probe of a particle counter in the critical area where during normal operations the product is exposed, and taking continuous total particle counts while generating particles in the surrounding air (e.g. by using air current test tubes) to a challenge level of more than 300,000 particles equal to and larger than 0.5 µm per cubic foot (~ 10⁷ particles per m³). These measurements were carried out during simulated tub transfer production activity.
3. The third step is to evaluate the risk situation by calculating the risk factor, which is defined as the ratio between measured particle concentration (number/ft³)
in the critical region and the challenge level in the surrounding air. Because of limited measurement accuracy at high concentrations, a value of 300,000/ft³ is used as a challenge level in all risk factor calculations.

**Experiment 2: Contamination transfer challenge studies**

The standard environmental monitoring technique selected to assess surface contamination transfer was contact plating. More extensive environmental monitoring was carried out as a control during set up to confirm the contamination control status of the testing environment. Due to the accuracy of Experiment 1 (L-R method) in visualising airborne contamination risk at ‘mouse-hole’ entry, settle plates were not sampled during NTT as it was considered there was no added value.

In this experiment, surfaces of the manufacturing set up were purposefully contaminated with human commensals as previously stated to be a ‘worst case’ scenario including the bag opening cutting knife and outer single steri-bag. A simple method of non-gloved hand inoculation was selected as the most likely ‘real world’ source of contamination over test isolates as a simulation for operator error. NTT was carried out and to check for contamination in Grade A areas via contact plating on the tub post-NTT, sampling of both the outer tub surfaces and inner Tyvek® cover was conducted to confirm maintained sterility (Figure 6).

The first step of the contamination transfer challenge studies was to confirm environmental control zones met EU GMP Annex 1/ISO 14644-1 environmental classifications. The zones included RABS (de-bagger) grade B zone, Grade A air supply at tub transfer point into Grade A filling isolator (de-lidding section), and de-lidding/filling Grade A isolator. The small batch isolator interior conformed to GMP Class A/ISO grade 5 conditions concerning particle limits and microbiological air quality. The de-bagger conformed to GMP Class B conditions concerning particle limits and microbiological air quality.

Furthermore, the UDF unit used for opening the first steri-bag (when used) conformed to Grade C and the cleanroom Grade D. Additionally, as a pre-qualification to the NTT studies, the tub outer surface was confirmed sterile inside a Grade A microbiology laboratory isolator independent of an NTT step. For this control test, the bag was manually surface disinfected then opened under Grade A conditions with good aseptic technique and contact plate samples of the tub surfaces taken to confirm they were sterile as per the manufacturers guarantee. Furthermore, active air sampling in the RABS–NTT at the critical material transfer location was carried out as a prequalification to ensure the RABS environment conformed to Grade B and critical tub transfer zone conformed to Grade A air supply (particulate and microbiological levels). Settle plating was also carried out in classification to prove the controlled environments met classification conditions. The following experiment was then carried out.

1. Inoculation of the challenge surfaces were carried out as shown in Figure 7. Initially, the tub outer bag was inoculated. The inoculum was human commensal from finger dabs. Inoculation of the outer bag was via human commensal skin contact onto each of the 10 tubs before the transfer process. The sample size selected was 10 tub transfers (single wrapped) from Grade C (preparation area) to Grade B (debagger, RABS) through the mouse-hole into a Grade A isolator. Bioburden studies were completed to confirm the human commensal challenge.
2. The study design for environmental monitoring sampling was via contact plates for each consecutive steri-bag before the NTT process step (outside the Grade A isolator) and directly on tub outer surfaces after the NTT process step and arrival into the Grade A filling isolator.

To reduce the amount of activity and materials in the Grade A isolator, tubs were recovered (in sterile bags) from the filling isolator after NTT and moved to a test isolator in an adjacent microbiological laboratory for inner Tyvek® tub lid surface contact plating.

3. Completion of an actual (not simulated) tub transfer procedure with NTT de-bagging into de-lidding/filling isolator.

4. Following the initial five tub transfers at the midway point in the experiments, the cutting knife (which opens the bag) was also inoculated. As before, it was inoculated with human commensals via direct skin contact and then the remaining five tub transfers were completed.

5. The focus of the study microbiological sampling during the NTT process steps was via contact plates on outer surfaces of the tub after transfer into the Grade A process isolator to confirm maintained sterility. Surface contact plate sampling of the sterile tub outer surfaces after transfer was undertaken as shown in Figure 8 (a) and in additional steps in a laboratory isolator (Figure 8 (b) and (c)) of inside the Tyvek® tub lid and on the top of the tub liner.

Contact plating was completed on the outer single steri-bag before NTT as a bioburden confirmation.

The first eight tubs had a single contact plate sample after the NTT process and the last two (worst case) tub transfers had duplicate contact plate samples to check tub top side and underside for sterility.

Figure 7. Inoculation procedure and example of recovered bioburden.

Figure 8. Contact plating of the tub inner and outer surfaces.
6. Incubation of contact plates for 36 hours then a further 7 days, which gives the best chance of detecting/visualising a range of microorganisms at formation growth states. The CFU were counted and recorded at these two timepoints\(^3,11\).

**Results**

**L-R method**

The challenge test (see step 2 in Experiment 1 method), was performed first with no activity in the preparation area or in the RABS de-bagger (Table 1), and then with a bag in the transfer opening (Table 2). After that, the challenge test was carried out during simulated activity (Table 3). From the measurements taken during these simulated situations, the third step – calculation of the risk factor – was performed. The results and calculated risk factors are shown in Tables 1 to 3.

When the risk factor is less than $10^{-4}$ (0.01%) during the challenge test, it is assumed there are no risks of airborne microbiological contamination during normal operational conditions according to experimental findings from more than 30 studied aseptic production lines\(^16\). The evaluation of NTT undertaken here with the L-R method demonstrated that the risk factors are low, thus there was no airborne microbial contamination during the tested activities.

Analysis of the L-R method highlighted that the following points should be considered. Firstly, in the tub loading preparation area, bags should not be stored along the inner wall of this zone and only on the pathway to ‘mouse-hole’ entry to the RABS–NTT zone as this was shown to disrupt airflow. Secondly, at entry to the RABS–NTT zone, a further NTT technique (using double bags) would provide a more controlled tub entry not only reducing risk of contamination transfer but also prevent possible adverse airflow movements at operator intervention process points.

**Results of Experiment 2: Contamination transfer studies**

Experiment 2 results are shown in Tables 4 and 5. A deviation from an expected result was that the initial bioburden at the cutting knife (before inoculation) was 1 CFU, but the plate growth was outside the streak line of the swab indicating a false-positive. However, false-positive or not, the 1 CFU was still below the 5 CFU not to exceed level of the de-bagging RABS–NTT zone so does not influence results. The results per sample type for contact plates are shown in Table 6.

Even with this worst case challenge, no contamination was detected in the Grade A area on tub surfaces.

The most probable root cause for the high counts at outer bag in bioburden studies (marked as red) is finger contact of contact plate edge due to operator error.

