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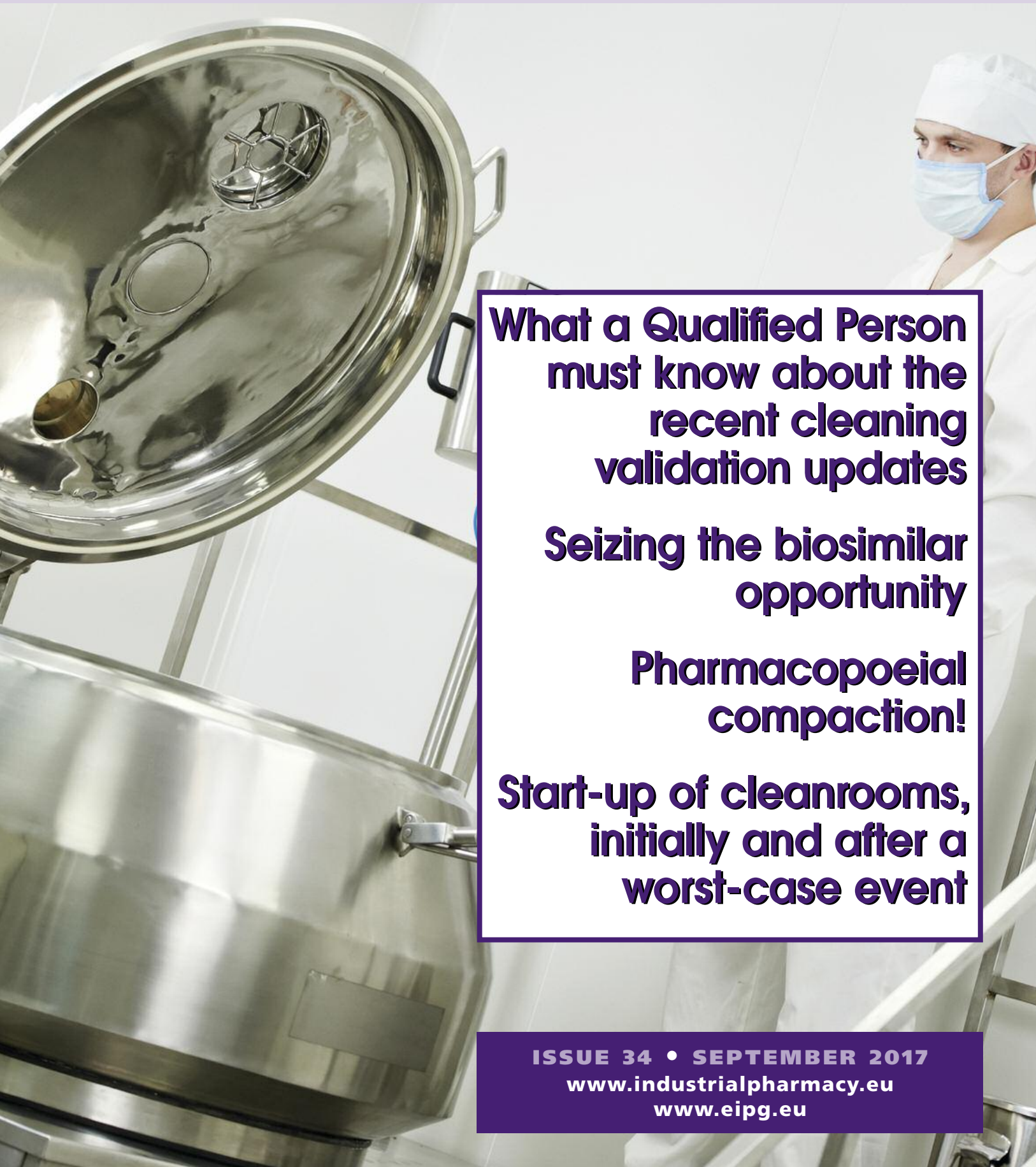

What a Qualified Person must know about the recent cleaning validation updates

Seizing the biosimilar opportunity

Pharmacopoeial compaction!

