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European Journal of Parenteral & Pharmaceutical Sciences 2015; **20**(2): 43-44

Editorial: **Cross-contamination control – new requirements**

This is my last editorial as Editor-in-Chief of *EJPPS*. I have really enjoyed my time in the role, and hope my contributions have helped galvanise some thoughts in important regulatory and technical aspects of our industry. I would like to openly thank Sue Briggs, our Managing Editor for all her hard work with papers and articles during my time as Editor-in-Chief, and for keeping me in-line and on-time. I'm delighted to welcome our new Editor-in-Chief, Kay O'Hagan. Kay, of course, is a scientist by profession, and so will bring a different perspective to the role.

Kay is a qualified person and a microbiologist by training. She has experience in research and development, production, quality control and quality assurance. Most of her time in the industry has been with the manufacture, testing and release of steriles. Those who have worked with Kay know her as a compliance perfectionist, but with a wide pragmatic streak. I wish Kay best wishes for her time in the post.

So, for my final piece, I thought I should look at the new requirements for controlling cross-contamination in multi-product facilities. Chapters 3 and 5 of the *EU Guidelines to Good Manufacturing Practice* (GMP) were eventually revised in August 2014, for a phased implementation between 1 March 2015 and the 1 June 2016.

The most important aspect of these changes is to understand why the change was required, and to comprehend the fundamental nature of the new requirements. Prior to the revision, these chapters contained rather generalised and confusing language related to managing cross-contamination risk in multi-product facilities by a rather simplistic bracketing of active pharmaceutical ingredient (API) types. The language used was all around cytotoxic and highly potent compounds as well as sensitising agents. As the industry increasingly developed new APIs that could be considered toxic or sensitising agents, there was a strong probability that separate and dedicated facilities could become increasingly common because of the lack of a scientific rationale. The firms developing new therapeutic compounds were also finding that the production volumes of the new products were unlikely to be of blockbuster proportions, and, of course, this is compounded by undesirability of highly fragmented manufacturing operations. At the same time, manufacturing technology has significantly improved, in particular, the application of closed processing and isolator systems. These technologies themselves inherently reduce the risk of cross-contamination by environmental and personnel routes.

Taking all this into account, the time was clearly right for a scientific and risk-based approach to evaluating cross-contamination risk, the likelihood of occurrence, and suitable mitigation measures. Such evaluation then enables appropriate mitigation measures to be deployed by technical or management approaches. The European Medicines Agency Inspector's Working Party spent more than 5 years developing the thoughts before eventually coming up with the new requirements we now see in Chapters 3 and 5.

Prior to the final publication of the new regulatory guidance in August 2014, the International Society for Pharmaceutical Engineering developed its so-called "RiskMaPP" initiative. Within this initiative, the focus was on developing a clear understanding of the allowable daily exposure (ADE) to a medicine that would have no effect on the patient. In simple terms, the ADE became the amount of cross-contamination that could be tolerated, and one would assess the mechanisms of cross-contamination to establish if this level might be exceeded. Then appropriate measures should be applied to prevent crossing the boundary, and ultimately these measures might include completely separated and dedicated facilities. In the event that a substance presented a sensitisation risk at levels below detectable limits, then separated and dedicated facilities would be the norm. This expectation and requirement is still clearly in place for sensitising APIs, such as beta-lactams. It seems very likely that this industry initiative had some influence on the development of the EU Guidelines to GMP revisions, and I'll look at some of the key principles in the GMP guidance now.

Clause 3.6 sets out the requirements quite clearly. Most importantly, the default position is that separate and dedicated facilities are required when you cannot or fail to justify that the risk of cross-contamination cannot be adequately controlled. The controls can be technical and/or operational. The key determinant is the relevant residue limit of one

product in another derived from a toxicological understanding. If for some reason this cannot be satisfactorily determined by a validated analytical method, then safety should prevail, and segregation should apply. In clause 5, there are useful lists of mitigation measures that should be considered.

We are just starting to come to terms with these requirements, and they clearly present different problems for different parts of the industry. Those firms developing new APIs should have ready access to all the toxicological data, and should find it relatively easy to define the limits. Those firms manufacturing generic forms may find the new requirements very challenging initially, but it is anticipated that some common practice will be evolved quite quickly, whereby products are bracketed in a somewhat similar way to the approach we adopt for managing occupational health exposure to active substances. Furthermore, a reverse-acting approach has been suggested by some practitioners; whereby one evaluates the amount of cross-contamination that would be required to cause a problem, and then review the facility and process systems to establish if such a level of cross-contamination could realistically occur. From evaluations undertaken using a classic failure modes and effects analysis style of cross-contamination risk assessment, it is clear that dirty equipment is likely to present the greatest route for potential cross-contamination, and that transfer via ventilation systems is usually a very low risk, particularly when high-efficiency particulate air filters are inserted in a recirculation heating, ventilation and air-conditioning system.

So my final thoughts are that this is a really good positive example of constructive risk-based GMP, founded on science rather than confusing language or edict. It will, however, be challenging to reach consistent implementation across the breadth of the markets influenced by these new requirements in the EU and Pharmaceutical Inspection Cooperation Scheme GMPs.

Gordon Farquharson

CALL FOR PAPERS & ARTICLES

Dear Colleague,

We hope you enjoy the *EJPPS* and find it useful in your own speciality.

We are currently seeking new papers and articles for future issues of the journal and would like to invite you to contribute an article or review paper to the journal.

Our areas of interest are original papers and reviews on subjects that cover all aspects of the parenteral and pharmaceutical sciences, both practical and scientific, including but not limited to the following:

Sterilisation techniques; Isolator technology; Validation; Aseptic processing; Microbial detection methods; Packaging; Lyophilisation; Cleanroom design; Biotechnology; Preservatives; LAL testing; Process filtration.

One important area that has only received limited coverage in the journal is the hospital sector. We are specifically interested in covering areas such as contamination control in hospital pharmacies and also contamination control in the clinical settings such as operation theatres and hospital wards. We are also interested in articles on drug delivery/medical devices.

You may be aware that the journal has extended the range of submissions it will consider. The primary focus still remains the peer-reviewed paper. We have recently broadened the editorial policy to allow us to consider science and technology articles which are often more product or technology based, or provide important reviews on a facet of our industry. These articles receive editorial review, but will not be subject to the same strict peer-review process. They are classified under a separate Science and Technology heading in the journal.

We are writing to invite you and your colleagues to consider addressing some of the above suggestions in a paper for the journal. We would welcome any original papers or reviews you have researched on any of the above topics.

Thank you for your continued support

Yours sincerely

Gordon J Farquharson
Editor-in-Chief, *EJPPS*

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Settle plate exposure under unidirectional airflow and the effect of weight loss upon microbial growth

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Settle plates play an important part in the environmental monitoring programme and for the assessment of microbial settlement at key locations within cleanrooms, particularly when situated within unidirectional airflow devices. It is important that the exposure time of the settle plate is assessed to ensure that the proportion of weight loss (through the loss of moisture) does not result in a loss of growth-promoting properties. A second important concern is with avoiding cracks in the agar which might render reading sections of the exposed plate impossible. This paper outlines a case study to assess the exposure time through microbial growth promotion.

Key words: Environmental monitoring, cleanrooms, unidirectional airflow, settle plates, agar, microorganisms, microbial recovery.

Introduction

Environmental monitoring forms an important part of the bio-contamination control of pharmaceutical facilities. One element of this concerns the assessment of airborne microorganisms[1]. Monitoring the airborne contamination level of unidirectional airflow (UDAF) devices used for aseptic filling is an important part of environmental monitoring[2]. There are two 'standard' methods to assess the microbiological quality of the air: active (volumetric) air samplers[3] and settle plates. Both methods, although seeking to assess microbial airborne contamination, assess something different[4]. An active air sampler estimates the number of microorganisms, free-floating or carried on particles within a given size, within a cubic metre of air[5]. Whereas the settle plate provides an indication of any microorganisms which might settle out of the air due to gravitational effects. Here, most microorganisms are associated with physical particles which are large enough to settle out of the air-stream due to gravity (refer to Whyte, 1986[6]). Additionally, settle plates can provide information about interventions into the unidirectional cabinet, provided that the plate is in a representative location, as the person working within the critical zone could potentially deposit microorganisms into the air stream.

Settle plates typically consist of Petri dishes filled with a culture medium, such as tryptone soya agar (TSA), which is a general purpose medium. The amount of culture medium in a 90 mm diameter settle plate is typically 20–30 mL. Sometimes plates of a 140 mm diameter are used in order to provide a larger surface area. The work summarised in this paper refers to 90 mm diameter plates only.

Agar is a polymer made up of subunits of the sugar galactose, and is a component of the cell walls of several species of red algae (Class Rhodophyceae, of which the species Gelidium is the preferred choice of agar manufacturers) that are usually harvested in eastern Asia and California. Laboratory agar has a gelatinous appearance and the gel is maintained at room temperature. Agar is typically used in a final concentration of 1–2% for solidifying culture media, although different agars have different gel strengths. Agar has traditionally been used to grow bacteria rather than gelatine because the majority of bacteria will not degrade the agar, as would be the case with gelatine-based media. Specifications for bacteriological grade agar include good clarity, controlled gelation temperature, controlled melting temperature, good diffusion characteristics, absence of toxic bacterial inhibitors and relative absence of metabolically useful minerals and compounds.

TSA is a medium which contains enzymatic digests of casein and soybean meal, which provides amino acids and other nitrogenous substances making it a nutritious medium for a variety of organisms. To this, dextrose is added to provide the energy source and sodium chloride to maintain the osmotic equilibrium, whilst dipotassium phosphate acts as a buffer to maintain pH. These ingredients are added to agar which acts as the gelling agent.

Settle plates are exposed in aseptic filling zones, at determined monitoring locations, ideally positioned and exposed either side of the main activity in the room or UDAF cabinet, where the lids of the dishes are removed. The settling rate depends partly on the characteristics of the particles and

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on the airflows. Larger particles will tend to settle faster (due to gravitational effects) and settling is facilitated by still airflows (which should not occur within a correctly designed UDAF zone). Smaller particles have a lower tendency to settle due to air resistance and air currents. The principle behind settle plates is that most microorganisms in air are in association with particles. Generally the 'complete particle' (microorganism in association with the 'carrier') is 12 µm diameter or larger[7].

Outside of unidirectional air, such as a cleanroom, there is a greater degree of turbulence. The amount of air turbulence is proportional to the amount of time that particles remain suspended in the air. Thereby, the greater the amount of air turbulence the longer the particles will remain suspended in the air. This can influence the reliability of the settle plate; however, the additional use of active air samplers provides a further monitoring method for assessing the cleanroom cleanliness.

Settle plates are typically exposed for periods of up to 4 hours. An exposure time of 4 hours is recommended in the *EU Guidelines to Good Manufacturing Practice*, although individual settle plates may be exposed for less than 4 hours (and for pharmaceutical operations subject to other regulatory requirements, alternative exposure times may be considered.) The origin of the 4-hour time period is not recorded; although the reasoning will have included some attempt to quantify the deposition rate, as with x microorganisms being detected at a given location per hour(s) of exposure. Thus, the results from settle plates are normally recorded in terms of the number of colony forming units (CFU) settling per 4 hours of exposure.

Guidelines, such as the *EU Guidelines to Good Manufacturing Practice*, express recommended levels as CFU/4 hours. It is important to note that a CFU, as defined, can consist of one microorganism, or a pair, chain or bunch of microorganisms. Therefore, with the interpretation of settle plate data, the actual 'value' obtained, such as 1 CFU on a settle plate, could represent one microorganism or several microorganisms that were carried on a raft of skin detritus. Such uncertainty restricts the interpretative value of the settle plate[8].

Another major variable is the performance of the agar medium as this is likely to be affected by water loss (desiccation) over a 4-hour exposure period. The process of desiccation can be considered in terms of water loss or in terms of reduced access to moisture due to the formation of a 'skin layer' on the agar surface. Reduced access to moisture will reduce the growth-promoting properties of the culture medium leading to a failure of the plate to grow some or all of the microorganisms which might settle onto it. This can lead to an underestimate of the number of microorganisms through loss of culturability or viability, because different species respond to the sampling stress differently[9]. Desiccation tolerance in relation to microbial survival is linked to a switch to a metabolically inactive state as well as the ability to repair protein oxidation and DNA damage upon rehydration[10]. Recovery of such organisms is also influenced by the quality of the agar used to revive them.

It is incumbent upon each user of settle plates to assess the impact of agar desiccation. This will vary depending upon how the medium is manufactured (and the consistency of the manufacturing process); how the plates are stored before use; the agar fill volume; as well as the environment in which the plate is exposed. The weight loss tends to be greater when plates are exposed under a UDAF cabinet compared with exposure within a turbulent flow cleanroom. This difference is a result of the air velocity from the unidirectional environment. A related factor is particle bounce, which, although a more significant factor with active air samplers, can also accelerate the 'drying' of agar[11].

The type of agar and the incubation conditions will also affect the types of microorganisms recovered. Importantly, there is no set of 'universal' conditions, although the microbiologist can take steps to ensure that the agar is suitable for the types of microorganisms expected from cleanroom environments, especially in relation to aseptic processing. Research suggests that such microorganisms are typically Gram positive, with human skin commensals, such as the Staphylococci and Micrococci, representing the overwhelming majority of isolates[12]. The incubation conditions are related to whether the culture medium used in the settle plate is designed to capture both bacteria and fungi or whether two plates are to be used containing a general agar for bacteria and a selective agar for fungi. Where a single culture medium is used, a two-step incubation is often required, such as 20–25˚C for 2–5 days followed by 30–35˚C for 2–5 days. This is an important area that requires assessment[13].

This paper presents a possible approach in examining the effect of desiccation for settle plates exposed within a UDAF device and summarises a study that was undertaken to assess the weight loss of settle plates.

Study to examine the effect of weight loss

The purpose of the assessment was to show if settle plates retain the ability to support microbial growth after the maximum exposure time (which, as indicated above, is 4 hours). When designing a validation test protocol to examine the impact of weight loss, there are a number of factors which can be considered.

a) The type of culture medium.
b) The use of neutralisers in the culture medium (this may or may not be a factor depending on the application of the plates).
c) The placement of plates (locations and schedule).
d) The hydration state of the medium and the impact of this on the rate of desiccation.
e) The metabolic and physical state of any microorganism that may be deposited onto the plate surface.
f) The length of the exposure time.
g) The environment used (for example, exposure under a UDAF unit).

Considering these factors, there are different approaches which can be taken when designing a study. Three such approaches are as follows.

Approach 1

This approach is centred on the question: "should settle plates be exposed first and then inoculated with a microorganism post-exposure?" This condition demonstrates whether a plate retains the ability to support growth during the incubation period. The advantage with this approach is that exposing plates and inoculating them *after* 4 hours is a greater challenge because a microorganism is more likely to be deposited onto the surface of a settle plate some time during exposure rather than at the start of the exposure time. Furthermore, at the end of 4 hours the plates will have undergone maximum weight loss.

Approach 2

This second approach examines the question: "should settle plates be inoculated with a microorganism and then exposed?" The disadvantage with this approach is that it does not assess the ability of the plate to recover microorganisms at the end of the exposure time. Furthermore, inoculating the plates at the start of the incubation could potentially result in microorganisms being carried from the surface as the moisture evaporates, leading to an inaccurate challenge.

Approach 3

The third approach considers the question: "should plates be exposed first, then incubated for the maximum incubation time, and then inoculated with a microorganism to assess growth?" This is a variation of the first approach. Although it is of interest, it has too many variables to give meaningful data. For example, is the study an examination of settle plate exposure or of incubation time?

Weighing up the advantages of the different approaches, the first approach presents the greatest challenge because it accounts for physiological effects that occur during exposure and as a result of post-exposure incubation. For the example presented in this paper, the first approach was adopted.

Example study

The paper summarises a study that was undertaken at a cleanroom facility located in South-East England. The study was carried out using TSA settle plates of 90 mm diameter (approximate internal area 64 cm^2), with a 25 mL fill. The plates weighed 17 g prior to the agar fill. The plates were pre-poured commercially and subject to irradiation. Prior to use, the plates were stored at 20–25˚C for 5 days and were within the expiration date recommended by the manufacturer.

For the study, a combination of standardised type cultures were used (sourced from the American Type Culture Collection (ATCC)). These were the organisms recommended by the culture media manufacture for the assessment of growth promotion. These organisms were used to assess the suitability of each incoming batch. It was, therefore, deemed appropriate to use the same panel of organisms to assess the media after it had been subject to the exposure study. Moreover, these organisms generally presented the types that could be found within cleanrooms. In addition, two Gram-negative rods were added because settle plates can be used to monitor wash bays. The Gram-negative organisms selected were those described in the European Pharmacopoeia for media testing, representing Pseudomonad and non-Pseudomonad type Gram-negative organisms. Furthermore, two fungi were included. These represented the taxonomic groups filamentous fungi and yeast-like fungi, as well as being indicative of cleanroom fungi[14]. In addition to type cultures, two environmental isolates, isolated from cleanrooms in a manufacturing facility, were included.

The microorganisms were selected to be representative of different contamination sources: people, equipment and water. The microorganisms (bacteria and fungi) used in the study were as follows.

1. *Bacillus subtilits* (ATCC 6633)
2. *Candida albicans* (ATCC 10231)
3. *Staphylococcus aureus* (ATCC 6538)
4. *Escherichia coli* (ATCC 8739)
5. *Aspergillus niger* (ATCC 16404)
6. *Pseudomonas aeruginosa* (ATCC 9027)
7. *Staphylococcus epidermidis* (environmental isolate)
8. *Ralstonia pickettii* (environmental isolate)

The inoculation level used was designed to be of a low level (that is less than 100 CFU). This is a standard microbial challenge for the assessment of growth promotion.

The first part of the study was to measure the weight loss. Under a UDAF cabinet, four plates were exposed in the approximate locations shown in **Figure 1**. The plates were exposed on the surface of the cabinet (at 'working height'). The measured air velocity at the location of the plates was 0.49 m/s (this was within the range recommended in the *EU Guidelines to Good Manufacturing Practice*: 0.35 to 0.54 m/s).

The exposure time was 242 minutes. One set of four plates was exposed in preparation for testing against each of the eight microorganisms. Each microorganism was assessed on three occasions. Therefore, during the course of the study, 24 test sessions were performed and 72 test plates were exposed, incubated and challenged with microorganisms.