<table>
<thead>
<tr>
<th>Challenge region</th>
<th>Probe position</th>
<th>Particles per ft(^3)</th>
<th>Risk factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inside preparation area (II)</td>
<td>P2 In de-bagger</td>
<td>52</td>
<td>$1.7 \times 10^{-4}$</td>
<td></td>
</tr>
<tr>
<td>Outside, in front of de-bagger (III)</td>
<td>P4 In de-bagger</td>
<td>19</td>
<td>$&lt; 10^{-4}$</td>
<td></td>
</tr>
<tr>
<td>Inside de-bagger, on table</td>
<td>P4 In de-bagger</td>
<td>7192</td>
<td>$2.4 \times 10^{-2}$</td>
<td></td>
</tr>
<tr>
<td>Inside de-bagger, on table</td>
<td>P6 In de-bagger</td>
<td>5</td>
<td>$&lt; 10^{-4}$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Challenge region</th>
<th>Probe position</th>
<th>Particles per ft(^3)</th>
<th>Risk factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside, in front of preparation area (I)</td>
<td>P1 In preparation area</td>
<td>11</td>
<td>$&lt; 10^{-4}$</td>
<td>Bag in transfer area</td>
</tr>
<tr>
<td>Inside preparation area (II)</td>
<td>P2 In de-bagger</td>
<td>27</td>
<td>$10^{-4}$</td>
<td>Bag in transfer area</td>
</tr>
<tr>
<td>Outside, in front of de-bagger (III)</td>
<td>P4 In de-bagger</td>
<td>22</td>
<td>$10^{-4}$</td>
<td>Bag in transfer area</td>
</tr>
<tr>
<td>Outside, in front of de-bagger (III)</td>
<td>P6 In de-bagger</td>
<td>0</td>
<td>$&lt; 10^{-4}$</td>
<td>Bag in transfer area</td>
</tr>
<tr>
<td>Inside de-bagger, on table</td>
<td>P4 In de-bagger</td>
<td>11,585</td>
<td>$3.9 \times 10^{-2}$</td>
<td>Bag in transfer area</td>
</tr>
<tr>
<td>Inside de-bagger, on table</td>
<td>P6 In de-bagger</td>
<td>0</td>
<td>$&lt; 10^{-4}$</td>
<td>Bag in transfer area</td>
</tr>
</tbody>
</table>
### Table 3. L-R method – results from tests with simulated activity, transfer and opening of bags.

<table>
<thead>
<tr>
<th>Challenge region</th>
<th>Probe position</th>
<th>Particles per ft³</th>
<th>Risk factor</th>
<th>Response to activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inside preparation area (II)</td>
<td>P2 In de-bagger</td>
<td>53</td>
<td>1.8 x 10⁴</td>
<td>Low</td>
</tr>
<tr>
<td>Outside, in front of de-bagger (III)</td>
<td>P4 In de-bagger</td>
<td>8</td>
<td>&lt; 10⁴</td>
<td>Low</td>
</tr>
<tr>
<td>Outside, in front of de-bagger (III)</td>
<td>P7 In de-bagger at working height</td>
<td>15</td>
<td>&lt; 10⁴</td>
<td>Low</td>
</tr>
<tr>
<td>Inside de-bagger, in front of opening to isolator</td>
<td>P8 In isolator, close to opening to de-bagger</td>
<td>0</td>
<td>&lt; 10⁴</td>
<td>Low</td>
</tr>
</tbody>
</table>

### Table 4. Environmental monitoring results per sample type.

<table>
<thead>
<tr>
<th></th>
<th>Active air</th>
<th>Swab</th>
<th>Contact plates</th>
<th>Laboratory isolator settle plates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only sampled during qualification for classification of controlled areas</td>
<td>Swab of the cutting knife before and after deliberate contamination to confirm the bioburden (see Table 5)</td>
<td>Contact plates were taken before and after NTT from tub surfaces. The steri-bag outer was sampled before and after deliberate inoculation to confirm bioburden. After the steri-bag is removed by NTT the tub outer surfaces were plated in the test isolator. The tub inner surfaces with the Tyvek® lid removed were recovered from the test equipment and tested in a laboratory isolator to confirm sterility was not compromised during NTT as an independent confirmation study (see Table 6 for results).</td>
<td>Only sampled during qualification for classification of controlled areas. Settle plate positioning is shown in Figure 6. All settle plates showed 0 CFU recovery in critical test areas.</td>
<td></td>
</tr>
<tr>
<td>Isolator: 0 CFU</td>
<td>RABS: 1 CFU</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Confirmation of bioburden after inoculation.

<table>
<thead>
<tr>
<th>Position</th>
<th>Plate 1 (CFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knife bioburden in Grade B before inoculation</td>
<td>1</td>
</tr>
<tr>
<td>Knife after inoculation (positive control)</td>
<td>59</td>
</tr>
</tbody>
</table>

### Table 6. Results per sample type: contact plates.

<table>
<thead>
<tr>
<th>Position/tub sample number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer bag bioburden</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Outer bag after inoculation</td>
<td>9</td>
<td>27</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>15</td>
<td>9</td>
<td>83</td>
<td>34</td>
</tr>
<tr>
<td>Tyvek® outside, inside study isolator</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tyvek® inside laboratory isolator</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inner lid, laboratory isolator</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Growth round the edge of the plate is a possible sampling error and this was evident when investigated. Fortunately, these errors did not occur on the critical Grade A samples, i.e., those testing if the process is successful. Also higher bioburden on the outer bag at starting may be due to use of the ‘worst case’ challenge single steri-bagged tub passing through the lower class cleanroom. Usually the process would use double steri-bagged tubs at this stage and bioburden would be extremely low.

- For the outer bag No. 6, the CFU count of 29 was higher than the positive control (10).
- For the outer bag No. 10, it was visible that someone had touched the agar surface.

Discussion and conclusion

Although the sample size is small, the high level of ‘worst case’ challenge conditions make for compelling data to support the concept of NTT. No surface or airborne contamination was found in the Grade A zone after NTT. Visualisation of air movements alone provides an understanding of the situation but does not assure or measure the degree of microbiological safety of aseptic processes. Taken together, both the risk assessment with the L-R method and contamination transfer study are a good test of the NTT method and concept.

L-R method demonstrates NTT is a robust process

This study had some limitations, one of which is the fact that the experimental set up was a simulation of a real life medicinal product aseptic manufacturing filling line with the preparation area for initial tub loading limited for the study as a loading table and not having a raised conveyor as the final design for actual processing. The airflow movement in the experimental RABS–NTT with airflow protection (high-efficiency particulate air filters) suggest that the RABS–NTT barrier could be improved at the preparation entry. As this was a mock-up, it was useful to understand the impact of having a less well engineered tub entry zone on airflow movement in the RABS–NTT entry point as turbulence was found that should be avoided in a real world scenario to maintain good aerodynamic protection.

Classical microbiological sampling methods provide further evidence for method

Despite the high chance of contamination, these NTT studies show that the NTT process for tub transfer via a debagger unit complies with the stringent regulatory requirements for maintained sterility. Even with worst case situations (single packed tubs, transfer of human commensals, sub-standard gowning of operators, Grade D environmental surround), no contamination transfer occurred. Although the study was limited in challenge sample size and study runs, the significant worst case and compromised contamination conditions increased the confidence in the results.

To provide a high level of assurance that tub sterility is not compromised in transfer into filling lines, it is recommended that sterile tubs are double bagged on delivery. For an isolator filling line, as used in studies, the first bag is typically removed under UDF together with an NTT technique on entry to the RABS–NTT de-bagging system. The second (final) steri-bag would typically remain sterile on the outside or only have very low bioburden before the final bag is removed with the semi-automated NTT de-bagging system at entry into the Grade A filling zone. In the case of the research study, only a single steri-bag was used and there was no disinfection step for the outer bag surfaces, so the outer bag was contaminated before it passed into the RABS–NTT de-bagging zone presenting a further contamination challenge.

Next steps to further interrogate NTT

These experiments indicate that NTT is a secure process but further studies would be optimal to fully test the method. Furthermore, it may be appropriate to do case-by-case qualifications on site. Further studies could include analysis of a greater array of microbiological isolates, but in principal the most likely challenge from human commensals (handling of tubs, i.e. by fingers) has been tested.

More studies are recommended to add assurance and reference data, including more extensive environmental monitoring sampling, and an increased number of tub transfers to allow statistical analysis.