Start-up of cleanrooms, initially and after a worst-case event

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Cover photo: Visual inspection of a bulk vessel after automated cleaning (see What a Qualified Person must know about the recent cleaning validation updates on page 4)

editorial

Science without boundaries and pharmacy across frontiers

Over the last 20 years working in the industry, I have witnessed, if not experienced first-hand, the many changes that the industry has undertaken and the evolution of medicines development.

What I have also seen evolve is how the industrial pharmacist role has developed in tandem. It was fair to say that many pharmacists entering industry would usually work in quality, regulatory and development functions. In the last 10 years, I have seen more and more pharmacists entering more clinically and medically focused roles – as opposed to more technically focused career pathways.

I, for one, welcome this diversity of opportunities for pharmacists entering industry, as it demonstrates my belief, my passion, that pharmacists with a balance of clinical, medical and scientific skills underpin our roles as medicines development experts. Pharmacists are important cogs in the machinery that is healthcare – particularly as there are a number of challenges facing the global stage such as the following.

Living longer – It has now been estimated that in the UK, 1 in 3 women and 1 in 4 men will live to 100 years of age. This increased longevity combined with diseases related to age onset, will provide enormous challenges for healthcare systems.

Anti-microbial resistance – We need new antibiotics but also need to curb the resistance of microbial organisms to antibiotics.

The rise of obesity and diabetes – This is not just a European problem – estimates show that there are over 65 million diabetics in China alone where inactivity combined with western diets has caused a diabetes explosion.

These social and healthcare issues present enormous challenges for healthcare providers, but they also provide enormous opportunities for pharmacists working across the sectors of industry with community and hospital to provide the right therapy to the right patient at the right dose and at the right time.

At the heart of all these complex interactions – is collaboration – the healthy exchange of scientific debate, discussion and communications. Increased communication on all matters pharmacy is the main reason why I am a strong advocate of the European Industrial Pharmacists Group and for Claude Farrugia who is the current President.

The EIPG has been supporting the industrial pharmacist for over 50 years (imagine that) and has worked tirelessly in entering the various consultations to make sure that the voice of the industrial pharmacist and ultimately of patients is heard.

With that in mind, I believe that the EIPG ensures that science crosses boundaries and that pharmacists work across frontiers.

Professor Gino Martini FRPharmS FEIPG
EIPG Past President

WHAT A QUALIFIED PERSON MUST KNOW ABOUT THE RECENT CLEANING VALIDATION UPDATES

by Walid El Azab

Prevention of cross-contamination is one of the topics in the centre of the recent European Guidelines to Good Manufacturing Practice (GMP) updates. Various EU Guidelines to GMP chapters and annexes were updated to set new requirements regarding cross-contamination control. Robust cleaning validation and setting health-based exposure limits have been identified as effective ways to prevent cross-contamination.

Walid El Azab is a Technical Services Manager for STERIS Life Science and a former QP. He currently provides technical support related to cleaning chemistries, disinfectants and sterility assurance products and their application and validation. His areas of expertise include both upstream and downstream biopharmaceutical operation and validation. Walid earned a Master's degree in Industrial Pharmaceutical Sciences from the University of Liège, Belgium and is a certified Lean Six Sigma green belt. Walid also gives Industrial Pharmaceutical Sciences Master courses at the University of Liège (Belgium). Finally, Walid is an active member of the PDA, ISPE, ECA, A3P and is Secretary of the Belgium QP Association (UPIP-VAPI).