During the course of the study, plates were weighed at the following time intervals: pre-exposure (time zero); after 2 hours exposure, after 4 hours exposure and then at the end of incubation. The incubation conditions were 5 days at 20–25˚C followed by 2 days at 30–35˚C. This was undertaken because it conformed to the standard environmental monitoring regime applicable to the test laboratory. The weight of the test plates was compared with unexposed, but incubated, control plates.

Results

Data from one session, pertaining from one organism, is displayed in **Table 1**. The weight of the test plates was compared with unexposed, but incubated, control plates.

Table 1. Weight loss assessment for plates prepared for testing against one microorganism. The data relates to three control plates and three sets of four plates.

Test	Plate reference	Weight (g)				Percentage weight loss*
		Zero hours	2 hours	4 hours	Post-incubation	
Control	A	40.8648			40.3368	1.3%
Plates	B	41.4935			40.9675	1.3%
	C	40.2479			39.6236	1.6%
	Mean	40.87			40.31	1.4%
Test 1	A	40.8656	37.6864	33.0955	32.7016	19.98%
	B	41.7061	38.4254	34.6685	34.1966	18.01%
	C	41.2053	39.3663	36.4186	35.9480	12.76%
	D	40.3667	38.8215	36.0909	35.6763	11.62%
	Mean	41.04	38.57	35.07	34.63	15.61%
Test 2	A	40.6046	39.5601	34.4747	34.1558	15.88%
	B	40.2326	35.9606	34.2161	33.7754	16.05%
	C	41.8610	38.5509	37.6134	37.2118	11.11%
	D	42.7275	39.8943	36.4376	36.008	15.73%
	Mean	41.36	38.49	35.69	35.29	14.67%
Test 3	A	42.1058	39.2699	36.9409	36.4876	13.34%
	B	41.0372	38.1036	34.8957	34.4577	16.03%
	C	41.0017	38.1627	35.4506	35.0046	14.63%
	D	40.9041	38.9069	37.3340	36.9195	9.74%
	Mean	41.26	38.61	36.16	35.72	13.44%

* Calculated from: $\frac{\text{Post-incubation}}{\text{Zero hours}} \times 100 - 100$

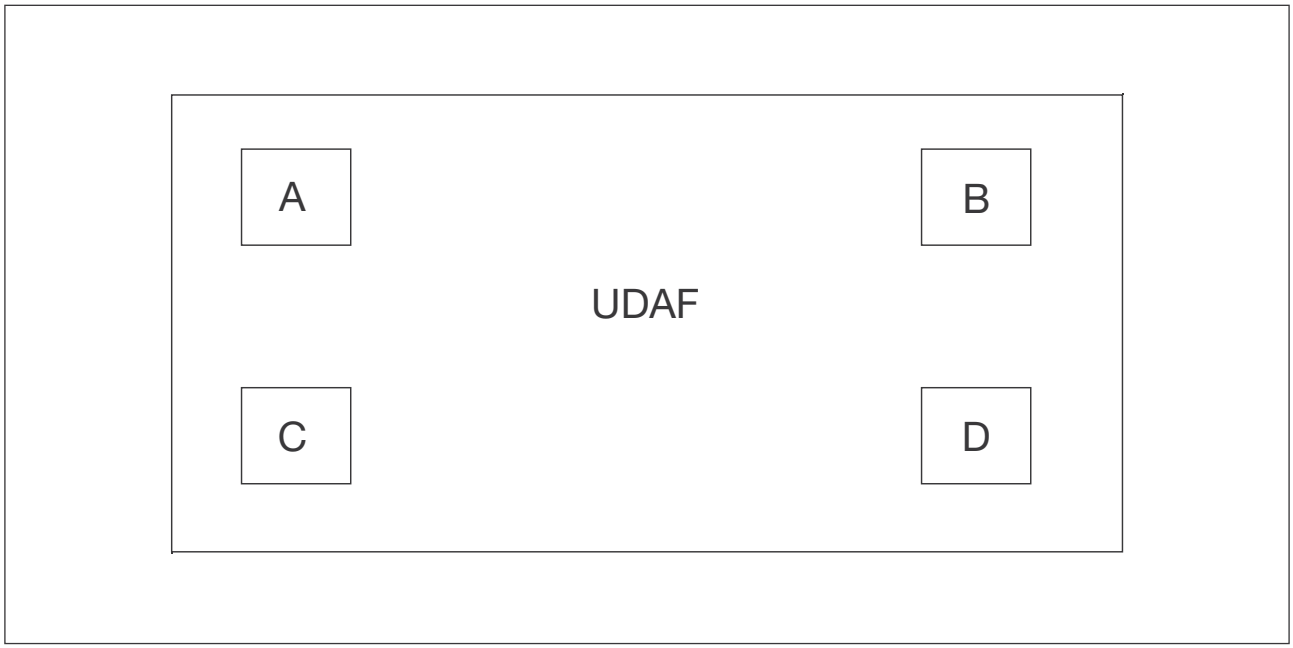

Figure 1. Approximate settle plate locations.

The data is summarised as the mean of all 72 exposed plates in the graph shown in **Figure 2**.

The graph demonstrates an initial rapid weight loss and then a steady reduction through to the end of the 4-hour exposure. A further reduction, albeit of a far smaller volume, occurred during incubation. Although the temperature and time post-incubation will vary across different laboratories, the data presented here suggests that it is not a major contributor to weight loss within the temperature range 20–35˚C over a 7-day period.

The data indicated that the typical weight loss was approximately 6 g (on average) from initial exposure to the end of the incubation. The minimum and maximum values and the standard deviations indicated that the values did not vary greatly and that most plates underwent a similar level of weight loss. In subtracting the highest recorded mean weight from the lowest mean weight (42.15–35.72 g), the maximum mean weight loss recorded was 6.43 g (or approximately 16% of the agar). The greatest weight loss from an individual plate was 20.2 g and the lowest weight loss recorded was 10.9 g. This was a relatively wide range.

The second part of the study involved testing the plates for microbial growth promotion after exposure. Following the inoculation of the plates with the microbial challenge, the plates were incubated for 3 days for plates challenged with bacteria and for 5 days for plates challenged with fungi. The microbial recovery from the test plates was compared with control plates, which were not subject to exposure. The acceptance criteria, using the US Pharmacopeia validation recommendation for microbiological examinations (chapter <1227>), was that the test plates had to recover ≥70% of the challenge. The study was repeated for each microorganism on three occasions.

The results of the study are summarised in **Table 2**. (The microbial counts are the mean counts across the replicate studies for illustrative purposes.) The microbial recovery data indicates that all the microbial challenges from the test plates were recovered within 70% of the control plates, with the lowest range of recoveries being recorded for the environmental isolates. This is unsurprising given that these bacteria would be in a relatively greater stressed state compared with laboratory cultures. With the successful recovery of all the microorganisms, it was demonstrated that settle plates can lose approximately 6 g (or 16%) of their weight and retain their ability to support growth.

A visual examination was made of each plate to look for evidence of cracks being formed across the agar surface. None were detected. Agar is generally resistant to shear forces; however, the addition of additives can cause chemical reactions that reduce the strength of agar. None of the plates used in the study contained additives like disinfectant neutralisers.

Conclusion

This paper has described a method which can be used to assess the weight loss from settle plates. Such a study is an important one for microbiologists who use settle plates to assess the environment within a UDAF setting. This is because a high weight loss may lead to the failure to grow microorganisms. Moreover, this is likely to be something that the microbiologist will need to demonstrate to a regulatory agency.

With the study presented, the air velocity remained relatively constant under the UDAF cabinet and the initial weights of the plates were within a relatively narrow range. However, the final weights of the plates were more varied, with the difference between the plate showing the greatest weight loss and the plate showing the least weight loss being around 12 g, suggesting that as the agar sets the solidification process is subject to biological variation.

Although the process of preparing agar and its use as a culture medium are much better understood, the process is still prone to variation. Culture media manufacturers will, by design (or sometimes accident), produce agars of different characteristics. Examples include processing with either a low or high temperature gelling or practising low syneresis (moisture loss). What is important is that the media has a constant gel strength to ensure good colonial growth[15]. Different characteristics suit different purposes. For example, high gel strength media will grow small colonies because the flow of nutrients and removal of toxins is reduced; whereas low gel strength media will allow the growth of larger colonies, but can be difficult to streak. Something midway is important for settle plates – robust enough to capture colonies, however, soft enough to allow colonies to be removed for subculturing and

Table 2. Microbial recoveries.

Microorganism	Test plate mean count (CFU) [A]	Control plate mean count (CFU) [B]	Percentage difference [A÷B × 100]	Comment
Bacillus subtilits	52	64	81%	Satisfactory
Candida albicans	31	33	94%	Satisfactory
Staphylococcus aureus	44	43	102%	Satisfactory
Escherichia coli	27	31	87%	Satisfactory
Aspergillus niger	45	44	102%	Satisfactory
Pseudomonas aeruginosa	62	70	89%	Satisfactory
Staphylococcus epidermidis	24	32	75%	Satisfactory
Ralstonia pickettii	19	25	76%	Satisfactory

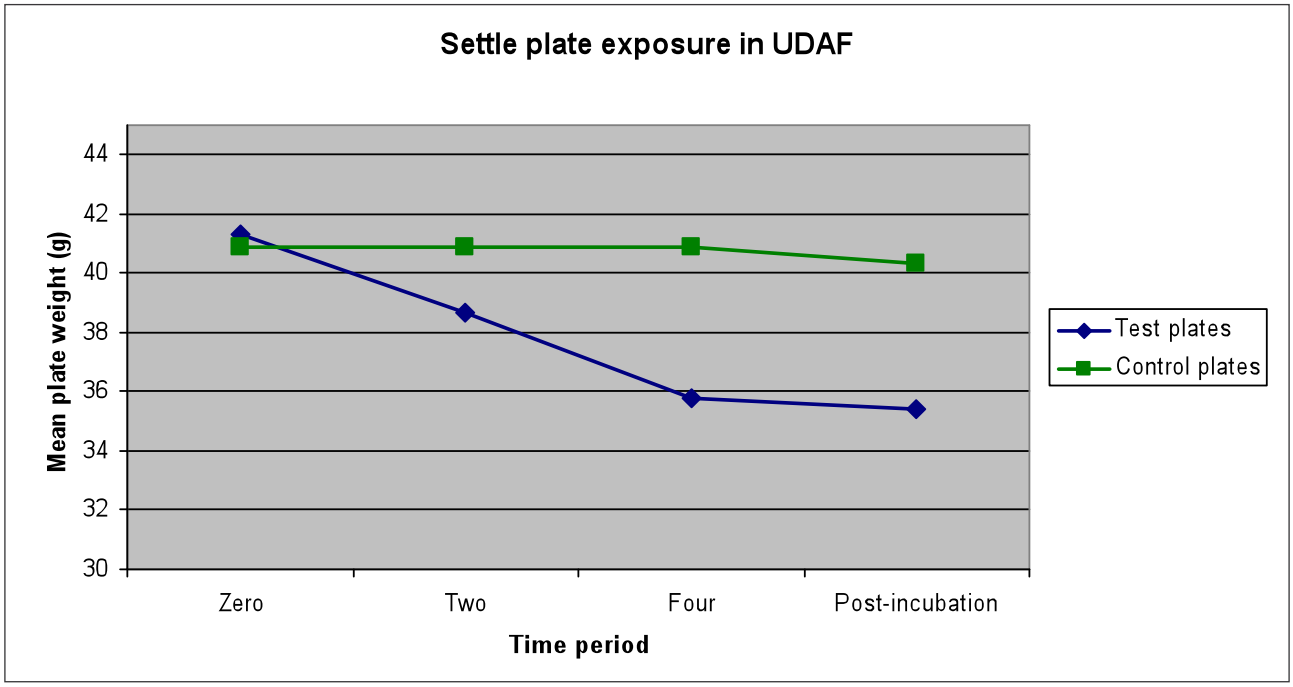

Figure 2. Plate weight loss over time.

eventual identification.

Ensuring adequate fill volume is similarly important and it is most likely that 90 mm plates prepared for use as settle plates will be designed to have a larger fill volume than those used to take personnel finger dabs or those that remain within the laboratory for plating out.

Despite the variation in weight demonstrated, each of the plates was able to recover successfully each microbial challenge and at a level high enough to meet the requirements of the acceptance criteria.

An important point with the study outlined is that of a case study. Such a study can only be performed by the microbiologist within a given facility because different types of culture media (different agars may have different gel strengths or degrees of stiffness) and the presence of additives (such as neutralisers, needed when plates of a similar design are used as finger plates) are important variables. In addition, different incubation regimes, and different unidirectional or cleanroom environmental conditions are further variables and ones that can only be demonstrated locally.

In the event that a study indicates that microbial growth is not recovered at a sufficiently high level then either the environmental conditions should be examined (such as rate of air velocity or the temperature and humidity of the environment). In most cases, these cannot (and probably should not) be adjusted since they serve a contamination control purpose. This brings attention to the way that the plate is prepared, including an assessment of the volume of agar added to the Petri dish.

There are some scenarios which might require a follow-up study. A further reassessment might be required if the type of culture media changes (such as the introduction of a dual media monitoring regime); or if the supplier of the media changes (which could result in a different fill volume); or if there is a major change to the design of the unidirectional air space.

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Assessment of degree of risk from sources of microbial contamination in cleanrooms; 1: Airborne

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The degree of risk from microbial contamination of manufactured products by sources of contamination in healthcare cleanrooms has been assessed in a series of three articles. This first article considers airborne sources, and a second article will consider surface contact and liquid sources. A final article will consider all sources and the application of the risk method to a variety of cleanroom designs and manufacturing methods.

The assessment of the degree of risk from airborne sources of microbial contamination has been carried out by calculating the number of microbes deposited from the air (NMD_A) onto, or into, a product from various sources. A fundamental equation was used that utilises the following variables (risk factors): concentration of source microbes; surface area of product exposed to microbial deposition; ease of microbial dispersion, transmission and deposition from source to product; and time available for deposition. This approach gives an accurate risk assessment, although it is dependent on the quality of the input data. It is a particularly useful method as it calculates the likely rate of product microbial contamination from the various sources of airborne contamination.

Key words: Risk assessment, degree of risk, source, airborne contamination, micro-organisms, microbe carrying particles, MCP.

Introduction

The requirements for minimising microbial contamination in pharmaceutical cleanrooms are in regulatory documents published by authorities that include the European Commission[1] and the Food and Drug Administration in the USA[2]. These authorities also suggest the use of risk management and assessment techniques to identify and control sources of microbial contamination[3,4]. The authors of this article have described risk management methods for products manufactured in cleanrooms[5–7], and risk assessment techniques to determine the relative importance of sources of microbial contamination[8,9]. An overview and discussion of other approaches is provided by Mollah *et al*. (2013)[10].

Risk is defined[11] as 'the combination of the severity of harm and the probability of occurrence of that harm', and can be calculated from Equation 1.

Equation 1

$$\textit{Degree of risk} = \textit{severity of harm} \times \textit{probability of harm}$$

The word 'criticality' is often used as a synonym for 'severity of harm'. 'Severity of harm' from microbial contaminants, when applied to products manufactured in cleanrooms, can be determined by the following risk factors.

a. The concentration of source microbes.
b. The area of the product exposed to airborne deposition or surface contact.
c. The ease by which source microbes are dispersed, transmitted and deposited into, or onto, a product.

The 'probability of harm' can be assessed by the frequency of deposition, which is either the number of surface contacts, or the time available for airborne deposition.

Actual values of these risk factors are often not available and surrogate descriptors, such as 'high', 'medium' and 'low', etc. are utilised. Scores are then assigned to these descriptors, and the scores combined in the best way to give an assessment of the degree of risk of a source[6,7].

The assignment of descriptors and scores to risk factors is subjective, and assigned values are often difficult to align with actual values. Also, the method of combining risk scores to obtain the degree of risk from a source may not accurately model the actual mechanisms of dispersion, transmission and deposition of microbial contamination. In addition, the mechanisms through air, surface contact and liquid are different, and the associated risks are, therefore, not readily comparable. Owing to these problems, inaccurate risk assessments are often

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completed, and it would be beneficial if a technique was available to overcome such drawbacks. This would be especially welcome if the risk assessment also calculated the product's contamination rate from various cleanroom sources, and would be a useful advance in the management of microbial contamination in cleanrooms.

Whyte and Eaton[8] have provided equations to calculate the exact amount of microbial contamination of a product and demonstrated their use in risk assessment; this approach is expanded in this article. This article deals with airborne sources and the next article will consider sources of surface contact and liquid contamination.

Calculation of airborne microbial contamination of a product

Equation 2 has been derived by Whyte and Eaton[8] to calculate the number of microbe-carrying particles (MCPs) deposited from air onto or into a product.

Equation 2

$$NMD_A = c*a*s_v*t$$

where, NMD_A = number of MCPs deposited from air onto a single product, c = concentration of microbes in the air next to the product, a = area of product exposed to microbial deposition, s_v = settling velocity through air of MCPs , t = time of airborne deposition.

It is important to ensure that the units of measurement are consistent in the risk equations, and those used in Equation 2 in this article are centimetres and seconds. Airborne concentrations are usually given as number per m^3, but to align the concentrations with other risk factors, number per cm^3 is used.

The above NMD_A is calculated from knowledge of the MCP concentration next to the product. However, some sources of airborne risk will be a distance away from the product, and in these situations it is necessary to know the proportion of MCPs transmitted to the area next to the product. This proportion is known as the transfer coefficient, which is the ratio of the concentration of MCPs at the product to the concentration at the source. This proportion is included in Equation 3.

Equation 3

$$NMD_A = c*p*a*s_v*t$$

where, p = proportion of MCPs that are transmitted from a source to the area next to the product (transfer coefficient).

The NMD_A onto one product unit is calculated, and gives the expected contamination rate of a product from a given source. Its numerical value is usually well below 1 but, if required, can be converted to a more conventional contamination rate. For example, if the NMD_A is 1×10^{-6}, the contamination rate of the product is 1 in 10^6, or 1 in a million units.