As the contamination control element of the NTT process relies on Grade A air supply, from down-flow air and out-coming air via the mouse-hole to the Grade A isolator, it is recommended that this airflow is well characterised with smoke studies and monitored (down-flow velocities) in process operations. As part of operational qualification, it is also recommended to include tub surface monitoring (to verify sterility and zero CFU recovery) in conjunction with environmental monitoring sampling for the controlled zones (RABS and isolator).

Adoption of new technologies for a new market

Alternative technologies are now starting to be considered for many applications in GMP, and NTT offers a simplicity and cost saving with flexibility that is much needed as new product profiles are developed with varying batch sizes and bio-compatibility requirements. Effectively the NTT process uses no decontamination chemicals and has no process residuals that can cause bio-compatibility challenges to biological products so provides added advantage at a cost saving.

This alternative process needs no bio-contamination step as tubs are assured as sterile in manufacture, through the supply chain to point of use and evidence is provided here that the NTT process is robust to prevent compromise of the tub sterility of Grade A filling environments.

The cost and expense of the existing tub decontamination technologies used in product manufacture such as eBeam do not necessarily suit small batch processing, e.g. clinical trial batches or small batch biological products.
Conclusions and recommendations

These microbiological and airborne particulate contamination studies were limited in study runs and range of environmental monitoring sampling but the challenge was considered greater than the aseptic processing worst case providing confidence in the results.

This is a very positive indication that NTT with tubs that start with sterile outer surfaces is a secure process without contamination transfer to the containers and filling environment; and that it is a viable alternative to transfer processes that require a tub surface decontamination step, e.g. eBeam or VHP®/vH202.

This is a contribution to knowledge and understanding and the indications are that NTT is a robust process and proves in principle the concept, but to ensure GMP compliance individual sites should independently undertake contamination control qualification testing and process monitoring. These results should apply to any isolator processing pre-sterilised containers but each site should conduct their own qualification studies and validation of all process steps, including NTT.

Following further research, microbiological contamination challenge studies at user sites may not be required with reference taken from peer-reviewed studies. User sites could benefit, however, from applying the L-R method with its visualisation and particle challenge test in NTT process qualification together with environmental monitoring of the controlled environments.

References

**Science and Technology Feature**

**Revision of ISO 14644-1:1999 and ISO 14644-2:2000 – A report on the changes, and explanation of some of the key issues and principles**

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**Introduction**

The October 2014 plenary meeting of the International Organization for Standardization (ISO) Technical Committee (TC) 209 made some important decisions about how a cleanroom should be characterised, and in December 2015 the revised versions of ISO 14644-1:1999 and 2 were published as ISO 14644-1:2015 and ISO 14644-2:2015. It is, therefore, a good time to look at some background to and principles of the changes.

The importance of ISO 14644-1 and 2 was emphasised at the TC 209 plenary meeting in Seoul when the TC members voted in favour of a resolution that required a cleanroom to be characterised first by air cleanliness by particle concentration, and then other attributes of cleanliness could be added as required by a specific application.

The development of these revised standards is important subject to the whole ‘cleanroom’ community because the specification of air cleanliness by particle concentration, and then other attributes of cleanliness could be added as required by a specific application.

The first DIS enquiry and vote in December 2010

It is useful to reflect on the publication of ISO draft international standard (DIS) 14644-1:2010 for review and national vote in 2010. Close followers of the ISO standardisation process for cleanrooms under ISO TC 209 will recall that ISO DIS 14644-1:2010 was published at the end of 2010 for the statutory 6-month first DIS review, comment and vote. As has been the case with the complete family of ISO TC 209 cleanroom standards, the technical enquiry and vote was undertaken in parallel within the Committee for European Normalisation (CEN) standards community. A convention, called the Vienna Convention, put in place to prevent unnecessary parallel work being carried out in CEN and ISO environments, was applied to this process and continues to be applied to all subsequent voting stages. ISO DIS 14644-2:2010 was also published in parallel.

The DIS enquiry and vote is always a very important stage in the standardisation process because it provides the essential forum for public comment and scrutiny of a proposed standard. A lengthy process of preparing equivalent English, French and German language versions is embarked upon, and formal comments are sought. The comments are then submitted back to the ISO central secretariat, together with a national vote. In the case of the first DIS enquiry in 2010, the national voting was in favour of approval of both ISO DIS 14644-1:2010 and ISO DIS 14644-2:2010 subject to comments being
addressed. There were numerous comments on these DIS documents, and the nature of the comments meant in reality that significant revision of the standards was required. The responsible ISO TC209 working group, WG1, decided that a second DIS enquiry and vote was required.

The second DIS enquiry and vote in November 2014
WG1 developed revised versions of the two standards for a second DIS enquiry and vote. This second DIS vote on ISO DIS 14644-1:2014 and ISO DIS 14644-2:2014 closed in November 2014. The voting outcome for both standards was a resounding positive vote to progress to a published standard. Participating members (P-members) of ISO TC 209 voted 18 from 20 for, and 2 from 20 against; and member bodies only offered 2 negative votes out of 23. Many of the P-member votes included constructive comments that WG1 were required to consider. The comments did not alter any key technical elements of the standards, but refined and improved some clauses. WG1 concluded that the standard should continue to the final DIS (FDIS) enquiry and vote stage. The WG1 experts worked on the revision in early 2015, and the FDIS enquiry and vote, with a parallel CEN process, was issued in August 2015 with a 3-month vote period. The vote passed with a strong majority, and the revised standards were published on 15 December 2015.

An overview of the revised documents ISO 14644-1:2015 – review of the key elements of the revised standard

Classification by table
The first most important change between the old 1999 standard is that classification Table 1 becomes the foundation and basis of classification. The advantage of doing this compared with the use of formula (as in the 1999 version) is that the table can be used more effectively to constrain and guide readers and users into choosing appropriate particle sizes and cleanliness levels. Historians of cleanroom standardisation will remember that this was the basis of US Federal Standard 209E5 and its United States predecessor standards.

Close inspection of the table will reveal some important changes compared to the 1999 version of the standard as follows.

- Removal of the 29 particle limit in ISO 5 for particle sizes ≥5.0 micron.
- A note identifying that ISO 9 should not be used for “at rest” classification.
- Significantly improved notes about the applicability of the table.

Informative Annex E has also been changed to include a new table on decimal cleanliness classes that

Table 1. Classification of air cleanliness by particle concentration.

<table>
<thead>
<tr>
<th>ISO Class number (N)</th>
<th>Maximum allowable concentrations (particles/m²) for particles equal to and greater than the considered sizes, shown below*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 µm</td>
</tr>
<tr>
<td>1</td>
<td>10⁶</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>1000</td>
</tr>
<tr>
<td>4</td>
<td>10,000</td>
</tr>
<tr>
<td>5</td>
<td>100,000</td>
</tr>
<tr>
<td>6</td>
<td>1,000,000</td>
</tr>
<tr>
<td>7</td>
<td>c</td>
</tr>
<tr>
<td>8</td>
<td>c</td>
</tr>
<tr>
<td>9⁹</td>
<td>c</td>
</tr>
</tbody>
</table>

* All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10,200 particles shown at 0.3 µm include all particles equal to and greater than this size.

b These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

c Concentration limits are not applicable in this region of the table due to very high particle concentration.

d Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

e Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

f In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size. (See C.7.)

g This class is only applicable for the in-operation state.
better recognises the sensitivity of particle counting instruments. The main changes in this Annex are as follows.

- **Removal of the graphical representation of the classes of cleanliness.**
- **A revised decimal class table with 0.5 steps from ISO 1.5 to ISO 8.5 in place of a table with 0.1 class number steps.**
- **Reintroduction of the well-known formula to allow calculation of the maximum particle concentration for classes between the defined particle sizes in Table 1.** For example if you wanted to know the maximum particle concentration for ISO 4 at 0.4 micron, you would use the formula (E1).