Introduction

Validation is still among the top 10 of the 2015 and 2016 GMP inspection deficiencies published by the UK Medicines and Healthcare Products Regulatory Agency (MHRA)[1,2]. With regards to cleaning validation and cross-contamination control observations, the MHRA expects the manufacturer to consider the toxicity and potency risk of a new product in order to determine the need for any degree of dedicated facility or equipment[1]. The quality assessment and cleaning risk assessment must integrate the toxicity or the potency, the sensitisation and the cleanability of existing and new products (i.e. including investigational medicinal product (IMP) and active pharmaceutical ingredient (API)) prior to receiving and using them on site[1].

The qualified person (QP) must have visibility of critical documents referring to, for example, the product quality, the cross-contamination and the cleaning risk assessments. Therefore, the QP must be aware of the cleaning validation strategy in place to implement the new set of requirements. The QP must further confirm that the product quality impact assessment demonstrates that the product is still safe for the patient, based on the gap analysis performed by the manufacturer. Finally, it is recognised that the QP will need to rely on the pharmaceutical quality system (PQS) and that the QP should have on-going assurance that this reliance is well founded[3]. Note that the quality system is in the first rank of top 10 inspection deficiencies observed by the MHRA during 2015 and 2016 while, in 2013 it was in the second rank[1,2,4].

The first part of this article covers key changes to cleaning validation guidance, including setting limits and identifying worst-case active residue that should be part of the cleaning life cycle program. The second part will discuss the various QP responsibilities regarding the new set of requirements for cleaning validation.

Regulatory requirements for cleaning validation

The following documents explain the new requirements on cleaning validation[5].

- The European Medicines Agency (EMA) revised its Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities, applicable since June 2015[6]. Active or detergent residue limits (maximum acceptable carry over – MACO) must be assessed through health-based limits using the permitted daily exposure (PDE). The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime. The PDE is calculated using the NOAEL (no observed adverse effect level), the body weight and five uncertainty factors. The lowest observable adverse effect level (LOAEL) would be acceptable to use if the NOAEL data could not be determined[7]. The PDE must be assessed by an experienced toxicologist. The toxicologist will gather toxicological, pharmacological and clinical or non-clinical data to define a starting point to calculate the NOAEL or LOAEL. This can be done in two different ways: (a) a review of the Safety Data Sheet (SDS) and data in the literature of the starting materials used in the API formulation and the final medicinal product formulations, or (b) through a review of different clinical or non-clinical data to assess if the product or cleaning agent residue is non-toxic, toxic, sensitiser, allergenic, etc. Finally, the toxicological data

must be part of the worst-case product identification assessment, except if the active residue is known to be degraded and may become pharmacologically or toxicologically inactive.

- The EU Guidelines to GMP Annex 15 Qualification and Validation (applicable since 1 October 2015[8]) requires cleaning validation to be based on a scientific and risk-based approach. As a result, a "visually clean only" criterion is no longer acceptable unless a scientific justification supports otherwise. The number of validation runs required may be determined through a risk assessment justification. To demonstrate robust cleaning, sufficient data is to be captured through continuous monitoring or on-going verification. The ongoing verification frequency will be driven by the quality and business risk assessment results. The guideline also requires that the active residue limit is calculated using toxicological data (health-based limit). As such, the worst-case residue should be determined based on solubility, cleanability and potency, including toxicological data review. Finally, dedicated equipment should be considered when a cleaning process is ineffective to render results below the calculated limit.
- The EU Guidelines to GMP Chapter 3 Premise and Equipment and Chapter 5 Production were also revised and applicable since 1 March 2015. The documents place emphasis on prevention of cross-contamination and on toxicological assessment[9,10].

Impact of the changes on cleaning limit to be used

The new regulations require the MACO calculation to include the use of the health-based exposure limits based on the method for establishing the PDE or other scientifically justified methods, as described in Appendix 3 of International Council for Harmonisation (ICH) Q3C (R4) and Appendix 3 of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) GL 18[6]. It is known that, for a compound, the PDE value could vary amongst toxicologist and route of exposure[5].