Most of the values of risk factors, i.e. the variables required to solve Equation 3, are known by cleanroom users, or can be determined. However, the settling velocity of MCPs falling through cleanroom air is not well known. MCPs rarely occur in cleanroom air in a unicellular form, but are found on skin or clothing detritus dispersed from personnel. The MCPs have an average equivalent particle diameter of about 12 μm[12,13], and settle under the influence of gravity at a velocity of about 0.46 cm/s[14]. It is assumed that the area of the product exposed to airborne contamination is the surface in the horizontal orientation. However, should the exposed surface be at an angle, the 'effective' area for MCPs that deposit under the influence of gravity will be reduced. It can be calculated by multiplying the area by Cos σ, where σ is the angle that the surface is to the horizontal.

Equation 3 uses the concentration of MCPs in a volume of air, as determined by a microbial air sampler. However, settle plates can be used to accurately and directly measure the deposition rate of MCPs. If a settle plate is used to sample air adjacent to product, its count can be used to calculate the NMD_A by proportioning and use of Equation 4.

Equation 4

$$NMD_A = \text{settle plate count} \times \frac{\text{area of exposed product}}{\text{area of settle plate}} \times \frac{\text{time product exposed}}{\text{time settle plate exposed}}$$

However, because of the greater popularity of air samplers in evaluating airborne microbial contamination, and greater availability of counts, air sampler concentrations are used in this article.

Description of cleanroom studied

A pharmaceutical cleanroom, where aseptic filling of vials is carried out, is used to demonstrate the NMD_A method. The cleanroom is fictitious but typical of those cleanrooms where aseptic filling of small batches of pharmaceutical products is carried out in a unidirectional airflow workstation, rather than in a restricted access barrier system (RABS) or isolator. Increasing regulatory expectations are leading to manufacturing facilities being designed with such separative devices, but to illustrate the wider application of the risk assessment method to a variety of healthcare facilities, the following cleanroom and manufacturing process is used as an example.

Vials with an internal neck area of 2 cm^2 are aseptically filled with 2 ml of an aqueous product solution and sealed with sterile closures. This is carried out in batches of 4000, which take about 4 hours to process.

1. The vials are heat sterilised in a depyrogenation tunnel and conveyed into a vertical unidirectional airflow (UDAF) workstation (EU Guideline to Good Manufacturing Practice (GGMP) grade A), which is known as the 'filling workstation', where they are automatically filled and sealed by inserting a stopper.

The average time the vial is open to airborne contamination, i.e. between exiting from the depyrogenation tunnel and being sealed, is 10 minutes (600 s).

2. Vial closures (rubber stoppers) are held in a hopper within the filling workstation, which has a capacity of 1000 closures, and is replenished every hour.
3. The air supply and extract system and the particle removal efficiency of the supply air filters are fully described in the relevant section of this article. However, all terminal filtration of the supply air is by H14 high-efficiency particulate air (HEPA) filters, as rated according to EN 1822: 2012[15].
4. The filling workstation is situated in a non-unidirectional airflow cleanroom (EU GGMP grade B) which is known as the 'filling cleanroom'. It is 10 m x 10 m x 3 m, i.e. 300 m^3 in volume, and supplied with 3.33 m^3/s of HEPA-filtered air, which is equivalent to 40 room air changes per hour.
5. Two people work in the filling cleanroom, with one of these attending to the filling machine within the filling workstation. Access into the filling workstation is through plastic-strip curtains that hang down to just above the floor.
6. Personnel wear cleanroom clothing consisting of a woven one-piece polyester coverall with hood, overboots, mask and goggles. Sterilised, latex, double gloves are worn over disinfected hands. There are no areas of exposed skin.
7. Hard surfaces, which do not come into contact with product, vials or closures, are disinfected. Hard surfaces, such as pipework that contact product, or product-contacting surfaces, such as sterile closures, closure's hopper and track-ways, are sterilised.
8. Eight litres of aqueous solution of product is prepared in an adjacent cleanroom (EU GGMP grade C) and piped from the preparation vessel through a sterilised, sterilising-grade filter, into the filling workstation. An aseptic connection is made in the filling workstation with the product filling equipment.

Sources of airborne contamination

Figure 1 shows the airflow in the cleanroom under consideration, and **Figure 2** gives a risk diagram that shows the various sources of airborne contamination, their control measures, and routes of transfer to product. Personnel are considered the prime source of microbial contamination in a cleanroom and disperse MCPs into the air of both the filling workstation and filling cleanroom. Airborne contamination may also enter the filling workstation and cleanroom through the HEPA supply filters, especially if they are damaged.

Calculation of degree of risk to product in cleanroom

The degree of risk from the sources shown in **Figure 2** can be determined by calculating the NMD_A into, or onto, one product vial. The NMD_A is calculated by use of Equation 3, using centimetres and seconds as the units of measurement. Each variable in the equation, i.e. the risk factors, is assigned a value that the authors consider 'typical' of the cleanroom described. For simplicity, and because it is peripheral and has a very small risk, the risk associated with 'air within adjacent cleanrooms', although included in **Figure 2**, is not calculated.

When sampling air in an EU GGMP grade A zone, only an occasional MCP is found, and most samples have zero counts. Average concentrations are, therefore, used, and calculated as the number of MCPs isolated from the total volume of air sampled over numerous consecutive operational periods. The average concentration of airborne microbes is required for the whole period when the product or closures are exposed

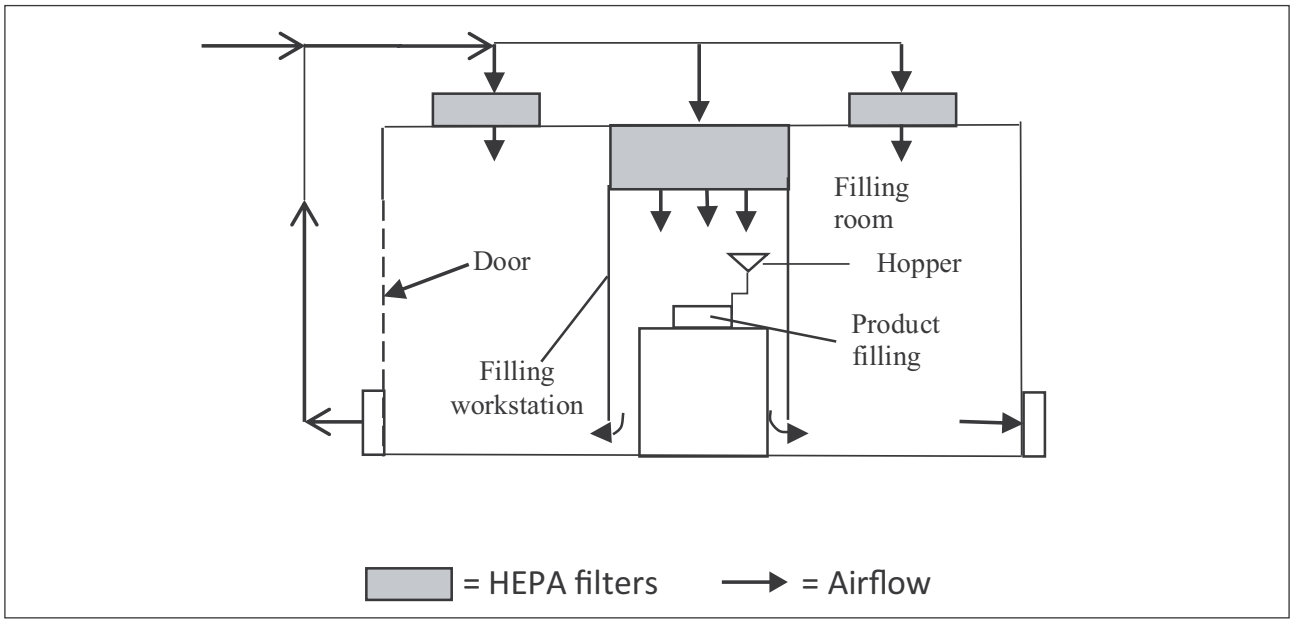

Figure 1. Airflow in a cleanroom.

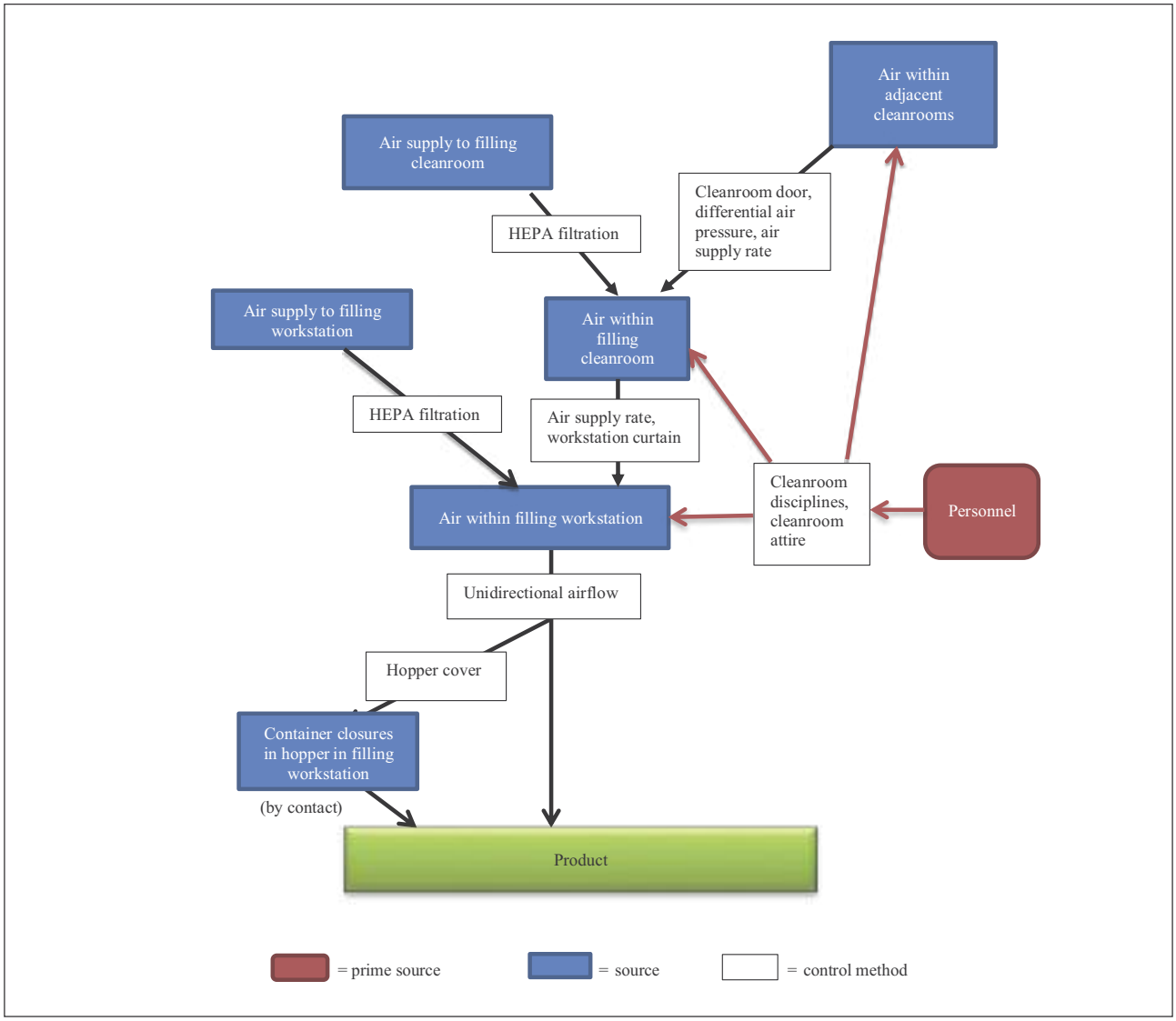

Figure 2. Risk diagram showing airborne sources of microbial contamination, control methods, and routes of transfer to product.

to microbial deposition. Microbial air sampling is often carried out for one single period during manufacture but, for the purposes of risk assessment, several samples should be taken to provide an average of the whole period of exposure, including periods when personnel are not in attendance.

Degree of risk from airborne MCPs dispersed by personnel within filling workstation

The average concentration of MCPs in the air of an EU GGMP grade A filling workstation during manufacturing depends on whether personnel work inside or from outside the workstation, the number of personnel involved, their time within the workstation, their activity, and type of cleanroom clothing worn. An average value should be ascertained over the whole of the manufacturing time. The lowest average value at the filling point is likely to be about 1 x 10^{-4}/m^3 (1 x 10^{-10}/cm^3) but the average concentration in our example is taken as 0.01/m^3 (1 x 10^{-8}/cm^3). To calculate the degree of risk to product from air in the filling workstation, the values of the variables (risk factors), and the solution of Equation 3, is considered as follows.

1. **Concentration of airborne MCPs (number/cm^3)**: An average concentration close to where vials are exposed during filling and over the whole of the manufacturing period is 0.01/m^3 (1 x 10^{-8}/cm^3).
2. **Transfer coefficient**: The air is sampled adjacent to the exposed vials, and, therefore, a transfer coefficient is not necessary, and taken as 1.
3. **Area of product exposed (cm^2)**: The inner neck area of the vial is 2 cm^2.
4. **Time of deposition (s)**: The time the vial is exposed is 600 s.
5. **Settling velocity of MCPs through air (cm/s)**: As discussed in the 'Calculation of airborne microbial contamination of a product' section, the average setting velocity of MCPs through the air and into the vial is assumed to be 0.46 cm/s.

Using Equation 3, the NMD_A can be calculated;
$NMD_A = c*p*a*t*s = 1 \times 10^{-8}*1*2*600*0.46 =$ **5.5×10^{-6}**

Degree of risk from airborne MCPs dispersed by personnel within filling cleanroom

The concentration of airborne MCPs in an EU GGMP grade B filling cleanroom during manufacturing is dependent on the effectiveness of the cleanroom ventilation system, the number and activity of personnel, and type of cleanroom clothing worn. Depending on these variables, the lowest average value is usually about $1/m^3$ ($1 \times 10^{-6}/cm^3$) but the average concentration in our example is taken as $5/m^3$ ($5 \times 10^{-6}/cm^3$).

It is necessary to know what proportion of MCPs in the filling cleanroom is transferred to product, i.e. the transfer coefficient. The filling workstation has a plastic curtain round its perimeter to minimise this transfer. However, personnel who move between the filling room and the filling workstation, or pass their arms through the curtains, will cause filling cleanroom air to be transferred into the filling workstation. Also, by working round the product and disturbing the unidirectional airflow, filling cleanroom air may be transferred to product.

Ljungqvist and Reinmuller[16] have measured the proportion of airborne particles that are transmitted from outside a unidirectional airflow workstation to product when personnel work through the curtain and around the workstation. Using this information, it is assumed that the proportion transferred (transfer coefficient) from the filling cleanroom is 1×10^{-4}. However, the time personnel spend in attending to machinery in the filling workstation is about 10% of the total time spent in the cleanroom. The time of airborne deposition of MCPs sourced in the filling cleanroom is, therefore, taken as 60s. The degree of risk to product from air in the filling cleanroom is now determined as follows.

1. **Concentration of airborne MCPs (number/cm^3)**: The average concentration in the filling cleanroom is taken as $5/m^3$ ($5 \times 10^{-6}/cm^3$).
2. **Transfer coefficient**: The proportion of MCPs in the filling cleanroom transmitted to product is assumed to be 1×10^{-4}.
3. **Area of product exposed (cm^2)**: The inner neck area of the vial is 2 cm^2.
4. **Time of airborne deposition (s)**: The time a vial is exposed to contamination originating in the filling cleanroom is 60 s
5. **Settling velocity of MCPs through air (cm/s)**: As discussed in the 'Calculation of airborne microbial contamination of a product' section, the average velocity of MCPs settling through the air and into the vials is 0.46 cm/s.

Using Equation 3, the NMD_A can be calculated;
$NMD_A = c*p*a*t*s = 5 \times 10^{-6}*1 \times 10^{-4}*2*60*0.46 =$ **2.8×10^{-8}**

Degree of risk from the filtered air supply

The previous two sections of this article have calculated the NMD_A of MCPs in the filling workstation and filling cleanroom. These calculations considered the risk from airborne MCPs dispersed by personnel working in these areas. However, there is also a degree of risk from the filtered air supply, and this is now considered.

Calculating the penetration of MCPs through air filters

The concentration of MCPs after an air filter is calculated by Equation 5.

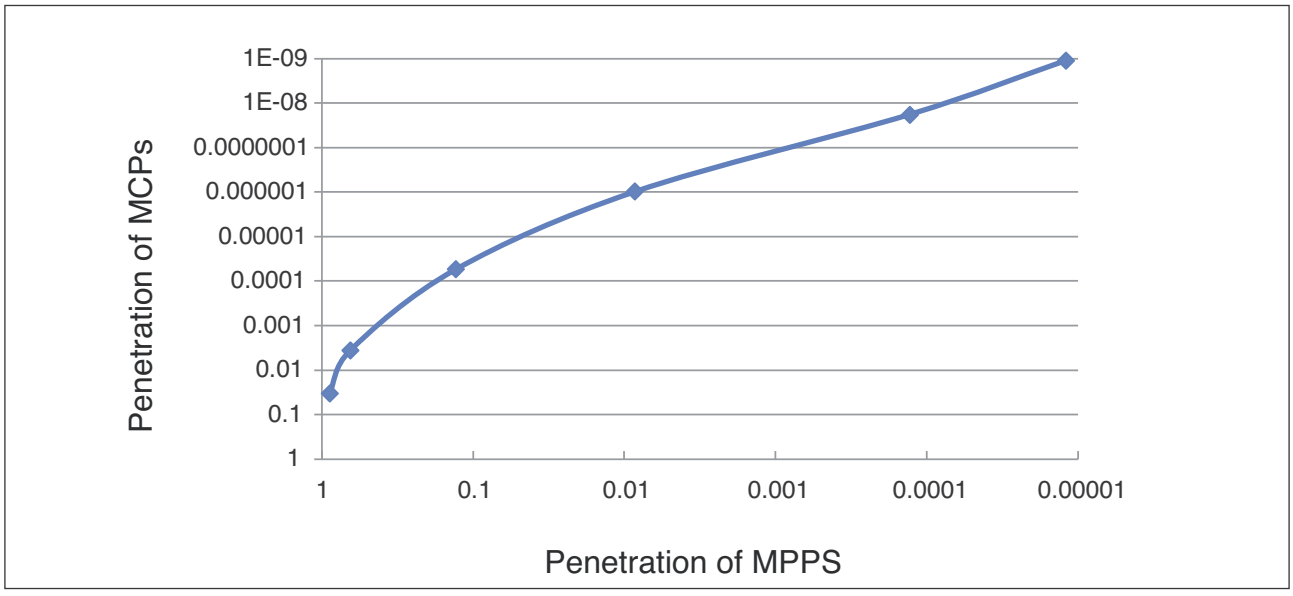

Figure 3. Relationship between penetration of most penetrating particle size (MPPS) and MCPs through high efficiency filters.