Formula E1

\[ C_x = 10^9 \times \left( \frac{K}{D} \right)^{2.08} \]

**The 5 micron problem – using the macro-particle descriptor for pharmaceutical GMPs requiring evaluation of 5 micron particles**

The removal of the 29 particle concentration limit in ISO 5 ≥5.0 micron has a significant meaning. It has been removed because it has been deemed an inappropriate particle size to consider for cleanroom or clean-zone classification. The large particle size threshold and low concentration of particles at the class limit is deemed to be unreliable for classification. In order that the Annex 1 requirements in the EU and PIC/S GMPs, as well as the similar requirements in the WHO and Chinese GMPs, are not left without a basis for classification or real-time monitoring, a new clause C.7 has been added in informative Annex C to address particle concentration of 20 and 29 particles per m² at the size threshold ≥5.0 micron. This Annex considers the so-called ‘Macro-particle Descriptor’ for characterising cleanliness for particle sizes ≥5 micron. Table 1 in the standard stops at the size threshold ≥5.0 micron, a subtle difference. The solution was to add a clause in the Annex to adapt the macro-particle descriptor specifically to address the 20 and 29 particle/m² limits for particle sizes ≥5.0 micron found in the GMPs. The clause includes guidance on the somewhat cumbersome nomenclature required. For the 29 particle limit, this would be expressed as “ISO M(29, ≥5µ); LSAPC”. This would be used in conjunction with the normal ISO 5 designation for particles ≥0.5 µm.

**Number of sampling locations and the statistics of sampling**

Now we come to probably the most important change in the classification standard. This concerns the number of sampling locations required, and the evaluation of the data collected. An abstract from the introduction to the revised standard best describes the principles.

“The most significant change is the adoption of a more consistent statistical approach to the selection and the number of sampling locations; and the evaluation of the data collected. The statistical model is based on the process of sampling from a finite population without replacement, and the statistical confidence obtained is based on an adaptation of the hyper geometric sampling model technique, where samples are randomly drawn without replacement from a finite population. The new approach allows each location to be treated independently with at least a 95% level of confidence that at least 90% of the clean room or clean zone areas will comply with the maximum particle concentration limit for the target class of air cleanliness. No assumptions are made regarding distribution of the actual particle counts over the area of the clean room or clean zone; while in ISO 14644-1:1999 an underlying assumption was that the particle counts follow the same normal distribution across the room. This assumption has now been discarded to allow the sampling to be used in rooms where the particle counts vary in a more complex manner. In the process of revision it has been recognised that the 95% UCL was neither appropriate nor was it applied consistently in ISO 14644-1:1999. The minimum number of sample locations required has been changed. A reference table is provided to define the minimum number of sampling locations required based on a practical adaptation of the sampling model technique. An assumption is made that the area immediately surrounding each sampling location has a homogenous particle concentration.”

To summarise, the major changes are as follows.

- **Introduction of a more consistent statistical probability of detecting out-of-specification locations in the classification process.**
- **Introduction of a look-up table to identify the number of sampling locations required.**
- **A simplified evaluation of particle counts data to determine the class of cleanliness of the space; with calculation of the 95% UCL now unnecessary for 1–9 sampling locations.**

The look-up table identifying the number of sampling locations ends at 1000 m². Thereafter, the number of locations is calculated pro-rata to the location density for 1000 m².

**Sample size at each sampling location**

This is unchanged from the current standard, and still applies the rule that the sample volume collected must be sufficient to ensure a count of 20 particles at the class limit for the largest considered particle size. The particle counting experts in ISO TC 209 WG1 were of the opinion that the current requirements, based on instrument sensitivity, were still reasonable.

**Evaluation of data from the classification test**

This is now a much simpler process than in the current standard. Effectively, each sampling location stands alone. If multiple separate samples are taken at any location, they should still be averaged, and then each location must simply comply with the class limit for the
cleanliness class of the cleanroom or clean zone to be confirmed.

ISO 14644-2:2015 – review of the key elements of the revised standard

The first most important aspect of this standard is the revised title. The focus is now clearly on monitoring of critical control points to provide evidence of being in control. In some circumstances, the minimum level of monitoring might be an annual classification of the cleanroom or clean zone. This explains the reason for the new title: “Cleanrooms and associated controlled environments — Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration”.

This revision of ISO 14644-2 emphasises the need to consider a monitoring strategy in addition to the initial or periodic execution of the classification of a cleanroom or clean zone in accordance with ISO 14644-1 clause 5.1. The monitoring activity provides a continuing flow of data over time, thereby providing a more detailed view of the performance of the installation.

Potential benefits gained from monitoring are as follows.

- Faster response to adverse events and conditions.
- Ability to develop trends from data over time.
- Integration of data from multiple instruments.
- Enhanced knowledge of installation and process allows more effective risk assessment.
- Improved control of operational costs and product losses.

The normative part of ISO 14644-2 specifies the requirements of a monitoring plan, based on risk assessment of the intended use. The data obtained provides evidence of cleanroom or clean zone performance related to air cleanliness by particle concentration.

In some circumstances, relevant regulatory agencies may impose supplementary requirements or restrictions. In such situations, appropriate adaptations of the monitoring procedures may be required. After a monitoring plan is initially established and implemented, it may be necessary to revise the plan when significant changes are made to the installation or process requirements. It is also prudent to conduct periodic reviews of a monitoring plan based on data obtained and experience in use.

The informative sections of the standard provide some guidance about the applications of continuous particle monitoring systems, and the monitoring of pressure differentials and airflow. There is also guidance on setting alert (if required) and action levels.

References


Background

Prior to the UK’s referendum on EU membership, the PHSS published a position statement entitled “The EU Referendum – Potential Impacts on the Pharmaceutical Industry and its Regulation”. Now that the referendum result is known, it is time for PHSS to update its members as to what is definitely known about potential impacts and the timescales which apply as well as our considered opinion as to future developments. This is the first such update, others will be provided as and when considered appropriate as new firm information/initiatives develop.

MHRA position

The Medicines and Healthcare Products Regulatory Agency (MHRA) has so far provided two position statements which, in general, serve to provide reassurance that all remains in control. The first such statement issued on 27 June 2016 could be summarised as:

- Continued focus on its public health role. Working with and supporting customers, partners and stakeholders to protect health and improve lives.
- Working closely with government to consider the implications for the work of the Agency.
- Continuing to make a major contribution globally to improving public health through the effective regulation of medicines and medical devices.

A further update on 15 July 2016 reassures that the MHRA will:

- Continue to provide the full service that companies in the UK have come to expect.

So, basically, the outcome for the present time of the Brexit decision appears to be “Business as usual”. See the full MHRA statements at https://www.gov.uk/government/news/medicines-and-healthcare-products-regulatory-agency-statement-on-the-outcome-of-the-eu-referendum

EMA position

The European Medicines Agency (EMA) recently issued a statement which may be summarised as:

- EMA acknowledges the outcome of the referendum of 23 June 2016. It is now up to the UK government to decide how to act upon the outcome of the referendum.
- EMA’s procedures and work streams are not affected by the outcome of the referendum. The Agency will continue its operations as usual, in accordance with the timelines set by its rules and regulations.
- No Member State has ever decided to leave the EU, so there is no precedent for this situation. The implications for the seat and operations of the EMA depend on the future relationship between the UK and the EU.
- The decision on the seat of the Agency will not be taken by the EMA, but will be decided by common agreement among the representatives of the Member States.
- The European Regulatory Network as a whole is a very strong and flexible system that is able to adapt to changes without jeopardising the quality and effectiveness of its work. For the time being, the Agency, its employees and all the European experts contributing to the EMA’s work will continue to focus on the EMA’s mission to protect human and animal health and ensure access to medicines that are safe, effective and of good quality.