The worst-case active residue is considered the one with the lowest MACO value including the results of the solubility and cleanability assessment (see **Figure 1**). Consequently, if for non-dedicated equipment the MACO based on health-based limits is lower than the established limit, a cleaning revalidation should be performed. The number of runs requires a risk-based justification. On the other hand, if the currently established limits are lower than the health-based limits, a simple justification should be written to demonstrate that the MACO currently used is the safest to prevent cross-contamination. In some cases, an increase of the cleaning limit can be justified[11].

The 10 ppm criterion does not comply with the scientific approach proposed by the International Society for Pharmaceutical Engineering Risk-Based Manufacture of Pharmaceutical Products or the EMA guidance[6,12,13]. Therefore, the use of the 10 ppm criterion without adequate justification from a health-based approach is unacceptable[13]. Moreover, the worst-case residue determined based on the health-

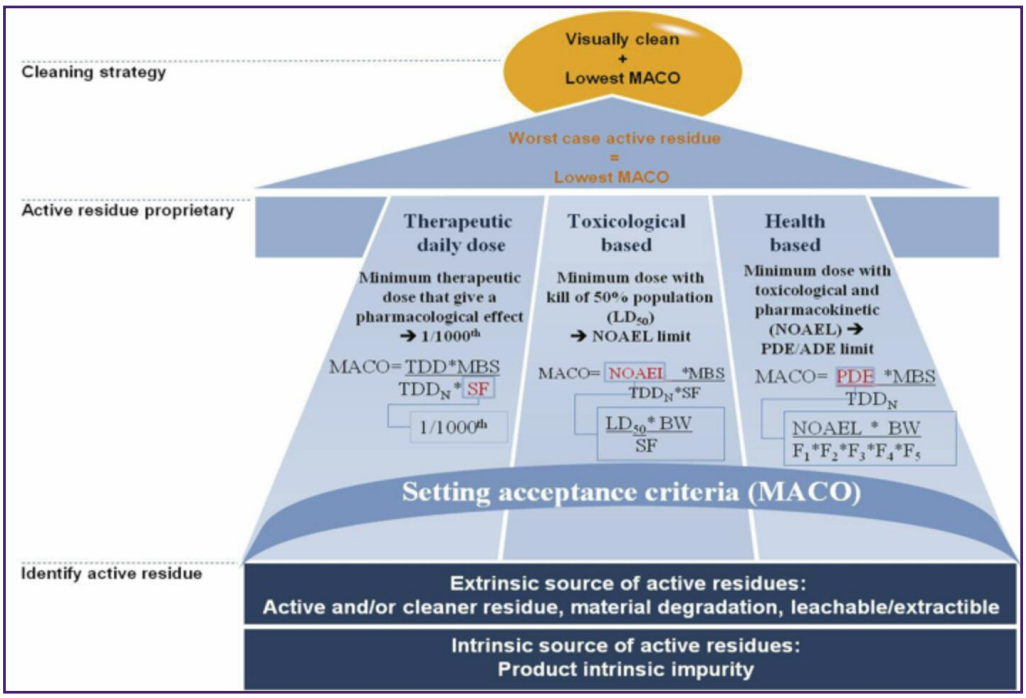

Figure 1. Cleaning program strategy for acceptance criteria setting[5,11,12].

based approach may be different compared to that using the 10 ppm criterion[14]. Note that the 10 ppm criterion was initially used in a publication by Fourman and Mullen to provide a default value and not as a substitute for a dose-based calculation[15].

QP responsibility regarding cleaning validation strategy

The QP needs to rely on the PQS[3,4,16,17]. A robust PQS should trigger an alert to the manufacturer when GMP guidelines are updated. In response, the manufacturer must assess the gap between the current cleaning validation practices and the new set of requirements. A gap analysis must be performed to assess the impact on the product quality, cross-contamination and cleaning risk assessments. Based on the gap analysis result, an implementation approach under a change control process must be developed to achieve compliance. It is the duty of the QP to ensure that these steps have been performed prior to certifying and releasing a batch[3]. When it is not the case, a deviation must be initiated and an action plan must be identified to achieve compliance.