Equation 5

Concentration after filter = concentration before filter × penetration through filter

Air filters are rated according to their removal efficiency, which is usually given as a percentage, or to the proportion of airborne contamination that penetrates the filters. These two quantities are related in Equation 6.

Equation 6

Penetration = 1 – (removal efficiency/100)

The high efficiency filters used in cleanrooms are classified by EN 1822: 2009[15], which uses the removal efficiency of the filter's most penetrating particle size (MPPS) of about 0.3 μm. Because of their much larger size, fewer MCPs penetrate HEPA filters, and this relationship has been investigated[17] and shown in **Figure 3**.

Calculating the MCP concentration in supply air

The design of a typical air ventilation system used in a cleanroom is shown in **Figure 4**. Air is extracted from the cleanroom, mixed with some fresh air, passed through an air conditioning plant, and returned to the filling cleanroom and workstation. Fresh air is added for the health of the personnel, and to make up the total air supply so that the cleanroom is continually pressurised. This proportion of fresh air is about 0.1 of the total air supplied to the cleanroom.

Typically, fresh air is mixed with recirculated air and filtered by a primary filter before being passed through the air conditioning plant. The conditioned air is then filtered by a secondary filter to extend the life of the terminal filter, and reduce the contamination risk to the product, should a terminal supply filter in the ceiling be damaged.

The concentration of MCPs in the air supplied to both the filling cleanroom and workstation can be calculated by Equation 7. If necessary, this equation can be modified for other designs of ventilation systems.

Equation 7

$$C_S = (p_1 * C_R + p_2 * C_{FA}) * \eta_P * \eta_S * \eta_T$$

where;

- Cs is the MCP concentration supplied to the filling cleanroom and workstation,
- C_R is the MCP concentration in the filling cleanroom and recirculated air,
- C_{FA} is the MCP concentration in fresh air,
- p_1 is the proportion of recirculated air in the total air supply volume,
- p_2 is the proportion of fresh air in the total air supply volume,
- η_P is the proportion of MCPs removed by the primary filters
- η_S is the proportion of MCPs removed by the secondary filters,
- η_T is the proportion of MCPs removed by the terminal filters.

Fresh air has an MCP concentration of about 50/m^3, and the concentration in the filling cleanroom is assumed to be 5/m^3. The proportion of fresh air is 0.1 and, therefore, the proportion of recirculated air is 0.9. The mixture of fresh and recirculated air is filtered by primary filters, which are E10 bag filters with a removal efficiency against the MPPS of about 85% (penetration = 0.15) and, as given in **Figure 3**, they have an MCP penetration of about 1 x 10^{-4}. The secondary filters are H13, with a removal efficiency against the MPPS of 99.95%, and an MCP penetration of about 1 x 10^{-7}. The terminal H14 filters have a removal

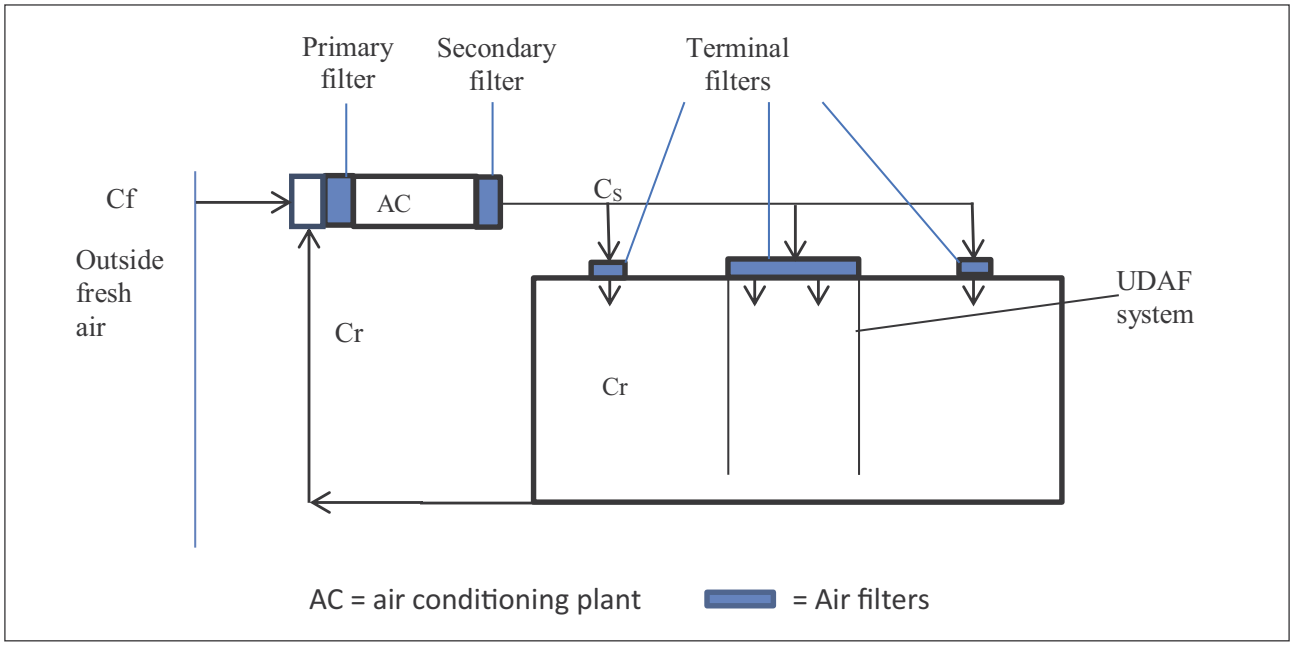

Figure 4. Typical cleanroom ventilation system.

efficiency against the MPPS of 99.995%, and an MCP penetration of about 1 x 10^{-8}.

The airborne concentration of MCPs supplied to the filling cleanroom and workstation is therefore:

$$C_S = \{(0.9*5 \times 10^{-6}) + (0.1*5 \times 10^{-5})\}*1 \times 10^{-4}*1 \times 10^{-7}*1 \times 10^{-8}$$
$$= \{(4.5 \times 10^{-6}) + (5 \times 10^{-6})\}*1 \times 10^{-19}$$
$$= 9.5 \times 10^{-25}$$

The concentration of airborne MCPs approaching and passing through a leak in the terminal HEPA filters will be required in later calculations. The air passing through the leak is assumed to be unfiltered by the terminal filter and, therefore, has the same concentration as the air supplied to the terminal filters. This can be calculated in the manner given in the previous paragraph, and is 9.5 x $10^{-17}/m^3$.

Degree of risk from air supplied into filling workstation by HEPA filters without leaks

If the filter system that supplies air into the filling workstation has no leaks, the NMD_A from the supply air can be calculated as follows.

1. **Concentration of MCPs in air supply (number/cm³)**: The filling workstation is supplied by air from the air conditioning plant that uses primary, secondary and terminal filters of the type described in the previous section. The average concentration of MCPs in the air supplied from the terminal HEPA filters, without leaks, has been calculated to be 9.5 x 10^{-25}.
2. **Transfer coefficient**: Air from the terminal HEPA filter in the filling workstation flows in a unidirectional manner to product and the airborne concentration at product is assumed to be the same as at the filter face, and the transfer coefficient is 1.
3. **Area of product exposed to microbial deposition (cm²)**: The inner neck area of the vial is 2 cm^2.
4. **Time of deposition (s)**: The time the vial is exposed is 600 s.
5. **Settling velocity of MCPs through air (cm/s)**: As discussed in the 'Calculation of airborne microbial contamination of a product' section, the average velocity of MCPs settling through air to vials is 0.46 cm/s.

Using Equation 3, the NMD_A can be calculated;
$NMD_A = c*p*a*t*s = 9.5 \times 10^{-25}*1*2*600*0.46 =$ **5.2×10^{-22}**

In some filling workstations, the air supply is not from the air conditioning plant but drawn from the filling cleanroom where the airborne concentrations of MCPs is 5/m^3 (5 x $10^{-6}/cm^3$). This air may be only filtered by the H14 terminal filters, with an overall removal efficiency of 99.995% (penetration = 0.00005) against the MPPS, and, therefore, a penetration of MCPs of about 1 x 10^{-8}. Thus, the airborne concentration of MCPs supplied by the terminal H14 filters in the filling workstation, as determined by Equation 5, is as follows:

$$C_S = 5 \times 10^{-6}*1 \times 10^{-8} = 5 \times 10^{-14}$$

Using the same approach as in the box above, the NMD_A is,

$$NMD_A = c*p*a*t*s = 5 \times 10^{-14}*1*2*600*0.46 =$$ **2.8×10^{-11}**

Degree of risk from air supplied into filling workstation by HEPA filters with a leak

HEPA filters are routinely tested for leaks by generating sub-micrometre particles before the filter and scanning the filter's supply face with a probe, so as to obtain the particle penetration through the filter. Leaks are considered to occur if the penetration of the particle challenge is greater than 0.01%.

The area of a leak is much smaller than the filter's supply face area, and as the airflow in the filling workstation is unidirectional, leaking air may pass through the filling workstation at sufficient distance away from the product vials that no contamination occurs. However, the leak may be directly above the vials, and this worst case situation is considered. Such a filter leak is considered when (a) air is supplied by the air conditioning plant or (b) air is drawn into the filling workstation from the filling cleanroom. A maximum leak of 100%, and a minimum of 0.01% are investigated in each of these situations.

(a) Air supplied by the air conditioning plant

A maximum leak of 100% in a terminal HEPA filter will only occur after an exceptional amount of filter damage, and it is assumed that the large hole made will allow the unfiltered supply air to pass through it. The NMD_A can be calculated as follows.

1. **Concentration of airborne MCPs (number/cm³)**: The average MCP concentration passing through a leak in the HEPA filter and into the cleanroom has been calculated in the 'Calculating the MCP concentration in supply air' section to be 9.5 x $10^{-17}/cm^3$.
2. **Transfer coefficient**: Air from the HEPA filter face flows in a unidirectional manner, and the concentration of MCPs at product is assumed to be the same as at the filter face, and the transfer coefficient is therefore 1.
3. **Area of product exposed (cm²)**: The inner neck area of the vial is 2 cm^2
4. **Time of airborne deposition (s)**: Although the time the vial is exposed is 600 s, vials are on a conveyor, and the time directly below a filter leak is considered to be 10 s.
5. **Settling velocity of MCPs through air (cm/s)**: As discussed in the 'Calculation of airborne microbial contamination of a product' section, the average settling velocity of MCPs through the air and into the vials is 0.46 cm/s.

Using Equation 3, the NMD_A can be calculated;
$NMD_A = c*p*a*t*s = 9.5 \times 10^{-17}*1*2*10*0.46 =$ **8.7×10^{-16}**

A minimum leak is taken as 0.01%, and these leaks are not usually an actual hole but broken fibres in the filter media, or a thinning of the depth of fibres. MCPs are, therefore, less likely to penetrate than the MPPS particles. However, the actual penetration of MCPs in this situation is unknown, and thus the worst condition is assumed, where the penetration of MCPs is the same as MPPS particles. It is also assumed that the filter leak is directly above the vials.

Therefore,

$$NMD_A = c*p*a*t*s = (9.5 \times 10^{-17}*0.0001)*1*2*10*0.46 = \mathbf{8.7 \times 10^{-20}}$$

(b) Air drawn from the filling cleanroom

If the filling workstation draws its air from the EU GGMP grade B filling cleanroom, the MCP concentration in the air approaching the filter can be assumed to be the same as in the filling cleanroom, which is 5/m^3 (5 x 10^{-6}/cm^3). For a maximum leak of 100% in the terminal HEPA filters, the NMD_A is,

$$NMD_A = c*p*a*t*s = 5 \times 10^{-6}*1*2*10*0.46 = \mathbf{4.6 \times 10^{-5}}$$

If the leak has a minimum penetration of 0.01%, the NMD_A is,

$$NMD_A = c*p*a*t*s = (5 \times 10^{-6}*0.0001)*1*2*10*0.46 = \mathbf{4.6 \times 10^{-9}}$$

Degree of risk from air supply to filling cleanroom

The risk to product from the air within the filling cleanroom has been considered in the 'Degree of risk from airborne MCPs dispersed by personnel within filling cleanroom' section. That section considers the airborne MCPs dispersed by personnel, but there may also be a contribution from the air supplied from the terminal HEPA filters. This may occur in a filter system with full integrity, or with a leak in the system.

(a) Full-integrity filtration system

The degree of risk from fully filtered air supplied to the filling cleanroom is calculated as follows.

1. **Concentration of MCPs in airborne source (number/cm^3)**: The average concentration of MCPs in the filling cleanroom attributed to the air supply is the same concentration as coming from the terminal air filters. Other MCPs in the air of the filling cleanroom that are dispersed by personnel are considered in the 'Degree of risk from airborne MCPs dispersed by personnel within filling cleanroom' section. The concentration from terminal filters has been calculated in the 'Calculating the MCP concentration in supply air' section and is 9.5 x 10^{-25}/cm^3.
2. **Transfer coefficient**: The MCPs in the cleanroom air must pass across the unidirectional airflow in the filling workstation, to reach the product. The proportion that does so has been discussed in the 'Degree of risk from airborne MCPs dispersed by personnel within filling cleanroom' section, and considered to be 1 x 10^{-4}.
3. **Area of product exposed (cm^2)**: The inner neck area of the vial is 2 cm^2.
4. **Time of deposition (s)**: The time the vial is exposed to MCPs from filters is 600 s.
5. **Settling velocity of MCPs through air (cm/s)**: As discussed in the the 'Degree of risk from the filtered air supply' section, the velocity of MCPs settling through the air and into vials can be assumed to be 0.46 cm/s.

Using Equation 3, the NMD_A can be calculated;
$NMD_A = c*p*a*t*s = 9.5 \times 10^{-25}*1 \times 10^{-4}*2*600*0.46 = \mathbf{5.2 \times 10^{-26}}$

(b) Leak in terminal filter system

The risk to product from a 100% penetration leak in a HEPA filter that supplies the filling cleanroom, is now considered.

The volume of air that passes through a hole in the filter system can be calculated by Bernoulli's equation. This requires knowledge of the area of the hole, the pressure difference across the hole, and the density of the air. The effect of the type of hole on the airflow volume is accounted for by a coefficient of discharge.

$$Q = C_D.A.\left[\frac{2\Delta p}{\rho}\right]^{0.5}$$

where, Q = flow rate (m^3/s), C_D = discharge coefficient, A = area (m^2), Δp = pressure difference (Pa), and ρ = air density (kg/m^3).

Using a pressure difference across a HEPA filter of 250 Pa, the area of a large hole in the filter media of 0.5 cm^2, a discharge coefficient of 0.7, and an air density of 1.225 kg/m^3, the air volume passing through the hole can be calculated to be 0.0007 m^3/s.

The air leaking through the hole in the filter will enter the filling cleanroom where it will mix with the rest of the air supply that has been correctly filtered. The total amount of air supplied to the filling cleanroom room is 3.33 m^3/s, and the volume of air from the leak is 0.0007 m^3/s. Therefore, 3.329 m^3/s of correctly filtered air will pass into the filling cleanroom.

The concentration of MCPs in leaking air has previously been shown to be 9.5 x 10^{-17}/cm^3 and in the filtered air it is 9.5 x 10^{-25}/cm^3. The air from the leak will mix in the filling cleanroom with the correctly-filtered air supply, and exit the room. The average concentration in the mixed air is obtained by proportioning the appropriate concentration of MCPs with the volumes of filtered and leaking air, is as follows:

$$\text{Average MCP concentration} = (9.5\times10^{-25}*3.329) + (9.5 \times 10^{-17}*0.0007) = 3.2 \times 10^{-24} + 6.7 \times 10^{-20} = 6.7 \times 10^{-20}/\text{cm}^2$$

Using this MCP concentration, the NMD_A can be calculated as previously shown.

$$NMD_A = c*p*a*t*s = 6.7 \times 10^{-20}*1 \times 10^{-4}*2*600*0.46 = \mathbf{3.7 \times 10^{-20}}$$

Degree of risk from airborne contamination of closures in the hopper

The hopper that contains closures is located within the filling workstation. If it is open to workstation air, MCPs may deposit from air onto closures and could subsequently be introduced into product.

If the hopper is cone shaped, the surface area of stoppers exposed to deposition of MCPs will diminish as stoppers are used. To give an approximation of the average area of closures exposed, the area is taken as half the surface of the top of the closures in the full hopper. The degree of risk to product of vial closures is now calculated as follows.

1. **Concentration of MCPs in the air (number/cm^3)**: The average MCP concentration over the period that the closures are exposed to airborne deposition is assumed to be the same as that suggested in the 'Degree of risk from airborne MCPs dispersed by personnel within filling workstation' section for the concentration at the filling location, and is 1 x 10^{-8}/cm^3.
2. **Transfer coefficient**: The concentration of MCPs is measured adjacent to the hopper, and a transfer coefficient is not necessary, or taken as 1.
3. **Area of product exposed to deposition (cm^2)**: The diameter of the hopper opening is 50 cm, with an associated surface area of 1964 cm^2. The average surface area exposed to airborne deposition is therefore assumed to be half of this surface area, i.e. 982 cm^2.
4. **Time of airborne deposition(s)**: The closures are replenished 4 times throughout the 4-hour filling operation. The time the closures are exposed to airborne deposition is therefore 3600 s.
5. **Settling velocity of MCPs through air (cm/s)**: As discussed in the 'Calculation of airborne microbial contamination of a product' section, the average settling velocity of MCPs in the air and into vials is 0.46 cm/s.