Other comment

It is now clear that Article 50 needs to be used as the mechanism for agreeing the terms of leaving the EU. It is unlikely that this will be started until towards the end of 2016 and the process must be complete within 2 years from that point.

EU and MHRA pharma regulators have, over the years, had good productive relationships and cooperation, particularly in the fields of product licence review, regulatory inspections and information sharing. There is considerable workload sharing and mutual dependency in these fields. Both parties may well be reluctant to give this up. A mutual recognition agreement (MRA) should be relatively easy to formulate and, subject to political will, put in place. Indeed, one would expect that civil servants would have been working on this in the event of a Brexit vote. It should be remembered that existing EU pharmaceutical sector MRAs with third parties were part of wider trade agreements and put in place long before the wider agreements. So why could this not be the case between the UK and EU in respect of the pharmaceutical sector? One sticking point might arise over the inclusion of future Member States (the EU would probably insist that they are included, the MHRA might possibly differ and, for example, reserve the right to inspect in those states). If the UK enters a pharma MRA with the EU then it probably should, by default, also have them automatically with existing EU MRA partners.

If the UK and MHRA enter into an MRA, would there still be a need to relocate the offices of the EMA from London?

EU and Pharmaceutical Inspection Cooperation Scheme (PIC/S) regulation is and will remain aligned. The MHRA is committed to PIC/S so pharma good manufacturing practices are unlikely to drift apart.

The MHRA has a confidentiality agreement with the US Food and Drug Administration – there should be no change of status to this.

Malcolm Holmes
Introduction

Developments in the “regulation” of the pharmaceutical industry since our last review include the following.

Europe

• Improving safety of first-in-human clinical trials
• European Union (EU) good manufacturing practice (GMP) questions and answers (Q&A) – data required for sterilisation processes of primary packaging materials subsequently used in an aseptic manufacturing process
• European Medicines Agency (EMA) statement on the outcome of the UK referendum
• Transatlantic Trade and Investment Partnership (TTIP) – EU proposal for an annex on medicinal products
• Eudralex Volume 3 Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container
• Implementation plan for the introduction of the safety features on the packaging of centrally authorised medicinal products for human use
• European Directorate for the Quality of Medicines (EDQM) Annual Report
• Water purified
• New European Pharmacopoeia (Ph. Eur.) general chapter on host-cell protein assays
• Revised general chapter on monocyte-activation test (MAT) to facilitate reduction in testing on laboratory animals
• Survey on microbiological control of tissues
• Brexit Medicines and Healthcare Products Regulatory Agency (MHRA) position
• MHRA GxP Data Integrity Definitions and Guidance for Industry
• MHRA Blog

USA

• Quality Attribute Considerations for Chewable Tablets – Guidance for Industry
• Review of Grouped Product Quality Supplements
• Updating ANDA [abbreviated new drug applications] Labeling After the Marketing Application for the Reference Listed Drug [RLD] has been withdrawn
• E2C(R2) Periodic Benefit Risk Evaluation Report (PBRER) – Guidance for Industry
• Quality metrics technical conformance guide
• Elemental impurities in drug products
• Final guidances on interim policy for certain bulk drug substances used in compounding
• Compounded drug products that are essentially copies of a commercially available drug product

International

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

• PIC/S Seminar, Manchester (July 2016)
• Thailand's Food and Drug Administration (Thai FDA) accedes to PIC/S

World Health Organization (WHO)

• Technical Report Series, No. 996
• Supplementary guidelines on GMP for HVAC [heating, ventilation and air-conditioning] systems for non-sterile pharmaceutical dosage forms QAS/15.639/rev.1
• International Pharmacopoeia – Proposed revision of General Chapter 1.11 Colour of Liquids

Products

• Proposed reduction of use in animals of “last resort antibiotic” colistin to manage risk of resistance
• EMA recommends suspension of medicines over flawed studies at Semler Research Centre, Bangalore, India

Documents

• European Federation of Pharmaceutical Industries and Associations (EFPIA) annual regulatory GMP/good distribution practice (GDP) inspection survey
• Can regulators influence the affordability of medicines?
• Guide to information on human medicines evaluated by EMA
Europe

EMA

Improving safety of first-in-human clinical trials
The EMA has started a review of the guidelines that describe first-in-human clinical trials and the data needed to enable their appropriate design and allow initiation. This is being done in cooperation with the European Commission and the Member States of the EU. The review will identify which areas may need to be revised in light of the tragic incident which took place during a Phase I first-in-human clinical trial in Rennes, France in January 2016. The trial led to the death of one participant and hospitalisation of five others.

The aim of the review was to agree a concept paper by July 2016 identifying areas for change and proposals to further minimise the risk of similar accidents. The concept paper will form the basis for an EU-wide review of the guidelines. This process will include targeted discussions with stakeholders and a public consultation on proposed changes later in 2016.

EU GMP Q&A – data required for sterilisation processes of primary packaging materials subsequently used in an aseptic manufacturing process
Terminal sterilisation of the primary packaging, used subsequently during aseptic processing of the finished product, is a critical process and the sterility of the primary container is a critical quality attribute to ensure the sterility of the finished product. Both need to be assured for compliance with relevant pharmacopoeial requirements for the finished product and product approval.

The site where sterilisation of the packaging materials takes place may not have undergone inspection by an EU authority and consequently may not hold an EU GMP certificate in relation to this activity.

When GMP certification is not available, certification that the sterilisation has been conducted and validated in accordance with specific International Organization for Standardization standards would be considered to provide an acceptable level of sterility assurance for the empty primary container.

Statement on the outcome of the UK referendum
The EMA acknowledges the outcome of the referendum of 23 June 2016. It is now up to the UK government to decide how to act upon the outcome of the referendum.

The EMA’s procedures and work streams are not affected by the outcome of the referendum. The Agency will continue its operations as usual, in accordance with the timelines set by its rules and regulations.

No Member State has ever decided to leave the EU, so there is no precedent for this situation. The implications for the seat and operations of the EMA depend on the future relationship between the UK and the EU. The decision on the seat of the Agency will not be taken by the EMA, but will be decided by common agreement among the representatives of the Member States.

The European Regulatory Network as a whole is a very strong and flexible system that is able to adapt to changes without jeopardising the quality and effectiveness of its work. For the time being, the Agency, its employees and all the European experts contributing to the EMA’s work will continue to focus on the EMA’s mission to protect human and animal health and ensure access to medicines that are safe, effective and of good quality.

European Commission

TTIP – EU proposal for an annex on medicinal products
Under Article 1 of this agreement, points 8 & 9 state that:

- The Parties shall remove unnecessary duplications of testing, including animal testing and clinical trials carried out during the research and development phase of new medicinal products and remove duplications of inspections of manufacturing facilities. This can be achieved through the harmonisation of the Parties’ requirements for applications for authorisations of medicinal products and through the mutual recognition of their manufacturing facilities inspections.
- The Parties shall promote existing international and bilateral regulatory cooperation in the development, authorisation and access to medicinal products.

Furthermore, in Article 4 it is noted that:

- The Parties recognise that international organisations and bodies, in particular the World Health Organisation (WHO), the World Organisation for Animal Health (OIE), the Organisation for Economic Cooperation Development (OECD), the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), are relevant for developing scientific and technical guidelines with respect to medicinal products.