The implementation approach must be supported by a cleaning risk assessment which can be used to prioritise the PDE residues evaluation. The cleaning risk assessment, in addition to the other cleaning parameters, must take into consideration data such as minimum therapeutic dosage, minimum lethal dose 50 (L/D50), NOAEL, LOAEL, lowest-observed-effect level, thresholds of toxicological concern, occupational exposure level or occupational exposure band. The QP must have visibility of the cleaning risk assessment and monitor the PDE evaluation progress. Finally, based on the prioritisation results, it is acceptable to justify generating the PDE value over a defined schedule.

The QP must confirm that the API manufacturer follows the current EU Guidelines to GMP and Active Pharmaceutical Ingredients Committee document on cleaning validation[13,18]. The API manufacturers must calculate the residue MACO based on the PDE value[18]. The PDE value can vary depending on the route of exposure[11]. It is the responsibility of the QP to ensure that the API PDE value is calculated based on the final drug route of administration. Otherwise, a correction factor for route-to-route extrapolation should be applied if there are clear differences (e.g. > 40%) in route-specific bioavailability[6].

Equation 1: SAL = MACO (mg)/shared area surface (cm^2) = mg/cm^2

Any activity outsourced to a contract manufacturer (CM) should be appropriately defined[19]. The CM must be qualified in accordance with Chapter 7 of the EU Guidelines to GMP[19]. It is the responsibility of the CM QP to ensure that the product certified is compliant with current EU GMP. Depending on the contract agreement, the marketing authorisation holder (MAH) must share the PDE value of the different products with the CM. The CM must calculate the new health-based MACO to confirm that the MACO currently used onsite is the safest one. The surface area limit (SAL) and the swab limit must be based on the shared surface area (**Equation 1**).

However, in the event that a part of the production process is started by the MAH and then finished by the CM, the CM should integrate the MAH shared surface area in order to calculate the SAL. The SAL must be applicable for both, unless a scientific justification supports otherwise. It is the responsibility of the QP, based on reliance on the PQS, to ensure that the correct MACO and SAL are calculated to prevent cross-contamination and risk to the patient. Finally, it is the responsibility of the MAH QP to ensure that the PQS of the CM is working and to inform the MAH QP of changes that may impact the decision to certify a batch.

In case the product is from a third country, the QP certifying and releasing the product for the European market is solely and fully responsible for all the manufacturing taking place in the third country[3]. Therefore, the QP must be able to guarantee that the manufacturing process follows EU GMPs. In addition, the PQS of the manufacturer in the third country should ensure the QP is informed of a change that may impact the decision of certifying and releasing the product.

One of the best ways for the QP to confirm reliance on the PQS is to conduct an assessment by visiting the operations to observe routine practices against the PQS and procedures in place. An example for deficiencies observed during a 2016 audit by the MHRA was that "The QP did not ensure that he had current knowledge of the company PQS"[2]. Amongst the top 15 deficiencies observed in the field by the United States Food and Drug Administration from FY13 to FY16 were as follows[20].

- 21 CFR 211.67(a) "Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product."
- 21 CFR 211.67(b) "Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product."

In addition, the MHRA shares examples of deficiencies observed in the field from April 2011 to April 2012, and during 2013, 2015 and 2016[1,2,21,22].

- The cleaning validation was deficient to ensure effective removal of residues.
- There was no cleaning validation of non-dedicated sampling tools.

- The cleaning verification was not performed.
- The effectiveness of the spray balls has not been demonstrated or controlled adequately.

It is expected that the QP goes to the manufacturing area and that he or she has sufficient understanding of the manufacturing process to judge compliance. Of course, the audit process is delegated to an experienced team of internal auditors. Finally, the QP must be informed of major to critical deficiencies that may impact his or her reliance on the PQS or assessment of product quality.