Using Equation 3, the NMD_A onto all closures in the hopper is;

$NMD_A = c*p*a*t*p = 1 \times 10^{-8}*1*982*3600*0.46 = 1.6 \times 10^{-2}$

This contamination will be deposited onto some of the 1000 closures in the hopper. Also, when a closure is inserted into a container, only about half of its area is in the container, and half the MCPs are introduced. Therefore, for one stopper, the NMD_A can be calculated;

$NMD_A = 1.6 \times 10^{-2}*1 \times 10^{-3}*0.5 = \mathbf{8.1 \times 10^{-6}}$

Hoppers can also be used with air-tight lids to minimise airborne contamination. However, when the lid is lifted and closures added to the near-empty hopper, the general air turbulence will cause most of the hopper air to be exchanged for filling workstation air. Also, because of higher activity of personnel during replenishment, and greater exposure to air transmitted across the curtains, the concentration of airborne MCPs round the hopper during the period of replenishment will be higher than the average taken over the whole of the manufacturing time, and assumed to be 1 x 10^{-7}.

The hopper has a height of 15 cm and radius of 25 cm, and hence its volume ($\pi . r^2 . h/3$) is 9818 cm^3. After the closures have been added, and the hopper lid shut, the number of MCPs sealed in the hopper are,

Number of MCPs sealed in hopper
= volume of air in hopper x concentration MCPs in air
= $9818*1 \times 10^{-7} = 9.8 \times 10^{-4}$

As MCPs have an average deposition velocity of 0.46 cm/s and 3600 s to deposit, it is reasonable to assume that most of the MCPs sealed in the hopper will deposit onto some of the 1000 closures in the hopper. Also, when a closure is inserted into a vial, only about half of its area is in the container, and thus only half the MCPs are introduced. Therefore, for one stopper, the NMD_A can be calculated to be,

$$NMD_A = 9.8 \times 10^{-4}*1 \times 10^{-3}*0.5 = 4.9 \times 10^{-7}$$

Relative importance of sources of airborne contamination

Shown in **Table 1** are the NMD_A of sources of airborne contamination found in the cleanroom used as an example. The NMD_A values are given in order of importance.

Discussion and conclusions

The risk to a product from sources of airborne microbial contamination in healthcare cleanrooms has been assessed. This was carried out by calculating the number of microbes deposited from air (NMD_A) into, or onto, a product. The NMD_A was calculated by use of Equation 3, which uses the following risk factors as variables: concentration of source microbes; area of product exposed to airborne deposition; the ease of microbial dispersion; transmission and deposition from a source to a product; time available for deposition to occur. Equation 3 is a fundamental equation and if the values of the risk factors are correct then the result will be exact. There are other advantages to this method, as the calculation of the degree of risk of sources is more accurate than typical methods in use, and it also gives the actual contamination rate of the product.

Many of the risk factors required to solve Equation 3 are available, or can be obtained. Even if this is not possible, an informed assessment will lead to a more accurate risk value than methods used at present. Much of

Table 1. Importance of sources of airborne microbial contamination in a pharmaceutical cleanroom.

Risk importance	Source of airborne microbial contamination	NMD_A
1	**Filling workstation (EU GGMP grade A) filters** – air drawn from filling cleanroom, 100% leak in filter directly above vials	4.6×10^{-5}
2	**Closures hopper** – closures in open hopper	8.1×10^{-6}
3	**Filling workstation (EU GGMP grade A)** – MCPs generated by personnel working in workstation	5.5×10^{-6}
4	**Closures hopper** – closures in lidded hopper	4.9×10^{-7}
5	**Filling cleanroom (EU GGMP grade B)** – MCPs generated by personnel in room	2.8×10^{-8}
6	**Filling workstation (EU GGMP grade A) filters** – air supply drawn from filling cleanroom, 0.01% leak in filter directly above vials	4.6×10^{-9}
7	**Filling workstation (EU GGMP grade A) filters** – air drawn from filling cleanroom, no leaks in filter	2.8×10^{-11}
8	**Filling workstation (EU GGMP grade A) filters** – air supply from air conditioning plant, 100% leak in filter directly above vials	8.7×10^{-16}
9	**Filling workstation (EU GGMP grade A) filters** – air drawn from air conditioning plant, 0.01% leak in filter directly above vials	8.7×10^{-20}
10	**Filling cleanroom (EU GGMP grade B) filters** – air supply from air conditioning plant, 100% leak in filter	3.7×10^{-20}
11	**Filling workstation (EU GGMP grade A) filters** – air supply from air conditioning plant, no leak in filter	5.2×10^{-22}
12	**Filling cleanroom (EU GGMP grade B) filters** – air supply from air conditioning plant, no leak in filter	5.2×10^{-26}

the required information is not difficult to obtain, e.g. average airborne concentration of MCPs, area of product exposed to airborne deposition, deposition velocity, and time product is exposed to contamination. However, the ease of transfer of MCPs from source to product, as given by transfer coefficients, may be missing. If this is so, then values can be obtained by the method advocated by Ljungqvist and Reinmuller[16].

To demonstrate how the NMD_A method can be used in a wide variety of cleanroom situations, a pharmaceutical cleanroom that uses a UDAF workstation and small-batch aseptic filling is given as an example, and the results summarised in **Table 1**. In this example, the higher risks are associated with personnel activities within the filling workstation, and the highest of these is caused by airborne contamination of vial closures within an open hopper, and subsequent transfer to product (8.1×10^{-6}). Use of a lidded hopper reduces this risk by approximately 16-fold to 4.9×10^{-7}. The risk from deposition of MCPs dispersed by personnel in the workstation is also high (5.5×10^{-6}). If a reduction in the levels of risk from personnel is considered necessary, a review of the associated risk factors will indicate where reductions can be best achieved. In this case, it may be appropriate to reduce the airborne concentration of MCPs by means of the use of a separative device, such as a RABS or isolator. Methods of managing risk in this situation, and in situations with different ventilation and manufacturing methods, will be considered more fully in the final article of the series.

The degree of risk from air supplied by the terminal HEPA filters in both the filling workstation and filling cleanroom was assessed. When the terminal air filters have no leaks, and the air conditioning plant supplies the air, the contribution from the supply air presents the lowest risk of product microbial contamination ($<1 \times 10^{-21}$) and the risk can be ignored. When there are no leaks in the workstation's supply filter system but the supply air is drawn from the filling cleanroom, there is an increase in the NMD_A to 2.8×10^{-11}.

Leaking filters were also assessed. The worst of these scenarios occurs when there is a leak in the HEPA filter directly above the product vials in the filling workstation, and when the supply air is drawn directly from the filling cleanroom and not the air conditioning plant. When a 100% leak occurs in these conditions, this gives the highest risk of product contamination (4.6×10^{-5}). However, when air is supplied from the air conditioning plant, the risk is substantially reduced by a factor of approximately 10^{11} to an NMD_A of 8.7×10^{-16}, which is caused by additional filtration in the air conditioning system prior to the filter with a 100% leak. A similar risk reduction for a HEPA filter with a 0.01% leak can also be achieved if the air is sourced from the air conditioning system. The risk of product contamination from a leaking HEPA filter within the filling workstation can, therefore, be effectively managed by using an

additional filter in the supply air.

This article only reports on the assessment of the degree of risk from airborne sources, and risks from surfaces and liquids will be considered in a second article. A final paper will consider the risks from all microbial sources in various types of healthcare cleanrooms, and methods of managing these risks.

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Science and Technology Feature

Quality by design in an evolving manufacturing sector

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Regulatory guidelines are changing product quality focus from a reliance on end product testing to a quality-by-design (QbD) approach across the entire pharmaceutical product life cycle. The introduction of QbD elements to pharmaceutical manufacturing has the ability to speed up the time to market by facilitating scale-up during product development, enable real-time release and reduce the risk of batch failures. Pharmaceutical manufacturing approaches to make plants more efficient and flexible include a move towards continuous manufacturing platforms. As continuous manufacturing processes have no defined batch size, proving rigorous process control and fault detection is crucial to validate these processes. Continuous manufacturing, therefore, requires that a much greater burden is placed on tight process control. To achieve this level of control, in-depth material and process knowledge is required. QbD principles are, therefore, essential to ensure process control during continuous production.

This article introduces and discusses the regulatory principles of the QbD approach across the pharmaceutical product life cycle. It explores the role of QbD within an evolving pharmaceutical manufacturing sector. The implementation of QbD is discussed together with the concepts of quality target product profiles, material quality attributes, process parameter control, design space, process models and process analytical technology.

Key words: Quality by design, ICH Q8, ICH Q9, ICH Q10, real-time release, continuous manufacturing, batch manufacturing, critical material quality attributes, process models.

Introduction

The unique focus on end product quality in the pharmaceutical sector lags significantly behind other manufacturing industries which have long since embraced the value of quality by design (QbD). QbD aims to build quality into the product through an in-depth understanding of the product, manufacturing process and associated risks in deviation from specification and potential compromise to product quality, efficacy and patient safety. Consequently, risk-based initiatives are employed together with rigorous control of the process as a replacement to the more traditional reliance on end product testing. Traditionally, pharmaceuticals have been manufactured, tested and released in batches. A batch is defined by the Food and Drug Administration (FDA) as *"a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture"*[1]. A batch, therefore, refers to the quality of the end product produced with no reference to the mode of manufacture.

In this article, we aim to introduce and discuss the regulatory principles of the QbD approach as it applies to pharmaceutical manufacturing. It explores the role of QbD within an evolving pharmaceutical manufacturing sector in response to

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changing pharmaceutical market place demands. The implementation of QbD is also discussed together with the concepts of quality target product profiles (QTPPs), material quality attributes, process parameter control, process models and process analytical technology (PAT).

Regulatory principles of the QbD approach

Between 2005 and 2009, a series of quality guidelines were published by the International Conference on Harmonisation (ICH), Q8 (R2), Q9 and Q10[2–4]. These guidelines deal with aspects of QbD, quality risk management and pharmaceutical development. The guidelines were designed to incentivise and encourage the pharmaceutical industry globally to adopt innovation and to embrace the possibilities of knowledge-based quality approaches. These internationally recognised documents are further supported by FDA and European Medicines Agency (EMA) publications, *"FDA Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance"*[5] and *"Guideline on the Use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations"*[6].

These publications outline guidance on QbD elements either retrospectively through variation applications or for new drug applications in the areas of critical quality attribute (CQA) risk assessment, the creation of a process design space or process monitoring and control employing PAT technologies. A new guideline currently in development, ICH Q12, is entitled, *"Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management"*. It is envisaged that this guideline will further reinforce the principles of QbD. The aim of ICH Q12 is to promote innovation and continual improvement of product manufacturing throughout its lifecycle. In particular, Q12 will provide a framework to better facilitate chemistry manufacturing control post-approval changes, and encourage enhanced process development and control strategies by providing opportunities for scientific and risk-based post-approval changes.

It is also important to note that the EMA encourages continuous process validation as part of the process control which includes off/at and in-line testing[7]. The FDA no longer accepts the traditional '3 validation batch' validation[8]. While complete QbD implementation is not currently mandatory, the principles of QbD are now expected as a standard in regulatory applications regardless of the complexity of the process or the end goal, i.e. real-time release (RTR) or traditional batch release.

In 2011, the FDA and EMA launched a pilot program for QbD parallel assessment of selected applications. The purpose of parallel assessment was two-fold; to enable sharing of regulatory decisions and to facilitate consistent quality pharmaceutical products throughout the United States and the European Union. To aid sharing of key findings with the public to facilitate QbD implementation in applications, the FDA and EMA have published two question-and-answer documents on QbD-related topics. In 2014, the agencies agreed to extend the pilot as there remained QbD areas for additional inter-agency harmonisation[9].

QbD in response to changing manufacturing requirements

Changes in the pharmaceutical market place are a driving force for innovation in the sector. Emphasis is shifting from adding capacity to making existing plants more efficient to meet the demands of increasing international competition, increasing production flexibility and decreasing product development time. QbD has the ability to speed up the time to market considerably by facilitating scale-up during product development, enabling RTR and reducing the risk of batch failures.

RTR is defined by ICH Q8(R2) as *"the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls"*[2]. QbD principles facilitate RTR as a product produced within the specification of the design space should have the desired QTPP.

Pharmaceutical manufacturing approaches to make plants more efficient and flexible include a move towards a continuous manufacturing platform. A continuous manufacturing train offers much needed manufacturing flexibility. Flexibility can allow the same site to develop clinical trial batch sizes if run for short periods or to supply an entire global market if the same process is run for a longer duration. The move to continuous manufacturing presents numerous challenges, particularly from a regulatory perspective. Currently in regulatory documentation, a batch process is outlined and validated using an agreed number of trial batch runs. The quality of the test batches are proven through end product testing to ensure each batch meets the required release product specifications. The current batch system is relatively straight forward as the batch size is defined and a problem batch of product is easily isolated for disposal or reprocessing. As a continuous manufacturing process has no defined batch size, proving rigorous process control and fault detection is crucial to validate the process. Continuous manufacturing, therefore, requires a revision of the 'traditional' regulatory approach. End product testing and release specifications are still of pivotal importance but a much greater burden is placed on tight process control, in-line and/or at-line sampling and the use of PAT techniques.

Tight process and material controls ensure problems within the manufacturing system are detected and resolved quickly before the end product quality is affected. To achieve this level of control during continuous processing, in-depth

material and process knowledge is required. QbD principles are, therefore, essential to ensure process control during continuous production. Ideally, continuous manufacturing allows a process to operate under a constant state of control resulting in a much lower risk of going out of specification compared to batch processing. The aim of continuous processing is to move to a variable process model to continuously ensure consistent in-specification end product output, and continuous process verification. Therefore, it may be necessary to adjust the process parameters to compensate for critical material differences to give consistent product as outlined in **Figure 1**[10]. Despite these challenges, the FDA supports the implementation of continuous manufacturing "using a science and risk based approach"[11]. Continuous manufacturing in particular can facilitate the production of exponentially more end product within existing plant dimensions while also potentially lowering the 'quality cost' of production, a loss suffered when an end product batch fails to meet specifications and cannot be released.

QbD implementation

QbD is defined by ICH Q8 as *"a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management"*[2]. QbD aims to design a product with consistent CQAs through the identification, evaluation, and control of critical material attributes and process parameters encountered during the production process. Before defining what is critical to monitor in a process, it is essential to define the overall goal of the product performance in terms of a QTPP. The QTPP is the first step in the QbD process. It identifies what is critical to the patient and links this to the drug product properties, such as the tablet appearance, hardness, dose (content uniformity) and drug release. **Table 1** lists examples of considerations when defining a QTPP. The next aim of the QbD process is to manufacture drug product that meets the QTPP by the design of a robust formulation and manufacturing process. From the QTPP, the end product's CQAs are defined. A CQA is defined as *"…a physical, chemical, biological or microbiological property or characteristic that should be within the appropriate limit, range or distribution to ensure the desired product quality"*[2].

Designing a process which ensures the drug product falls within the specifications of the QTPP and meets the CQAs specification involves considering the raw material attributes and process parameters. An attribute of a drug substance or excipient is considered critical when a realistic change in the attribute can significantly impact the quality of the output material and impact a CQA[12]. Material attributes may need to be monitored throughout the process as they can be altered during processing. A process parameter is described as a factor that can be monitored, e.g. temperature, cooling rate, pH, rotation speed. A process parameter becomes a critical process parameter (CPP) when variability in that parameter has an impact on a product CQA. The basic requirement to assigning criticality involves determining if there is a possible impact on product quality and assessing the severity of this risk. Assigning criticality is a step of paramount importance in the QbD process.

The process of carrying out a detailed risk assessment classifies all material attributes and process parameters to identify which are critical based on their effect on end product quality. The risk assessment process identifies possible risks and links the likelihood of them occurring with the severity of the consequences. Effective quality risk management can facilitate better and more informed decisions during processing along with providing the regulators with greater assurance of the company's ability to deal with potential risks. Following the risk

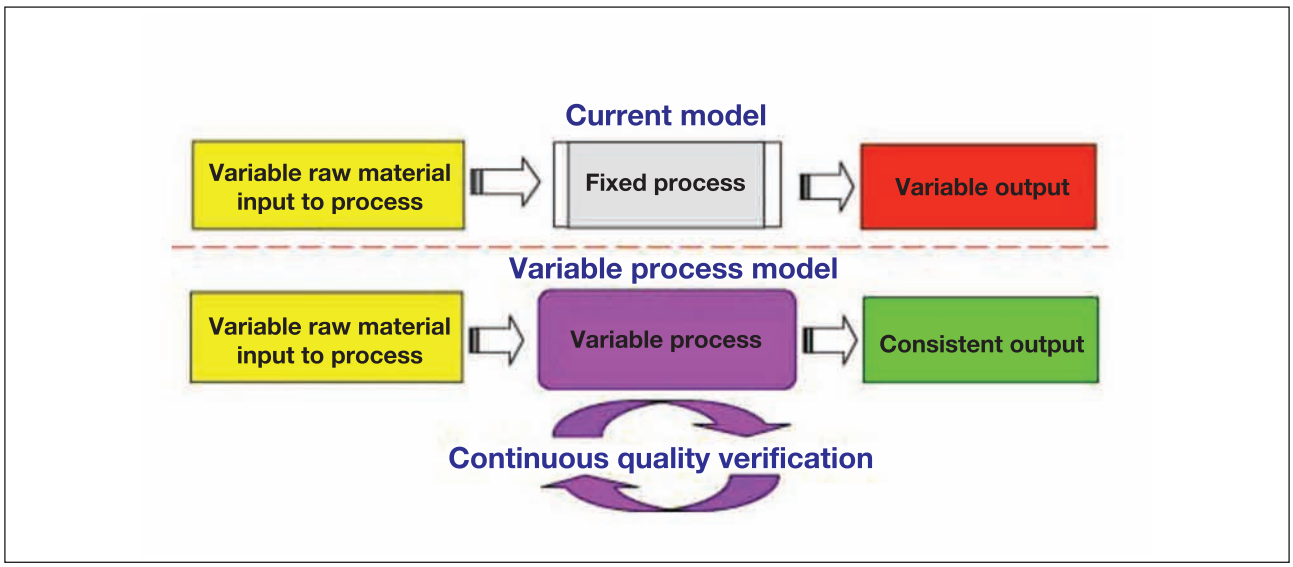

Figure 1. Traditional process model versus variable process model[10].