Article 7 provides that:

- A Party shall accept a certificate [corresponding US information] of Good Manufacturing Practice (GMP) compliance issued by a competent authority of the other Party, as demonstrating that the manufacturing facility that is covered by the certificate and located in the territory of that Party complies with GMP [corresponding US information]. The terms and conditions under which a Party accepts the GMP
will facilitate the implementation of the relevant standard of Documents Group (QRD) have revised the Human legislative requirements. The EMA and the Quality Review regulatory changes necessary to accommodate the new have prepared this implementation plan to guide applicants identification. The EMA and the European Commission medicines for the purposes of authentication and prescription medicines and certain non-prescription and an anti-tampering device (ATD) on the packaging of features, a unique identifier (UI) carried by a 2D barcode authorisation dossier; in particular, the placing of safety may impact on the product information and the marketing Regulation (EU) 2016/161 – “the Delegated Regulation”) Delegated Act on Safety Features (Commission Delegated Medicines Directive (FMD) 2011/62/EU and the new Certain aspects of the implementation of the Falsified medicinal products for human use of the Finished Dosage Form (human and veterinary) has been revised and included in this guideline.

Implementation plan for the introduction of the safety features on the packaging of centrally authorised medicinal products for human use
Certain aspects of the implementation of the Falsified Medicines Directive (FMD) 2011/62/EU and the new Delegated Act on Safety Features (Commission Delegated Regulation (EU) 2016/161 – “the Delegated Regulation”) may impact on the product information and the marketing authorisation dossier; in particular, the placing of safety features, a unique identifier (UI) carried by a 2D barcode and an anti-tampering device (ATD) on the packaging of prescription medicines and certain non-prescription medicines for the purposes of authentication and identification. The EMA and the European Commission have prepared this implementation plan to guide applicants and marketing authorisation holders (MAHs) through the regulatory changes necessary to accommodate the new legislative requirements. The EMA and the Quality Review of Documents Group (QRD) have revised the Human Product Information templates. The updated QRD template will facilitate the implementation of the relevant standard statements on the UI and its carrier under Sections 17 and 18 of Annex IIIA, in order for the MAHs to implement the safety features by 9 February 2019 as required by the Delegated Regulation. The inclusion of the safety features standard statements under Sections 17 and 18 of Annex IIIA does not indicate that the safety features have been actually implemented on the packaging placed on the market, but rather that the product information has been updated to confirm that the safety features will be implemented on the marketed packaging in line with the provisions of the Delegated Regulation (i.e. by 9 February 2019). The implementation of the ATD is not expected to impact the product information. However, when the ATD is placed on the immediate packaging because there is no outer packing, certain section(s) of the marketing authorisation dossier may be impacted.

EDQM
Annual Report
Within this document, it is reported that the EDQM’s Certification Division received 391 new applications for Certificates of Suitability (CEPs) in 2015, which is a significant increase compared to previous years (10% higher compared to 2014), and in addition the number of requests for revision rose by some 16% (almost 1900 requests). Most of the new applications and requests for revision which originated outside Europe came from India and China, reflecting the global trend for production of generic drugs.

As part of the EDQM inspection programme, 38 manufacturing sites located mostly in Asia were inspected with the participation of inspectors from national supervisory authorities. In addition, information on GMP compliance of 42 other sites was obtained by exchanging data with inspectorates from member states and international partners. This led to action being taken on CEPs where relevant. The rate of non-compliance for sites inspected by the EDQM was 18% in 2015. The EDQM inspection programme is fully embedded in the certification system and it is estimated that about 60% of the sites located in Asia and linked to CEPs have been covered by this programme.

Water purified
In this text for comment, in line with the Ph. Eur. implementation strategy of the ICH Q3D Guideline on Elemental Impurities, the test for heavy metals is deleted. However, to retain the aspect of control for elemental impurities, the ‘Purified Water in Bulk’ section of the monograph is revised to address the situation where purified water in bulk does not comply with the requirements for conductivity prescribed in Water For Injections (0169) in bulk.

New Ph. Eur. general chapter on host-cell protein assays
This general chapter provides guidance on the selection,
development and validation of a host-cell protein assay and describes specific considerations for process-specific, platform and generic assays.

**Revised general chapter on MAT to facilitate reduction in testing on laboratory animals**
The MAT is used to detect or quantify substances that activate human monocytes or monocyctic cells to release endogenous mediators which have a role in the human fever response. The MAT is suitable, after product-specific validation, as a replacement for the rabbit pyrogen test (RPT). The MAT offers significant advantages over animal testing: based on the human fever response, it provides a more relevant prediction of pyrogenic activity than the RPT. It can detect endotoxin and non-endotoxin pyrogens and is applicable to a greater variety of products than the RPT; moreover, it is more accurate as well as more cost- and time-effective than the RPT.

It is hoped that this revision of the general chapter will lead to a further reduction in the use of laboratory animals. The revised general chapter Monocyte Activation Test (2.6.30) will be published in the Ph. Eur. Supplement 9.2 and will come into effect in July 2017.

**Survey on microbiological control of tissues**
The aim of the survey is to gather information from relevant stakeholders to enable the Ph. Eur. experts in charge of the elaboration of this chapter to have a clear vision on the current situation regarding the characteristics of tissue preparations used in Europe and how they are monitored with regard to microbiological control. Completing the survey should take 5–10 minutes and should be done by 2 September 2016.

**MHRA**

**Brexit position**
The MHRA has so far provided two position statements which, in general, serve to provide reassurance that all remains in control. The first such statement issued on 27 June 2016 could be summarised as follows.

- Continued focus on its public health role. Working with and supporting customers, partners and stakeholders to protect health and improve lives.
- Working closely with government to consider the implications for the work of the Agency.
- Continuing to make a major contribution globally to improving public health through the effective regulation of medicines and medical devices.

A further update on 15 July 2016 reassures that MHRA will:

- Continue to play a full, active role in European regulatory procedures.
- Continue to contribute significantly in both the centralised and decentralised regulatory procedures, including new rapporteur and Reference Member State appointments.
- Maintain the programme for implementing the clinical trial regulation.
- Be actively engaged in European and national scientific advice services.
- Continue to participate fully in EU inspection-related duties.
- Continue to provide the full service that companies in the UK have come to expect.

So, basically, the outcome for the present time of the Brexit decision appears to be “business as usual”.

**GxP Data Integrity Definitions and Guidance for Industry**
This draft version for consultation provides guidance on the data integrity expectations that should be considered by organisations involved in all aspects of the chemical and pharmaceutical development lifecycle. The guidance should be read in conjunction with the applicable regulations and the general guidance specific to each GxP. Where GxP-specific references are made within this document (e.g. ICH Q9), consideration of the principles of these documents may provide guidance and further information.

Arrangements in place within an organisation with respect to people, systems and facilities should be designed, operated and, where appropriate, adapted to support a working environment and organisational culture that ensures data is complete, consistent and accurate in all its forms, i.e. paper and electronic. The effort and resource applied to assure the validity and integrity of the data should be commensurate with the risk and impact of a data integrity failure to the patient or environment. When taken collectively these arrangements fulfil the concept of data governance.

Organisations are not expected to implement a forensic approach to data checking on a routine basis, but instead design and operate a fully documented system that provides an acceptable state of control based on the data integrity risk with supporting rationale. In addition to routine data review, the wider data governance system should ensure that periodic audits are capable of detecting opportunities for data integrity failures within the company’s system, e.g. routine data review should consider the integrity of an individual data set, whereas the periodic system review might verify the effectiveness of existing control measures and consider the possibility of unauthorised activity. It should be noted that data integrity requirements apply equally to manual (paper) and electronic data. Organisations should be aware that reverting from automated/ computerised to manual/paper-based systems will not in itself remove the need for appropriate data integrity controls. Where data integrity weaknesses are identified, either as a result of audit or regulatory
inspection, companies with multiple sites should ensure that appropriate corrective and preventive actions are implemented across the organisation. Appropriate notification to regulatory authorities should be made where applicable.

Although not included in this guidance, the impact of organisational culture and senior management behaviour on the success of data governance measures should not be underestimated.

MHRA Blog
The latest editions of the MHRA Blog cover the following topics.