Finally, for product non-contact areas (e.g. cleanroom, dust collector, facility environment), the cross-contamination risk assessments must be updated to integrate the toxicity and potency risk of existing or new product. Based on the risk assessment result, the decision to dedicate facility, equipment or re-validate the cleaning and disinfection process must be discussed and justified. The QP must be aware of any changes that may impact the cross-contamination prevention procedures in place or the product quality.

Conclusion

It is the responsibility of the QP to make sure that the PQS in place is capable of alerting about any changes in the regulatory requirements for the manufacturing or the cleaning processes that may impact product quality. Adequate and formal communication processes between departments is one of the key features of a robust PQS. The QP will need to rely on the PQS, but should have on-going assurance that this reliance is well founded[3]. A best practice to confirm reliance on the PQS is by testing it through field observations of routine practices against procedures in place. Finally, the QP must monitor and have an overview of the critical parameters and documents that confirm the product is safe for the patient, including cross-contamination management and control.

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SEIZING THE BIOSIMILAR OPPORTUNITY

by Warwick Smith

Biological medicines are playing a significant role on a global scale in providing effective treatments for patients and contributing to improved survival rates, as well as providing a better quality of life. However, biosimilar medicines – equivalent products which have no meaningful differences from the original or reference product in terms of quality, safety or efficacy – also have important roles to play in providing choice for clinicians, increasing access for patients by driving down cost and ultimately improving patient outcomes. Warwick Smith, Director General of the British Biosimilars Association (BBA) outlines the challenges and opportunities in the UK.

Warwick Smith is the Director General of the British Generic Manufacturers Association (BGMA) and the British Biosimilars Association (BBA). He is a member of the Board and Executive of Medicines for Europe, and was previously one of its Vice Presidents.

During Warwick's period as Director General of the BGMA, the Association has negotiated a long-term market-based reimbursement system for generic medicines giving the industry freedom of pricing, and has agreed work sharing schemes with the national regulatory agency (MHRA) to reduce significantly the workload on members. He led the launch of the BBA in 2016 to help raise awareness and increase education on the topic of biosimilars.

Biological medicines and their follow-on equivalent biosimilar medicines have a significant role to play in future healthcare delivery in the UK, and the crucial impact of biosimilar medicines cannot be ignored or underestimated for patients and payers alike.

Biological medicines are protein-based and made or derived from living organisms. Unlike traditional chemical equivalents, they can be tailor-made so they bind to specific targets in the body. A biosimilar medicine is manufactured to be highly similar to an existing licensed "reference" biological medicine after expiry of its patent, with no meaningful differences in terms of quality, safety or efficacy. Biological medicines are dominating global lists of the best-selling prescription drugs. Very successful treatments for rheumatoid arthritis and autoimmune diseases have led the way and, as we move forward, in other disease areas, such as oncology, biosimilar medicines are increasingly coming to the fore.

With UK healthcare budgets stretched by ageing populations, technology investment and advances – which mean diseases can be detected earlier and treated later – affordability and value are key elements of widening patient access. So, as biological medicines play a more significant role in providing life-saving and life-enhancing treatments, greater uptake of biosimilar medicines is critical.

The competition they bring will create savings which will allow already stretched budgets to be more efficiently spent, and crucially increase patient access to these vital treatments. These are the same principles which have always underpinned the generic medicines market in the UK which is among the most successful in the world and on average saves the National Health Service (NHS) more than £13bn every year according to figures from the British Generic Manufacturers Association.

Typically, generic competition will quickly deliver savings of up to 90% of the originator's price. For biosimilars, it is unclear what a typical price decay will be – even if such a thing exists – due to the relative newness of the market and the complexity of these medicines. However, while overall percentage savings are likely to be less than for generic medicines, they will be from a comparatively higher starting price than a generic medicine meaning savings are likely to be very significant.