Table 1. QTPP example considerations (adapted from Chatterjee[11])

Factors to consider for QTPP	Example considerations
Dosage form	Tablet, oro-dispersible tablet, capsule
Route of administration	Oral, topical, inhalation, rectal, vaginal
Dosage strength	Range of appropriate dosages
Pharmacokinetics	Fasting state versus fed state, active pharmaceutical ingredient pharmacokinetics studies, bioequivalence studies if appropriate
Stability	Shelf life determination, storage conditions
Drug product quality attributes	Identification, content uniformity, microbiological content, residual solvents, water content
Container closure system	Air tight, protect from light, desiccant if hygroscopic

assessment stage, a series of experimentation is required to establish the product design space. The design space allows relationships between material attributes, process parameters and CQAs to be described. A design space, therefore, is a multi-dimensional combination and interaction of input variables, such as material attributes and process parameters that have been demonstrated to provide a quality product. Regardless of how a design space is created, it must be proven that working within the design space will result in product meeting the defined CQAs and QTPP. From a regulatory view point, working within the design space would not be considered a change to the manufacturing process. Movement outside the design space would result in waste product or would require a regulatory post-approval change for batch release onto the market. **Figure 2** is a schematic diagram which links QTPP, CQAs, critical material attributes and CPPs to design space, control strategy and continual process improvement.

Critical material quality attributes

A key element of the QbD approach is the identification of the critical material quality attributes of the raw and in-process materials. A series of review articles by Chris Moreton (FinnBrit Consulting), published in the *American Pharmaceutical Review*, gives a comprehensive explanation of the issues which can be encountered as a result of pharmaceutical excipient variability in a QbD environment[13]. This series discusses excipient performance in QbD from excipient composition, changes in the supply of source material for the manufacture of excipient and the quality risk management of excipients. The *United States Pharmacopeia and The National Formulary*, Excipient Performance Chapter <1059> (USP 30-NF 25) is designed to provide an overview of typical material attributes for many functional categories, along with additional tests that may be useful in evaluating and controlling excipient attributes that are not typically included in compendial monographs. This general chapter recognises that not all critical physical and chemical properties may be identified in excipient monographs via compendial tests and specifications. Manufacturers must identify and control critical excipient properties in relation to their specific formulation and process. In addition, manufacturers should anticipate lot-to-lot and supplier-to-supplier variability. Chapter <1059> attempts to generally list important excipient properties classifying excipients under their functionality. It is important to note that the chapter does not impose limits or specifications since the properties of an excipient required will vary and depend upon the product, manufacturing process, quantity and intended function[14].

Another interesting development in the area of critical material quality attributes is a project led by the Academy of Pharmaceutical Sciences in the UK to establish a Drug Manufacturing Classification System (MCS)[15]. The cost of drug development and manufacturing is high and resource-intensive. Chemistry manufacturing control failures comprise a significant number of failures for new drug applications[16]. A manufacturing classification system which helps identify the desirable properties of a drug substance for a particular processing route would aid drug developers when designing a suitable cost-effective manufacturing process. The MCS is initially intended as a tool to rank the feasibility of different processing routes for the manufacture of solid dosage forms based on the physicochemical properties of the drug substance being developed. However, by identifying desirable properties of a drug substance in a particular processing route, it will

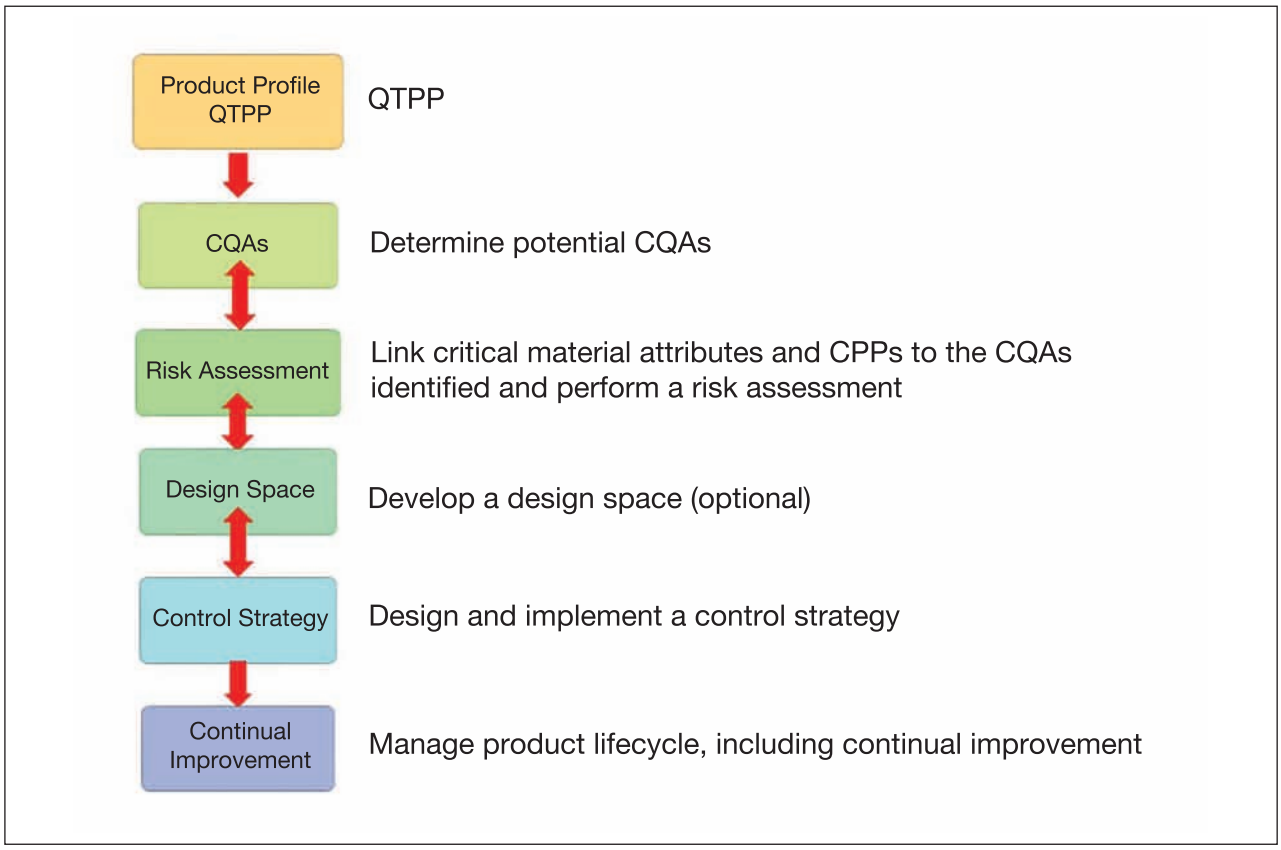

Figure 2. Schematic diagram showing pathway linking QTPP to critical material attributes, CPPs, CQAs and subsequent linkages to design space, control strategy and continual improvement.

also facilitate the identification of properties less desirable and thereby inform the risk assessment stage of the QbD process.

Process models

Under QbD, process models have an important role as they can be applied through the different stages of production manufacture from chemical reactors and crystallisation to compression and PAT monitoring and control. Process models can be used to describe relationships between critical material quality attributes, process parameters and CQAs of the end product. Mathematical models are used in other process industries to describe the different chemical and/or physical phenomena taking place during production. Process models are mathematical models that simply describe a process using mathematical language in the form of an equation.

Process models can be divided into three types; theoretical models, empirical models or hybrid models. A theoretical model (or mechanistic model) can be derived when the system being studied is thoroughly understood and can be expressed in the form of an equation. Theoretical models are, therefore, often regarded as fundamental laws of science. In most cases, however, the mechanism of a system is not well understood or may be too complex to permit a model based on theory. An empirical model is applied in such cases based on experimental data. Empirical models are data-based models and can be derived using experimental data from different sources. Casual empirical models use Design of Experiments data to create design spaces. Hybrid (or semi-empirical) models combine theoretical models with empirical data when some prior knowledge of the system is well understood[17].

For regulatory purposes, models can be assigned as high, medium or low impact. High impact is assigned to models which predict a significant feature of product quality, e.g. a chemometric model for uniformity of content. A medium impact model assures product quality but is not the only assurance of quality, e.g. models for in-process control or design space models. Low impact models support process and product development at the formulation stage.

PAT

PAT has greatly advanced over the last decade from developmental concepts of novel techniques to the emergence of practical and robust equipment which are capable of monitoring a process, e.g. drying, milling or roller compaction. Spectroscopic techniques, such as near infrared (NIR), mid infrared, UV-Vis, Raman and X-ray diffraction, are popular PAT techniques applied in-line/at-line[10]. NIR spectroscopy is a commonly

used PAT technique and has a broad number of applications from chemical analysis, moisture analysis, particle density and particle size applications. In response to the variety of uses of this technique and in an effort to support and facilitate applications which include aspects of a QbD approach to manufacturing control, the EMA are encouraging the inclusion of such techniques in new drug applications and post-approval applications.

In 2011, the EMA released a draft guidance document *"Guideline on the Use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations"* for consultation. After a consultation period of 6 months, the document was reviewed and adopted by the Committee for Human Medicinal Products and was published in June 2014[6]. The guidance document outlines the expectations of regulators when implementing an NIR technique to a process and covers all stages from data collection and setting up a calibration model right through to redevelopment as seen in **Figure 3**. The publication of this guidance and the level of detail indicates how advanced, accepted and applicable NIR has become as a pharmaceutical PAT technique. The degree of control and regulation associated with the technique will depend on its use, i.e. as a supplementary method of process control or as an end product test for RTR.

Continual process monitoring to enable real-time process control has resulted in a data explosion. Appropriate data analysis methods are required to extract meaningful information form large amounts of raw data and develop process models. Multivariate analysis (MVA) is a set of statistical techniques which can be used to study several variables at a time and can be applied to large complex data sets. These statistical methods allow for the interpretation of large complex data[18]. The most commonly used methods of MVA are principle component analysis (PCA) and partial least square (PLS) analysis. Both PCA and PLS techniques have been referenced in recent EMA guidelines[6] and FDA and EMA presentations[19,20].

Summary

Aspects of a QbD approach are now a standard requirement of pharmaceutical development and manufacturing. QbD principles are integral parts of current regulatory guidance. New drug product applications must risk assess and define drug product and raw material CQAs and process parameters. The extent to which QbD will be incorporated into a finished product application will depend on the complexity of the manufacturing process. However, an indication of a scientific knowledge-based understanding of the manufacturing

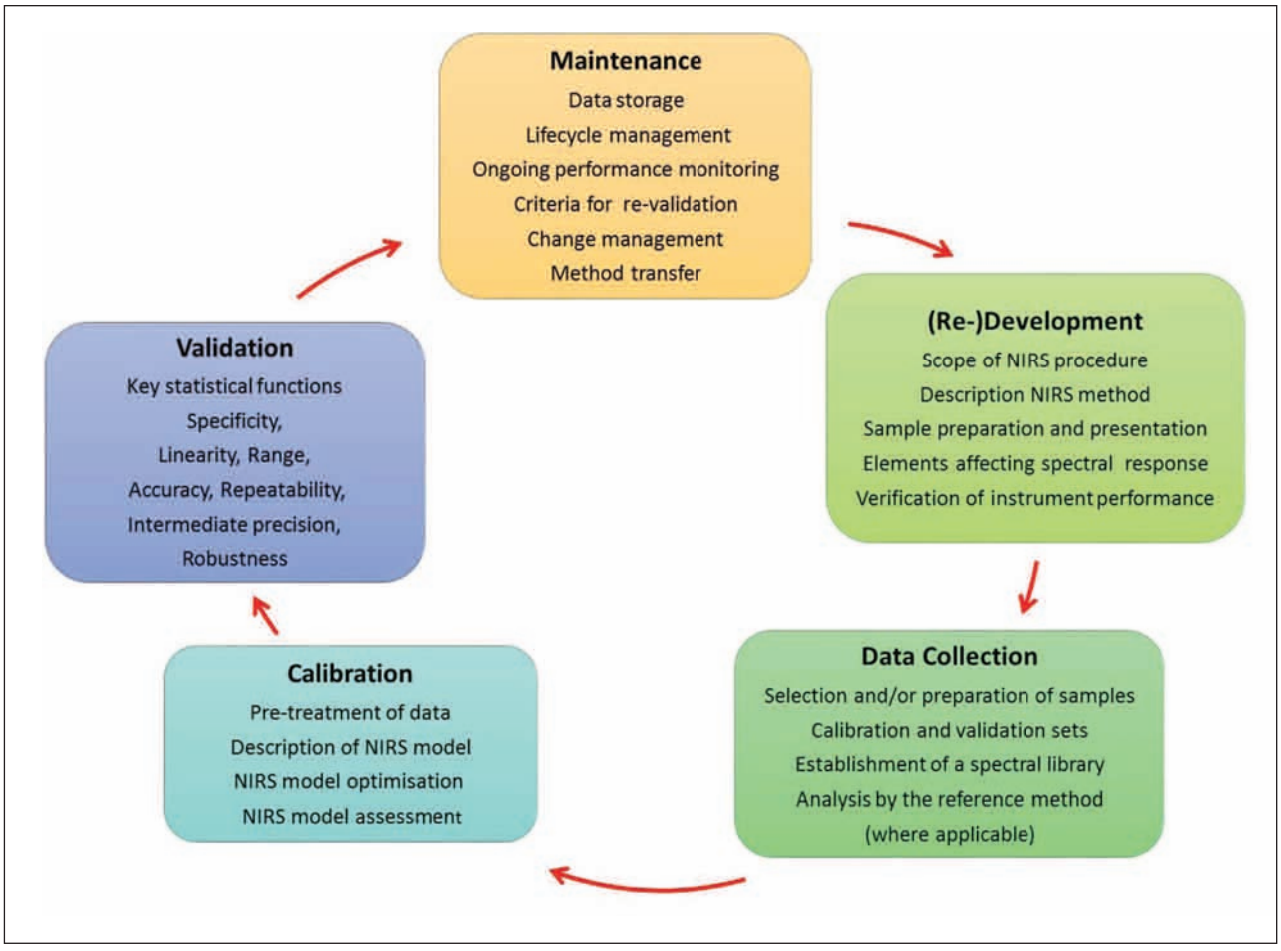

Figure 3. NIR implementation and maintenance expectations life cycle[6].

process, as is required by QbD, should be clearly demonstrated. Regulatory authorities have previously been criticised as an obstacle to innovation and were seen as discouraging in the assessment of new PAT techniques and modelling. Now regulatory authorities encourage the inclusion of QbD in applications, the use of different PAT techniques and the application of MVA statistical techniques to verify the suitability of PAT and QbD principles during routine manufacture. The continuing evolution of pharmaceutical manufacturing approaches and regulatory guidelines support and encourage the principles of QbD. These advancements make innovation in the areas of continuous processing and RTR attainable.

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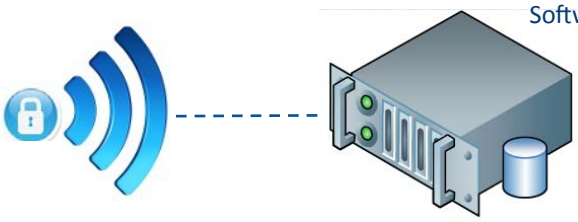

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Regulatory Review

Introduction

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

Europe

- EU [European Union] Guideline to Good Manufacturing Practice [GMP] Annex 15: Qualification and Validation
- GDP of active substances for medicinal products for human use
- Water for injection (bulk)
- Specification for sub-visible particles in eye drops and eye lotions
- Conclusion of prospective pharmacopoeial harmonisation pilot project
- New strategy for European Pharmacopoeia (Ph.Eur.) general methods
- New Indian state of Telangana – impact on Certificates of Suitability (CEPs)
- Safety monitoring of medicines: European Medicines Agency (EMA) to screen medical literature for 400 active substance groups
- EU Medicines Agencies Network Strategy to 2020
- First Early Access to Medicines Scheme (EAMS) scientific opinion granted in the UK
- GMP Data Integrity Definitions and Guidance for Industry
- Registrations for the brokering of human medicines.
- Mandatory use of electronic common technical document (eCTD) for decentralised procedures
- An innovative approach to developing malaria vaccine (Medicines and Healthcare Products Regulatory Agency (MHRA))
- Development of a UK manufacturing site for BTG plc for varicose veins treatment.
- Certificates of Free Sale (CFSs) to be issued by the MHRA
- GMP and good distribution practice (GDP)

USA

- New and revised draft guidances the Center for Drug Evaluation and Research (CDER) is planning to publish during calendar year 2015
- Final guidance on the evaluation and labelling of abuse-deterrent opioids
- Critical Path Innovation Meetings Guidance for Industry
- Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity – Guidance for Industry
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product – Guidance for Industry
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product – Guidance for Industry
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 – Guidance for Industry
- Providing regulatory submissions in electronic format
- Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)
- ANDA [abbreviated new drug applications] Submissions – Refuse-to-Receive Standards
- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- Reportable CMC [chemistry, manufacturing and controls] Changes for Approved Drug and Biologic Products
- Draft guidance on animal drug compounding from bulk drug substances
- Development and Submission of Near Infrared Analytical Procedures – Guidance for Industry
- Food and Drug Admistration (FDA) approves first biosimilar product
- Public docket on drug compounding
- Final guidance on reprocessing of reusable medical devices
- Electronic Submission of Lot Distribution Reports – Guidance for Industry (Biologics)
- CDER Ombudsman's 2014 Annual Report

International

Australia

- Consultations on adoption of EU guidelines in Australia
- Evaluation of biosimilars

Canada

- Inspections database
- Inspection Tracker: Drug Manufacturing Establishments

Pharmaceutical Inspection Cooperation Scheme (PIC/S)

- Membership updates
- Strengthening of international regulatory cooperation in the field of GMP
- PIC/S Inspectors Academy (PIA)

Products

- Treanda Injection (solution) and closed system transfer devices
- Oxytocin in 5% dextrose injection products were not withdrawn from sale for reasons of safety or effectiveness
- GVK Biosciences: EMA confirms recommendation to suspend medicines over flawed.

Europe

European Commission (EC)

EU Guidelines to GMP Annex 15: Qualification and Validation

Since Annex 15 was published in 2001, the manufacturing and regulatory environment has changed significantly and an update is required to reflect this changed environment. This revision takes into account changes to other sections of the EudraLex Volume 4, Part I, relationship to Part II, Annex 11, International Conference on Harmonization (ICH) Q8, Q9, Q10 and Q11, Quality Working Party guidance on process validation, and changes in manufacturing technology. The deadline for coming into operation is 1 October 2015. The document has also been adopted by PIC/S with the same operational date.