- Qualification of customers, what wholesalers need to know.
- Manufacture of Investigational Medicinal Products – Frequently Asked Questions.
- Enforcement Group - tackling the illegal trade in medicines.
- Refrigerated medicinal products, part 2: Transportation, packing, temperature management, the use of third party couriers and returns – some things to consider.
- Handling of unexpected deviations.

USA

Food and Drug Administration (FDA)

Quality Attribute Considerations for Chewable Tablets – Guidance for Industry
This guidance provides manufacturers of chewable tablets for human use with the Center for Drug Evaluation and Research’s (CDER’s) current thinking on the critical quality attributes that should be assessed during the development of these drug products. This guidance also provides recommendations about submitting developmental, manufacturing and labelling information for chewable tablets that must be approved by CDER before they can be distributed.

Chewable tablets are an immediate release (IR) oral dosage form intended to be chewed and then swallowed by the patient rather than swallowed whole. They should be designed to have a pleasant taste and be easily chewed and swallowed. Chewable tablets should be safe and easy to use in a diverse patient population: paediatric, adult, or elderly patients, who are unable or unwilling to swallow intact tablets due to the size of the tablet or difficulty with swallowing. The availability of safe, easy-to-use dosage forms is important in clinical practice. Chewable tablets are available for many over-the-counter (OTC) and prescription drug products.

The United States Pharmacopeia (USP) recognises and differentiates between two types of chewable tablets: those that may be chewed for ease of administration, and those that must be chewed or crushed before swallowing to avoid choking and/or to ensure the release of the active ingredient. The concepts in this guidance are applicable to both types of chewable tablets.

Review of Grouped Product Quality Supplements
This MAPP outlines the policies and procedures for grouping supplements submitted concurrently that provide for the same CMC changes to multiple approved new drug applications (NDAs), ANDAs and biological license applications (BLAs) and are submitted by the same applicant. The goal is to improve efficiency and provide consistency when reviewing these grouped supplements.

- When applicants make identical CMC post-approval changes that affect multiple approved applications, the Center needs procedures for reviewing these groups of supplements. Implementing these procedures helps the Office of Pharmaceutical Quality (OPQ) manage the review of these changes in an efficient manner and ensures consistency.
- This MAPP has been revised to replace the term “bundled supplements” with “grouped supplements”.
- The previous version of this MAPP applied only to supplements to NDAs (sNDAs). A related MAPP applied only to supplements to ANDAs.

Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn
This draft guidance describes a process for updating labelling for ANDAs in cases where the FDA has withdrawn approval of the NDA for the ANDA’s RLD for reasons other than safety or effectiveness. Where approval of the NDA for the RLD has been withdrawn by the FDA under these circumstances and ANDAs are pending or generic drugs continue to be marketed under one or more ANDAs that rely on the withdrawn RLD, the labelling of those pending or marketed ANDA products may need to be updated to reflect changes that would have been necessary had the NDA for the RLD not been withdrawn.

E2C(R2) Periodic Benefit Risk Evaluation Report (PBRER) – Guidance for Industry
This guidance defines the recommended format and content of a PBRER, and provides an outline of points to be considered in its preparation and submission. The PBRER described in this guidance is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions. This guidance revises, combines and replaces two ICH guidances: E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (ICH E2C addendum).
only be achieved if the guidance is implemented and interpreted in a consistent way across the ICH regions. In November 2012, the ICH Steering Committee endorsed the establishment of an Implementation Working Group (IWG) on E2C(R2) to assist with the implementation of the guidance. The IWG has prepared a Q&A document to support implementation of the guidance in practice. The Q&A document is intended to facilitate practical implementation of the PBRER, including points to consider in addressing some of the more novel aspects of the new periodic safety report.

**MAPP – Applying ICH Q8(R2), Q9, and Q10 Principles to Chemistry, Manufacturing, and Controls Review**

The number of NDAs, investigational new drug applications (INDs), ANDAs and BLAs and their supplements containing quality-by-design (QbD) approaches has increased. Because of this increase, the Center recognises the need for reviewers to consistently implement the ICH guidances in their reviews. As a result, the OPQ product quality reviewers will consider ICH Q8(R2), Q9 and Q10 recommendations when reviewing applications that may or may not include QbD approaches.

**Quality Metrics Technical Conformance Guide**

This draft guide serves as the technical reference for implementation of the draft FDA Request for Quality Metrics – Guidance for Industry. Both documents continue the FDA’s policy efforts to ensure successful implementation of the CDER’s objectives outlined in the Pharmaceutical CGMPs for the 21st Century in 2004. The FDA expects that quality metrics calculated from data that it collects will provide objective measures that, when used with additional internal data, will provide the Agency with indicators of the effectiveness of pharmaceutical manufacturing quality systems.

The goal of these metrics is to assure quality drug products are available to patients. The objectives of the CDER’s quality metrics program can best be achieved through collaboration and a shared understanding of standards for metric indicators and data exchange/reporting. This guide supplements the draft FDA Request for Quality Metrics – Guidance for Industry and provides recommendations about submission of information that will support the FDA’s calculation of quality metrics.

**Elemental impurities in drug products**

The USP worked closely with the ICH to align its new General Chapters with ICH Q3D. General Chapter <232> endorses a risk-based approach to the control of elemental impurities, such as described in ICH Q3D. Of the 24 elements for which ICH Q3D provides a permitted daily exposure (PDE), 15 are covered by General Chapters <232> and <233>. The ICH Q3D PDE values for those 15 elements were adopted in the General Chapters.

General Chapter <232> requires control of elemental impurities in finished drug products but does not require routine testing of the drug product. Depending on the source of an elemental impurity and the risk that its level in the finished drug product will exceed the PDE, alternative approaches can be taken. For example, routine testing could be performed on the components (active pharmaceutical ingredient (API) and excipients) instead of the finished drug product. If the risk that the amount of an elemental impurity will exceed its PDE in the drug product is sufficiently low, no routine testing for that impurity need be performed. General Chapter <232> requires assurance of compliance to the specified levels when elemental impurities are known to be present, have been added, or have the potential for introduction. Upon implementation, General Chapters <232> and <233> will replace General Chapter <231> Heavy Metals.

**Final guidances on interim policy for certain bulk drug substances used in compounding**

The FDA has issued two final guidance documents regarding the use of bulk drug substances in compounding under Sections 503A or 503B of the Federal Food, Drug, and Cosmetic (FD&C) Act. These guidance documents explain the FDA’s policy regarding the conditions under which the agency does not intend to take action against state-licensed pharmacies, federal facilities and licensed physicians (under Section 503A) or outsourcing facilities (under Section 503B) that compound drug products from bulk drug substances that cannot otherwise be used in compounding under these sections.

The FDA is issuing these guidance documents to avoid unnecessary disruption to patient treatment while the FDA evaluates the bulk drug substances nominated for use in compounding under Sections 503A or 503B of the FD&C Act. Additionally, these guidance documents clarify the process the FDA is using to evaluate these substances.

**Compounded drug products that are essentially copies of a commercially available drug product**

The FDA has created two draft guidance documents for comment only.

To qualify for exemptions under Section 503A of the Federal FD&C Act, a drug product must be compounded by a licensed pharmacist or physician who does not compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product, among other conditions. This guidance sets forth the FDA’s policies regarding this provision of Section 503A, including the terms commercially available, essentially a copy of a commercially available drug product, and regularly or in inordinate amounts.

Similarly, for a drug product compounded by an outsourcing facility to qualify for the exemptions under Section 503B of the FD&C Act, it must not be “essentially a copy of one or more approved drug products,” and must meet the other conditions in Section 503B. This guidance sets forth the FDA’s policies concerning the essentially a copy provision of Section 503B.
International

PIC/S

2016 PIC/S Seminar, Manchester (July 2016)
MHRA hosted the PIC/S Committee meeting, the PIC/S Executive Bureau meeting, and the PIC/S Annual Seminar in Manchester, UK.

This seminar, which was open only to member and non-member authorities of PIC/S, explored the current landscape with regard to inspection findings and trends, with a particular focus on data integrity issues, followed by examining the changes industry have on the horizon.

PIC/S–PDA API (Q7) Training, Puerto Rico (US) August 2016
API suppliers are subject to regulatory oversight, and need to know what regulators are looking for. ICH Q7 is the international standard that many regulators use to define GMP requirements for APIs. This seminar which is open to all offers the opportunity to learn from regulatory and industry experts on how these requirements are being interpreted and enforced. Additionally, there is an evening session on “What is Data Integrity?”

Thai FDA accedes to PIC/S
On 1 August 2016, the Thai FDA became the 49th PIC/S Participating Authority.

WHO

Technical Report Series No. 996
WHO Technical Report Series No. 996 successfully passed the 139th session of the Executive Board on Tuesday 31 May 2016. The following guidelines, as contained in the Annexes to the Expert Committee’s 50th report, are now recommended for use.

- Annex 1: Good pharmacopoeial practices (new)
- Annex 2: International Pharmaceutical Federation–WHO technical guidelines: points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products (new)
- Annex 3: Guidance on good manufacturing practices for biological products (revision), following its adoption by the Expert Committee on Biological Standardization on 16 October 2015
- Annex 4: Guidance on good manufacturing practices: inspection report, including a model report (revision)
- Annex 5: Guidance on good data and record management practices (new)
- Annex 6: Good trade and distribution practices for pharmaceutical starting materials (revision)
- Annex 7: Guidelines on the conduct of surveys of the quality of medicines (new)
- Annex 8: Collaborative procedure between WHO’s Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO prequalified pharmaceutical products and vaccines (revision)
- Annex 9: Guidance for organizations performing in vivo bioequivalence studies (revision)
- Annex 10: WHO general guidance on variations to multisource pharmaceutical products (new).

Supplementary guidelines on GMP for HVAC systems for non-sterile pharmaceutical dosage forms QAS/15.639/rev.1
A copy of this document and the associated form for comment can be found in the Members Area of the PHSS website – MH.

International Pharmacopoeia – Proposed revision of General Chapter 1.11 Colour of Liquids
In order to replace chromium (VI) salts in The International Pharmacopoeia, the procedure previously used to determine the colour of liquids will be replaced gradually with the corresponding procedure taken over from the European Pharmacopoeia.

(Note this document for comment has been circulated to a limited audience only for comment – MH).

Products

Proposed reduction of use in animals of “last resort antibiotic” colistin to manage risk of resistance
The EMA has launched a public consultation on the advice drafted by its Antimicrobial Advice Ad Hoc Expert Group (AMEG), and endorsed by the Committee for Medicinal Products for Veterinary Use and Committee for Medicinal Products for Human Use, to minimise sales of colistin for use in animals and restrict its use in animals to last resort treatment only. The deadline to provide comments is 26 June 2016.

The new advice is an update to AMEG’s 2013 opinion, which was requested by the European Commission following the recent discovery of a new mechanism of resistance in bacteria to colistin (caused by the mcr-1 gene), which has the potential for rapid spread. The gene can easily be transferred between different types of bacteria, potentially leading to rapid development of resistance.

EMA recommends suspension of medicines over flawed studies at Semler Research Centre, Bangalore, India
The EMA has recommended suspending a number of nationally approved medicines for which bioequivalence studies were conducted at Semler Research Centre Private Ltd, Bangalore, India. The Agency has also recommended that medicines currently being evaluated for authorisation and which rely only on bioequivalence studies from this site should not be authorised until bioequivalence is demonstrated using alternative data. Bioequivalence studies usually form the basis for approval of generic medicines.
Documents

**EFPIA annual regulatory GMP/GDP inspection survey 2015 data**
The EFPIA has published the most recent version of its survey of regulatory inspections carried out by regulatory authorities outside of their own country borders. Data is gathered annually from member companies.

**Can regulators influence the affordability of medicines?**
The growing problem of high medicine prices and its impact on the sustainability of healthcare systems is getting more and more attention in many countries around the globe. Regulators are willing to play their part in solving the problem and in facilitating continued access of patients to safe and effective medicines. In an article recently published in the *New England Journal of Medicine*, two representatives of the EMA, i.e. its Executive Director and Senior Medical Officer, as well as Heads of two national agencies discuss possible regulatory interventions.

Even though the pricing of medicines is clearly out of their remit, medicine regulators cannot ignore the current debate on the cost of medicines and can make a contribution to affordable care, explain the authors.

**Guide to information on human medicines evaluated by EMA**
The EMA publishes information on human medicinal products at various stages of their life cycles, from the early developmental stages through to the EMA’s evaluation of authorisation applications, post-authorisation changes, safety reviews and withdrawals of authorisation.

This guide describes the different types of information the Agency currently publishes for both centrally and non-centrally authorised medicines, as well as publication times and location on the EMA’s website. It aims to help stakeholders know what kind of information to expect on medicines undergoing evaluations and other regulatory procedures.

*Further information on these and other topics can be found in recent versions of the “Regulatory Update” on the PHSS website and on the websites of the relevant regulatory bodies and international organisations.*

*In addition, a list of useful websites can be obtained from: info@euromedcommunications.com*

*Regulatory review is prepared by Malcolm Holmes, an independent consultant with over 40 years’ experience in senior roles within the pharmaceutical industry.*

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**Convenience**

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Following on from the success of the PHSS conference in Manchester, UK on the challenges in sterile product risk-based manufacturing with good manufacturing practice (GMP), where 140 attendees joined the conference, the PHSS University College of London (UCL)-Q3P Annual Conference in September is also set to be a success with another high level of attendance. These two conferences, free to PHSS members, are now established as annual events.

A feature of the conferences is Discussion Panels where challenging topics are discussed giving a chance to consider harmonised best practice, clarity on ‘grey areas’ in GMP and insight into regulation changes. The discussion panels include subject matter experts, key opinion leaders and regulatory authority members who provide a valuable addition to presentations that follow a conference theme.

Ahead of this year’s Annual Conference, the PHSS Bio-contamination Special Interest Group is also meeting to discuss the important preparation of commentary guidance to the published/peer-reviewed PHSS Bio-contamination Technical Monograph 20, covering case study worked examples on environmental control and environmental monitoring process monitoring. Seven case studies have been identified from pharmaceutical filling (in different formats); processing advanced therapy medicinal products/investigational medicinal products/biologic products; active pharmaceutical ingredient processing; sterility testing; material transfers between controlled zones; and hospital pharmacy compounding. Project candidates have been secured as a basis to develop worked example guidance covering controlled area disinfection; environmental classification; fully completed risk assessments for environmental monitoring sample locations; environmental monitoring sampling plans/programs; and supportive sample incubation regimes. Different focus groups within the Bio-contamination Special Interest Group are developing guidance for each section of the guidelines and for specific case studies.

At the PHSS UCL-Q3P Annual Conference, the first of the guidance worked example case studies will be overviewed and other case studies detailed, so it is clear what this initiative covers and how this can be a real help to those involved in risk-based GMP. It is the first time the PHSS have undertaken an initiative to expand Technical Monograph guidance into worked examples that can be directly compared to specific applications at user sites. This supportive guidance will be reviewed by the Medicines and Healthcare Products Regulatory Agency before publication and shared with the USA Food and Drug Administration.

The PHSS continues to be a major resource in best practice guidance with an experienced team in support, fully open to collaboration with other not-for-profit associations. There is a principle in the PHSS that there is no competition in providing best practice knowledge and we remain open to share with all interested parties that follow the same ethos.

James L Drinkwater
Chairman of the PHSS
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