(Note, this version is considerably longer than the previous version. Retrospective validation is no longer allowed. Newer (than 3 batch validation) approaches or hybrid approaches to validation are discussed. There will be significant impact in the area of cleaning validation where a toxicological approach is required – MH.)

GDP of active substances for medicinal products for human use

Distribution of active substances comprise activities consisting of procuring, importing, holding, supplying or exporting active substances. The EC has published new guidelines on good distribution practice (GDP) for active pharmaceutical ingredients (APIs) for medicinal products for human use. They come into force as of 21 September 2015. APIs intended for the manufacture of veterinary medicines are exempted from these guidelines.

European Directorate for the Quality of Medicines (EDQM)

Water for injection (bulk)

There have been ongoing discussions for many years as to whether there is a need to include non-distillation technologies as a method for production of water for injection (WFI). The main concerns had been linked to the microbiological safety of the water produced by membrane techniques. Following the survey issued by the EDQM in March 2010 to gather data on the use of non-distillation technologies for producing WFI, as well as the expert workshop organised by the EDQM in March 2011, it was considered that sufficient evidence had been provided for the the Ph.Eur. Commission to recommend initiating discussions with stakeholders regarding the potential use of membrane systems for the production of WFI.

A revision of the monograph is proposed to take into account current manufacturing practices using methods other than distillation for producing water of injectable quality. The monograph has been revised to include, in addition to distillation, reverse osmosis coupled with suitable techniques, for the production of WFI; a requirement for regular total organic carbon monitoring has been added to emphasise further the specific test controls required in the production section.

As a result of introducing non-distillation technologies into this monograph, the monograph *Water, Highly Purified <1927>* will be made redundant and will be deleted from the Ph.Eur. The deadline for comment was 30 June 2015.

The EDQM organised a free webinar on 22 April 2015 which explained the context of the revision and gave an overview of the steps taken by the Ph.Eur. towards revising the WFI monograph.

Specification for sub-visible particles in eye drops and eye lotions

The Ph.Eur. monograph *Eye Preparations <1163>* does not set requirements/limits for sub-visible particles. In other regions of the world (e.g. USA and Japan), such requirements are considered very important for patient safety when eye preparations are administered to an injured eye. Furthermore, sub-visible particles are a reflection of the quality of the manufacturing process and may indicate a risk of microbial contamination. Even if the eye is subjected to particles in everyday life, this is not considered a valid reason to tolerate sub-visible particles in medicines beyond a certain limit.

Therefore, the Ph.Eur. Commission is currently considering updating this monograph to add a specification for particulate contamination for eye drops and eye lotions that are solutions.

The Ph.Eur. Commission would, therefore, like to obtain further information supported by actual data from stakeholders in the field (manufacturers, regulatory authorities and other users). Based on the responses received, the final decision will be taken as to whether a specification is appropriate, and, if so, a proposal (revised draft) will be formulated for publication in Pharmeuropa.

The Ph.Eur. Commission invited responses to the following questions.

- Is such a specification necessary?
- If not, why not?
- If so, why, and what should the specification be?

Feedback was requested by 30 June 2015.

Conclusion of prospective pharmacopoeial harmonisation pilot project

As an outcome of this project, four monographs (Celecoxib, Montelukast Sodium, Rizatriptan Benzoate, and Sildenafil Citrate) were elaborated using a modified Ph.Eur. P4 procedure; eleven reference standards were established in support of these four monographs.

The collaboration revealed complexities as the US Pharmacopeia (USP) and the EDQM attempted to align their respective processes, which ultimately did not provide added value to the harmonised standards published. After a thorough evaluation of the outcome of the pilot project, and a critical review of the resources utilised, the USP and the EDQM jointly decided to officially conclude the Prospective Harmonisation Pilot Project.

Both organisations remain fully committed to pharmacopoeial harmonisation and will continue to collaborate on prospectively harmonised monographs in a

less formal manner.

New strategy for Ph.Eur. general methods
In order to stay state-of-the-art, it is crucial for the Ph.Eur. to closely follow new trends and technologies and to reflect them in its texts, where appropriate. In this context, general methods are of specific relevance as they provide the ground-rules applicable to specific monographs and the need to have a thorough review of the adequacy of the existing texts has been identified as a priority by the Ph.Eur. Commission. A newly established Working Party will be in charge of defining the content and degree of detail to be provided.

New Indian state of Telangana – impact on CEPs
The creation of the new Indian state of Telangana on 2 June 2014 has an impact for CEPs and applications for CEPs (new and revision).

Many of the addresses mentioned on CEPs and in CEP applications which are currently listed as being in Andhra Pradesh are now in this new state of Telangana.

For on-going applications (new and revision), companies should submit an application form as soon as possible with the new address details, as well as an updated section 3.2.S.2.1 if necessary.

EMA

Safety monitoring of medicines: EMA to screen medical literature for 400 active substance groups
This service will start with a limited number of active substances on 1 July 2015 and will be fully rolled out in September 2015. A guide, a training video and a document detailing the inclusion and exclusion criteria to be used when screening the literature are also available on a dedicated webpage.

This initiative aims to improve the safety monitoring of medicines by enhancing the quality and consistency of data reported in EudraVigilance. It is provided as a service to industry which, for the active substances and literature covered by the EMA activities, will no longer be obliged to enter the information on suspected adverse reactions into EudraVigilance. Individual cases of suspected adverse reactions found in the literature will be made available to marketing authorisation holders so they can include them in their safety databases and meet their reporting obligations outside the European Economic Area.

A total of 400 active substance groups will be monitored by the EMA, in particular substances that are contained in a high number of medicinal products, and over 4000 companies will benefit. The EMA will send updates on the implementation of its medical literature monitoring service to the qualified persons for pharmacovigilance as well as to pharmaceutical industry organisations. The dedicated webpage will also be regularly updated.

Heads of Medicines Agencies (HMA)

EU Medicines Agencies Network Strategy to 2020
This document outlines the high-level strategy for the network for the next 5 years. It is presented, for the first time, as a single strategy for the entire network to reflect the need for a coordinated approach to address the multiple challenges and opportunities that face the network. Advances in science affect the nature of the products regulated and the network must support new and innovative developments that contribute to public health. There is a need for efficiency and transparency, the need to address new and emerging threats, whether of a public health or criminal nature, and the need to work globally with other regulators given the increasing globalisation of the pharmaceutical industry.

This document focuses on key strategic priorities where the network can and should make a difference in the next 5 years. It is a high-level strategy explaining what needs to be taken forward and why. It builds on the previous EMA roadmap to 2015 and the HMA strategy document 2011–15.

The document presents key themes focusing on the contribution the network will make to human and animal health, optimising the operation of the network and the need to act and collaborate globally. The stakeholder comment period ended on 30 June.

MHRA

First EAMS scientific opinion granted in UK
This EAMS scientific opinion has been awarded for a medicine used to treat advanced melanoma. The scientific opinion describes the risks and benefits of the medicine and the context for its use, supporting the prescriber and patient to make a decision on whether to use the medicine before its licence is approved.

This UK-only scheme supports earlier access to unlicensed medicine in patients with seriously debilitating or life-threatening conditions where there is an unmet medical need.

GMP Data Integrity Definitions and Guidance for Industry
Following high levels of interest in response to the initial publication of this guidance on 23 January 2015, the MHRA has responded to questions from stakeholders by providing additional clarifications to the text.

Registrations for the brokering of human medicines
In order to be registered as a broker by the MHRA, companies must comply with GDP and pass regular GDP inspections of their site.

A company that is involved in independently selling or buying medicines on behalf of another company must be registered as a broker. A broker does not:

- buy or sell the products;
- own the products;
- physically handle the products.

Wholesale dealers who want to broker medicines must also register.

You can only broker a medicinal product that has a licence (marketing authorisation). The MHRA publishes a register of brokers that it has approved.

Initial applications are made via the HMA website. The

application will then be sent to the MHRA and should take 90 working days to process. MHRA may check the following.

- The identities of the 'responsible person' and other named staff.
- Contact you to arrange for an inspection of your site(s) (the inspection process is similar to that for GDP and you will be asked to prepare information in advance).
- Interview members of your staff.

Shortly after the inspection, you will receive a report with details of any issues raised. When the inspector is satisfied that these issues have been addressed, the MHRA will publish the information on a publicly accessible UK register.

Mandatory use of eCTD for decentralised procedures
From 1 July 2015, new market authorisation applications for decentralised procedures must be submitted in an eCTD format.

An innovative approach to developing malaria vaccine
The MHRA has published its fourth case study detailing how the regulator has helped researchers at the Jenner Institute, University of Oxford take a step closer to developing an effective vaccine against malaria.

Engagement with the University of Oxford MHRA's Innovation Office has helped contribute to the development of a viral vector, which is used as a carrier of genetic material to help treat a specific disease. The MHRA helped facilitate the strategic project planning by introducing Jenner Institute researchers to the relevant agency teams at the correct times. These included MHRA clinical trials teams, the GMP inspectorate, the pharmaceutical assessors and the toxicologists.

Innovation Office colleagues also reviewed the risk assessments and the descriptions provided on the vaccine in the information package. Finally, the MHRA helped by sending accurate constructive feedback. This was particularly helpful in aiding researchers to progress their project quicker.

Development of a UK manufacturing site for BTG plc for varicose veins treatment
This is the fifth case study from the Innovation Office who advised healthcare company, BTG plc, in their development of a UK manufacturing site for a novel drug–device combination product to treat varicose veins.

After successful clinical trials, BTG consulted the MHRA early to fully understand the manufacturing challenges and the decision was made to re-develop their existing site in Farnham, resulting in a £4m investment and creation of 50 additional jobs. Early dialogue with the MHRA helped to ensure regulatory compliance, mitigate risk and make timely decisions.

CFSs to be issued by the MHRA
The MHRA took over responsibility for issuing CFSs for medicines from the Department of Health from Wednesday 1 April 2015. A similar system is in place for CFSs for medical devices.

GMP and GDP
The MHRA has updated its GMP pages covering compliance with GMP, GDP and preparation for an inspection. GMP compliance report templates and guidance have been added.

USA

FDA

New and revised draft guidances the CDER is planning to publish during calendar year 2015

The list is subdivided into different categories. Within the CGMP category, just three new guidances are planned for 2015.

- A questions & answers (Q&A) on data integrity.
- CGMP rules for outsourced facilities (pharmacy compounding).
- Rules for the repackaging of certain drug products by pharmacies and outsourcing facilities.

Under the category "Pharmaceutical Quality/CMC", some 13 guidances are planned. *(Of these the following are likely to be of most interest to readers – MH.)*

- Development of near infrared (NIR) procedures (see later in this review).
- Microbiological quality considerations in non-sterile drug product manufacturing.
- Quality metrics and risk-based inspections.

Under biotechnology, there are two separate categories: biopharmaceutics and biosimilarity. *(Overall, the number of new GMP guidances planned for 2015 is relatively small; however, the topics data integrity and quality metrics could be very significant – MH.)*

Final guidance on the evaluation and labelling of abuse-deterrent opioids
The FDA has issued a final guidance to assist industry in developing opioid drug products with potentially abuse-deterrent properties. The document "Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling" explains the FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. It also makes recommendations about how those studies should be performed and evaluated, and discusses what labelling claims may be approved based on the results of those studies.

Critical Path Innovation Meetings Guidance for Industry
This guidance describes the purpose, scope, documentation and administrative procedures for a Critical Path Innovation Meeting (CPIM), including how to request such a meeting. The CPIM is a means by which the CDER and investigators from industry, academia, patient advocacy groups and government can communicate to improve

efficiency and success in drug development. The goals of the CPIM are to discuss a methodology or technology proposed by the meeting requester and for the CDER to provide general advice on how this methodology or technology might enhance drug development. The CDER will identify some of the larger gaps in existing knowledge that requesters might consider addressing in the course of their work. The discussions and background information submitted through the CPIM are non-binding on both FDA and CPIM requesters.

This guidance provides some examples of topics appropriate for a CPIM. It also describes the information that should be provided to the CDER in preparation for a meeting and potential outcomes from the CPIM.

Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity – Guidance for Industry

This guidance is intended to supplement the FDA's *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications*, issued in July 1998 (the EA Guidance), by addressing specific considerations for drugs that have potential estrogenic, androgenic, or thyroid hormone pathway activity in environmental organisms. It is intended to help sponsors of such drugs determine whether they should submit environmental assessments (EAs) for new drug applications (NDAs) and certain NDA supplements, and to clarify what information such sponsors should include if they submit a claim of categorical exclusion instead of an EA.

Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product – Guidance for Industry

This guidance is intended to provide recommendations to sponsors on the scientific and technical information for the CMC section of a marketing application for a proposed product submitted under section 351(k) of the Public Health Service (PHS) Act.

The Biologics Price Competition and Innovation (BPCI) Act of 2009 amends the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product. The BPCI Act also amended the definition of biological products to include "protein (except any chemically synthesized polypeptide)". A 351(k) application for a proposed biosimilar product must include information demonstrating biosimilarity, based on data derived from, among other things, "analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components".

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product – Guidance for Industry

This final guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product for purposes of the submission of a marketing application under section 351(k) of the PHS Act. Although the 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic protein products and gives an overview of important scientific considerations for demonstrating biosimilarity. The scientific principles described in this guidance may also apply to other types of proposed biosimilar biological products.

This guidance is one in a series of guidances that the FDA is developing to implement the BPCI Act. These guidances address a broad range of issues, and include the following.

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product.
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.
- Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product.

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 – Guidance for Industry

This guidance provides answers to common questions from sponsors interested in developing proposed biosimilar products, biologics license application (BLA) holders, and other interested parties regarding the FDA's interpretation of the BPCI Act of 2009. The Q&As are grouped in the following categories.

- Biosimilarity or Interchangeability.
- Provisions Related to Requirement to Submit a BLA for a "Biological Product".
- Exclusivity.

Providing regulatory submissions in electronic format

The FDA guidances ordinarily contain standard language explaining that guidance documents should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. **The FDA is not including this standard language in this guidance document because it is not an accurate description of all of the effects of this guidance document. Insofar as this document specifies the format for electronic submissions, or provides "criteria for exemptions" under section 745A(a) of the Federal Food, Drug, and Cosmetic (FD&C) Act, it will have binding effect.**

Twenty-four months after the issuance of this final guidance document in which the FDA has specified the electronic format for submitting submission types to the Agency, such content must be submitted electronically and in the format specified by the FDA. This guidance and the technical specification documents it incorporates by reference describe how sponsors and applicants must organise the content that they submit to the Agency electronically for all submission types under section 745A(a) of the FD&C Act.

In addition to this guidance and existing technical specification documents, further and more detailed technical instructions will be included in a separate eCTD technical conformance guide.

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)

This draft guidance provides recommendations for sponsors of investigational new drug applications (INDs), and applicants that submit NDAs, ANDAs, and supplements to these applications for immediate-release (IR) solid oral dosage forms, and who wish to request a waiver of *in vivo* bioavailability (BA) and/or bioequivalence (BE) studies. These waivers are intended to apply to the following.

- Subsequent *in vivo* BA or BE studies of formulations after the initial establishment of the *in vivo* BA of IR dosage forms during the IND period.
- *In vivo* BE studies of IR dosage forms in ANDAs.

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms. These are dissolution, solubility and intestinal permeability. In addition, some IR solid oral dosage forms are categorised as having rapid or very rapid dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors/applicants justify requests for bio waivers.

ANDA Submissions – Refuse-to-Receive Standards

This final guidance is intended to assist applicants preparing to submit ANDAs and prior approval supplements (PASs) to ANDAs to the FDA for which the applicant is seeking approval of a new strength of the drug product. The guidance highlights deficiencies that may cause the FDA to refuse-to-receive an ANDA. A refuse-to-receive decision indicates that the FDA determined that an ANDA is not sufficiently complete to permit a substantive review.

This guidance is not meant to be a comprehensive list of the deficiencies that may or will lead to a refuse-to-receive determination by the FDA, but identifies certain deficiencies and some recurrent deficiencies that in the FDA's experience have led the FDA to refuse-to-receive an ANDA. For example, in 2012, of the 100 ANDAs that the FDA refused-to-receive:

- 40 were refused because of serious BE deficiencies;
- 36 because of serious chemistry deficiencies;
- 13 because of format or organisational flaws;
- 6 because of clinical deficiencies;
- 4 because of inadequate microbiology (sterility assurance) information; and
- 1 was refused because an incorrect reference listed drug was cited as the basis of submission.

M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

The synthesis of drug substances involves the use of reactive chemicals, reagents, solvents, catalysts and other processing aids. As a result of chemical synthesis or subsequent degradation, impurities reside in all drug substances and associated drug products. While ICH *Q3A Impurities in New Drug Substances and Q3B Impurities in New Drug Products* provide guidance for qualification and control for the majority of the impurities, limited guidance is provided for those impurities that are DNA reactive.

The purpose of this guidance, therefore, is to provide a practical framework that is applicable to the identification, categorisation, qualification and control of these mutagenic impurities to limit potential carcinogenic risk. This guidance emphasises considerations of both safety and quality risk management in establishing levels of mutagenic impurities that are expected to pose negligible carcinogenic risk. It outlines recommendations for assessment and control of mutagenic impurities that reside or are reasonably expected to reside in final drug substance or product, taking into consideration the intended conditions of human use.

Reportable CMC Changes for Approved Drug and Biologic Products

This draft guidance has been developed to address the lack of clarity with respect to what CMC information in a marketing application constitutes an established condition or a "regulatory commitment" that, if changed following approval, requires reporting to the FDA. Clarification regarding which elements of the CMC information constitute established conditions and where in an application these elements are generally expected to be described should lead to a better understanding that certain CMC changes can be made solely under the Pharmaceutical Quality System without the need to report to the FDA. For those changes that do require reporting, a better understanding of established conditions could allow for a more effective post-approval submission strategy by the regulated industry.

Specifically, this guidance describes those sections in a CTD-formatted application that typically contain information that meets the definition of established conditions, and provides considerations for managing and communicating changes to the approved established conditions over the lifecycle of an approved product.

Draft guidance on animal drug compounding from bulk drug substances

FDA has released a draft *Guidance for Industry #230 Compounding Animal Drugs from Bulk Drug Substances* on this topic. Current law does not permit compounding of animal drugs from bulk drug substances, but the FDA recognises that there are limited circumstances when an animal drug compounded from bulk drug substances may be an appropriate treatment option. Guidance for Industry #230 outlines specific conditions under which the agency generally does not intend to take action against state-licensed pharmacies, veterinarians and facilities registered

as outsourcing facilities when drugs are compounded for animals from bulk drug substances.

There are circumstances where there is no approved drug that can be used or modified through compounding to treat a particular animal with a particular condition. In those limited situations, an animal drug compounded from bulk drug substances may be an appropriate treatment option.

"This draft guidance, once finalized, will help to ensure that animal drugs compounded from bulk drug substances are available for patient care without compromising the animal drug approval process or jeopardizing the safety of the food supply."

The FDA also withdrew Compliance Policy Guide Section 608.400 because it is no longer consistent with the FDA's current thinking on these issues.

This draft guidance is available for public comment for 90 days from the date of publication of the notice of availability in the Federal Register.

Development and Submission of Near Infrared Analytical Procedures – Guidance for Industry

This draft guidance provides recommendations to applicants of NDAs, ANDAs and drug master file holders regarding the development and submission of NIR analytical procedures used during the manufacture and analysis of pharmaceuticals (including raw materials, in-process materials and intermediates, and finished products).

NIR analytical procedures are increasingly being used in the pharmaceutical industry for the identification and assay of pharmaceutical starting materials, intermediates, and finished products. They are also used to monitor and control manufacturing processes. The development and validation of NIR analytical procedures are, therefore, important for ensuring the quality of pharmaceuticals. It is important for manufacturers who use such procedures to understand the factors that can affect the performance and suitability of the procedures and the approaches that can be used to validate them.

ICH Q2(R1) provides a discussion of the "characteristics that should be considered during the validation of analytical procedures", "guidance and recommendations on how to consider the various validation characteristics for each analytical procedure" and "an indication of the data that should be presented in a registration application". Although many of the concepts described in ICH Q2(R1) can apply in general to a wide variety of analytical methodologies, the ICH guidance does not address some unique characteristics of NIR analytical procedures.

NIR analytical procedures typically combine the following: (1) elements of instrumentation (analyser consisting of an NIR spectrophotometer, reflectance or transmission probe, spectral analysis software, etc.); (2) acquisition parameters; (3) sample presentation (interface) and sampling; (4) composition of spectral data sets; (5) spectral pretreatment; (6) wavelength range(s); and (7) a chemometric model. They can, therefore, be considered more complicated than the types of analytical procedures for which ICH Q2(R1) was written. This guidance is intended to discuss how the concepts described in ICH Q2(R1) can be applied to NIR analytical procedures that use chemometric models and to describe the CDER's current thinking about other issues related to the development and validation of NIR analytical procedures. This guidance is also intended to describe the type of information that should be submitted about NIR analytical procedures in applications.

FDA approves first biosimilar product

Zarxio (filgrastim-sndz) is the first biosimilar product approved in the US.

Biological products are generally derived from a living organism. They can come from many sources, including humans, animals, microorganisms or yeast.

A biosimilar product is a biological product that is approved based on a demonstration that it is highly similar to an already-approved biological product, known as a reference product. The biosimilar must also show it has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products.

Sandoz, Inc.'s Zarxio is biosimilar to Amgen Inc.'s Neupogen (filgrastim), which was originally licensed in 1991. Zarxio is approved for the same indications as Neupogen.

A biosimilar product can only be approved by the FDA if it has the same mechanism(s) of action, route(s) of administration, dosage form(s) and strength(s) as the reference product, and only for the indication(s) and condition(s) of use that have been approved for the reference product. The facilities where biosimilars are manufactured must also meet the FDA's standards.

The FDA has designated a placeholder non-proprietary name for this product as "filgrastim-sndz." The provision of a placeholder non-proprietary name for this product should not be viewed as reflective of the Agency's decision on a comprehensive naming policy for biosimilar and other biological products. While the FDA has not yet issued draft guidance on how current and future biological products marketed in the US should be named, the Agency intends to do so in the near future.

Public docket on drug compounding

The FDA has established a public docket to receive information, recommendations and comments on matters related to the Agency's regulation of compounding of human drug products under sections 503A and 503B of the FD&C Act. This docket is intended for general comments related to human drug compounding that are not specific to documents or issues that are the subject of other dockets.

Final guidance on reprocessing of reusable medical devices

The FDA has announced new actions to enhance the safety of reusable medical devices and address the possible spread of infectious agents between uses.

The new recommendations are outlined in a final industry guidance aimed at helping device manufacturers develop safer reusable devices, especially those devices that pose a greater risk of infection.

Medical devices intended for repeated use are commonplace in healthcare settings. They are typically made of durable substances that can withstand reprocessing, a multi-step process designed to remove soil and contaminants by cleaning and to inactivate microorganisms by disinfection or sterilisation. While the majority of reusable devices are successfully reprocessed in healthcare settings, the complex design of some devices makes it harder to remove contaminants. A device manufacturer's reprocessing instructions are critical to protect patients against the spread of infections. As part of its regulatory review for reusable medical devices, the FDA reviews the manufacturer's reprocessing instructions to determine whether they are appropriate and able to be understood and followed by end users. The guidance lists six criteria that should be addressed in the instructions for use with every reusable device to ensure users understand and correctly follow the reprocessing instructions.

Electronic Submission of Lot Distribution Reports – Guidance for Industry (Biologics)
This guidance provides licensed manufacturers of products distributed under an approved BLA with recommendations on how to submit lot distribution reports (LDRs) for biological products in an electronic format that the FDA can process, review and archive.

On 10 June 2014, the FDA issued a final rule which, among other things, amended the requirements as to biological LDRs required under 21 CFR 600.81. Specifically, under this rule, applicants are required to submit LDRs to the FDA in an electronic format that the Agency can process, review and archive (79 FR 33072). This reporting requirement is effective as of 10 June 2015. The rule does not change the content of these reports.

In addition, 21 CFR 600.81 provides that the Agency will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organisation of files). The purpose of this guidance is to provide that information. This guidance represents the Agency's current thinking on this topic.

CDER Ombudsman's 2014 Annual Report
The CDER Ombudsman receives inquiries and investigates complaints (in an informal, unbiased manner) from the regulated pharmaceutical industry, law firms or consultants representing industry, advocacy groups, public and private research institutions, healthcare practitioners, and consumers, and also provides general information on product development and regulation. The disputes or questions can be of a regulatory, scientific or administrative nature. The Ombudsman informally resolves disputes and disseminates information about established appeals processes and other formal mechanisms for dispute resolution. The Ombudsman also receives feedback about the CDER's programs and overall performance, advises management about program issues, and can assist with resolution of scientific differences of opinion amongst CDER staff. The Ombudsman makes recommendations for Center improvement to the Center Director and senior managers but cannot require action or mandate change because ombudsmen do not have disciplinary or enforcement powers.

International

Australia

Consultations on adoption of EU guidelines in Australia
ICH Q9, Q10 and several other EU guidelines below have been recommended for adoption or non-adoption by the Australian Therapeutic Goods Administration (TGA). These guidelines are open for comment on whether or not they should be adopted in Australia. The consultation process closed on 22 May 2015. This is a further step by the TGA towards harmonisation of legislation.

Evaluation of biosimilars
The understanding of biosimilar medicines is evolving and, as a result, the current TGA guideline *Evaluation of Biosimilars* may need to be updated.

Therefore, in addition to the TGA undertaking a review of the policy about the naming convention for biosimilars, it is currently reviewing the rest of the TGA guideline on the evaluation of biosimilars.

Parties intending to submit an application to register a biosimilar medicine are advised to seek advice early about the evaluation of biosimilars.

Canada

Inspections database
Health Canada has made available access to its inspection database for both foreign and domestic facilities. The database goes back to 2012, is extensive and easy to use.

Inspection Tracker: Drug Manufacturing Establishments
As part of Health Canada's ongoing commitment to openness and transparency, the Department is publishing information regarding emerging issues identified through its drug inspection program.

This tracker provides a snapshot of the potential health and safety issues Health Canada is tracking with companies that fabricate, package/label, test, wholesale, distribute or import drugs for sale in Canada. The information in the chart will expand to eventually include details about affected Canadian companies and products.

PIC/S

Membership updates
Thailand's Food and Drug Administration (Thai FDA) applied for PIC/S membership. The Pharmacy and Poisons Board of Hong Kong (PPBHK), Hong Kong SAR is to join the scheme from 1 January 2016 and will become PIC/S' 47th Participating Authority. China (CFDA) is set to join PIC/S in the near future.

Principal outcomes of the PIC/S meetings held 11–12 May were as follows

- **Strengthening of international regulatory cooperation in the field of GMP** – The aim being to encourage PIC/S members to accept inspection findings

on a voluntary basis, by relying on mutual trust and confidence building, based on the PIC/S accession process.

- **PIA** – Updates were provided on:
  - PIC/S Working Group on Harmonisation of Classification of Deficiencies;
  - PIC/S Working Group on Advance Therapy Medicinal Products;
  - EMA–PIC/S Joint Drafting Group on the revision of Annex 1 (Sterile Manufacturing) of the PIC/S-EU GMP Guide;
  - PIC/S Project Management Steering Committee in charge of the PIA;
  - PIC/S Working Group on Good Clinical Practices and Good Pharmacovigilance Practices;
  - In addition, the Committee decided to establish new working groups on:
    - o Data Integrity;
    - o Veterinary Medicinal Products;
    - o Controlling Cross-Contamination in Shared Facilities.

A number of external stakeholders such as the International Society for Pharmaceutical Engineering, the Parenteral Drug Association, International Federation of Pharmaceutical Manufacturers and Associations and the World Health Organization have expressed interest in the PIA project.

Products

Treanda Injection (solution) and closed system transfer devices

The FDA is warning healthcare professionals not to use Treanda (bendamustine hydrochloride) Injection (45 mg/0.5 mL or 180 mg/2 mL solution) with closed system transfer devices (CSTDs), adapters, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS). CSTDs are devices that are used to prepare and administer hazardous drugs for intravenous infusion, such as chemotherapy drugs. Most marketed CSTDs contain either polycarbonate or ABS and are not compatible with Treanda Injection (45 mg/0.5 mL or 180 mg/2 mL solution).

Oxytocin in 5% dextrose injection products were not withdrawn from sale for reasons of safety or effectiveness

This determination will allow the FDA to approve an ANDA for these oxytocin drug products, if all other legal and regulatory requirements are met.

GVK Biosciences: EMA confirms recommendation to suspend medicines over flawed studies

The EMA has confirmed its recommendation to suspend a number of medicines for which authorisation in the EU was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India. This is the outcome of a re-examination requested by marketing authorisation holders for seven of the medicines concerned.

Originally, an inspection of GVK Biosciences' site at Hyderabad by the French medicines agency (ANSM) raised concerns about how GVK Biosciences conducted studies at the site on behalf of marketing authorisation holders.

During the re-examination, the Committee for Medicinal Products for Human Use concluded that concerns about reliability of the clinical studies remain and, therefore, maintained its recommendation of January 2015 to suspend medicines for which no supporting data from other studies were available. This is with the exception of one medicine included in the re-examination for which concerns about studies were addressed. This medicine is now no longer recommended for suspension.

As a result of the re-examination, around 700 pharmaceutical forms and strengths of medicines studied at the Hyderabad site remain recommended for suspension. For around 300 other pharmaceutical forms and strengths, sufficient supporting data from other sources had been provided; these medicines will, therefore, remain on the market in the EU.

(This is yet another example of serious issues concerning lack of data integrity and evidences the firm actions which EMA will take when such issues are discovered – MH.)

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

European Journal of Parenteral & Pharmaceutical Sciences 2015; **20**(2): 80

PHSS Activity and Initiatives Report

The PHSS continues to restructure to grow international membership and provide significant advantages as a member, with free website downloads of technical monographs, regulation change impact papers, White Papers and regulation updates.

The conference focus has also changed, with two major annual (high interest) events scheduled including the Annual Conference and the Sterile Product Processing Conference. In addition, one hot topic event (reactive) will be considered each year. To complement UK conferences, the PHSS have commenced Webinars, free to members, at times suitable to engage international members, with the first topic covering Disinfection and Sterilisation.

The Annual Conference at University College London (UCL) School of Pharmacy, in association with the UCL Q3P course for qualified persons, will be of particular importance this year as there are more regulation changes than ever that have potential high impact.

The change to *EU Guidelines to Good Manufacturing Practice* (GMP) Annex 1 is expected to be significant, and at the Annual Conference together with a briefing on progress of revision from Andrew Hopkins, Senior MHRA Inspector and Chairman of the European Medicines Agency (EMA) Annex 1 Revision Working Group, a discussion session has been organised between representative organisations that put forward recommendations for Annex 1 revision to the EMA Working Group. Representatives to the discussion panel are from the PHSS, the Parenteral Drug Association (Europe and USA), A3P France, the International Society for Pharmaceutical Engineering (Europe and USA), N3 Nordic and the European Compliance Academy. Key topics of revision will be discussed.

There is also continuation of special interest groups (SIGs) to consider new challenges and develop best practice guidance as important peer reviewed references, all accessible as a free download to PHSS members.

The Bio-contamination SIG, who prepared monograph 20, is to reform in September to complete worked examples of risk-based environmental monitoring plans for a number of reference cases, e.g aseptic filling sterile products in restricted access barrier systems (RABS), isolators on small and large scale, and sterility testing and formulation/dispensing.

Guidance in setting environmental monitoring plans is much needed as aseptic processing develops, combining cleanroom and RABS/isolator monitoring in risk-based programs. New plans need to consider holistic monitoring initiatives, meeting risk assessment requirements, and recognising an environmental monitoring plan includes a number of linked programs, e.g. at start-up classification, through process simulations/media fills, during routine production operations and at shift/batch end.

The PHSS website developments continue to meet new membership profiles and interaction requirements.

To support all these new initiatives, the PHSS has been granted a Lottery fund award, as such changes require significant investment to maintain the PHSS as one of the leading contributors to GMP education and best practice guidance.

After many years of recognised and highly valued service, Gordon Farquharson is to step down as Editor-in-Chief of the *EJPPS*. The current Vice-Chairperson of the PHSS, Kay O'Hagan is to take over the role of Editor-in-Chief and the PHSS wish her well in this new role. Replacing Kay as Vice-Chairperson is Jenni Tranter of Synergy Health, a committed PHSS management committee member and, again, we all wish Jenni well in this new role.

Many changes are ahead, making it even more important to engage in the process of change via societies like the PHSS where information is provided and there is a chance to influence change.

James L Drinkwater
Chairman of the PHSS

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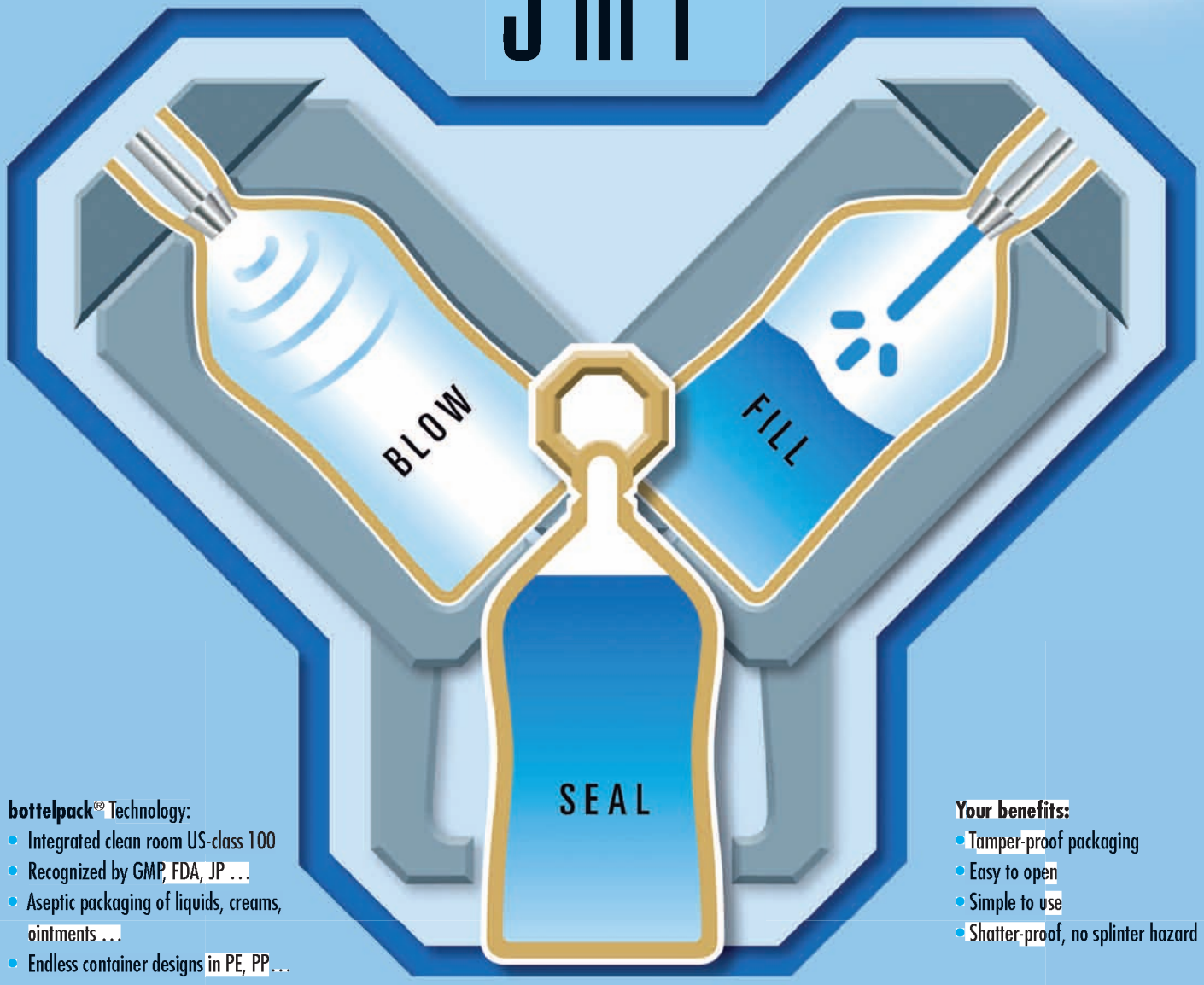

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