This potential for savings and increase of access via biosimilars is being recognised by NHS England at the very top. Earlier this year, NHS England Chief Executive Simon Stevens updated the organisation's 5-year forward view. This was a far-reaching announcement building on the original strategic blueprint for healthcare delivery which was outlined in October 2014.

The rationale was to share information on progress, as well as map out where NHS England would be focusing its priorities in the coming years and how it would manage the maintenance of the system which is facing increasing demands and budgetary pressures.

Among the detail, the document importantly said that four Regional Medicines Optimisation Committees (RMOCs) will drive medicines take-up and efficiency, for example, through the use of generics and biosimilars and by reducing wastage. The formation of RMOCs was first announced earlier this year with a remit to provide advice and make recommendations on the optimal use of medicines for the benefit of patients and the NHS. The rationale was that they would bring together decision makers and clinicians across the four regions of England, to share best practice, understand the evidence base, coordinate action and so reduce

unwarranted variation, thus improving outcomes and value.

Delivery activity for RMOCs has started and over the coming 12 months they will establish themselves looking at a wide range of areas to help patients, public and society more broadly get the best outcomes from medicines. Top of their agenda – and reflecting Simon Stevens' forward plan – will be ensuring a rapid increase in uptake of biosimilar medicines. This is a significant move and will ensure continued knowledge-sharing on biosimilars as well as take-up and, therefore, deliver further savings.

In the past few years, due to the relative lack of comparable clinical experience and thus real word understanding, some clinicians and patients have been more cautious to fully embrace the use of biosimilars, although there are areas of clear progress and success. The industry along with NHS England, regulators and the National Institute for Health and Care Excellence (NICE) have focused on driving forward broad awareness and education of biosimilars and their potential impact.

As a result, acceptance and usage has markedly increased in many areas of the UK. As experience has deepened, so has understanding, particularly around topics such as switching patients from the originator or reference product to a biosimilar, which is needed to drive the full benefit of biosimilars in enhancing patient access.

NHS England has done a great job in bringing together the full range of stakeholders – NICE, the Medicines and Healthcare Products Regulatory Agency (MHRA), pharmacy, industry groups, patient groups and doctors and nurses – to understand why biosimilar medicines should be routinely adopted, and why switching from the originator is a perfectly natural thing to do, that is underpinned by the regulatory science.

Elsewhere, interchangeability has also been an area of scrutiny partly driven by different understandings of the term. Biosimilar medicines are only approved in the EU when determined by the regulator to have the same clinical effect in a given clinical setting as the reference medicines. This means that biosimilar medicines are approved to be clinically interchangeable with the reference medicine; i.e. that the originator product or a biosimilar may be chosen by clinicians in the knowledge that each will have a comparable clinical effect on the patient.

The European Commission define interchanging as meaning – the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with agreement of the prescriber. Understanding this is essential in giving confidence to clinicians to prescribe a biosimilar medicine in new patients and to switch existing patients on to a biosimilar medicine.

Clinicians can confidently choose an originator product or a biosimilar of that product in clear anticipation of delivering a comparable clinical outcome. Interchangeability does not refer to automatic switching of patients from one product to another without the guidance of the clinician, or automatic substitution by a pharmacist at the point of dispensing the medicine.

In NHS England's document 'What is a Biosimilar Medicine?', NHS England recommends the switching of patients onto biosimilar medicines at the discretion of prescribers; which is consistent with the position taken in Finland where the Finnish Medicines Agency guidance states that biosimilars should be considered interchangeable with their reference product under the supervision of a healthcare person. French (Agence Nationale de Sécurité du Médicament et des Produits de Santé), Dutch (Medicines Evaluation Board) and German (Paul-Ehrlich-Institut) authorities have also developed clearer positions on interchangeability.

Elsewhere, a recent paper by the European Society for Medical Oncology (ESMO) stated that biosimilars present a necessary and timely opportunity for physicians, patients and healthcare systems. If suitably developed clinically, manufactured to the correct standards and used appropriately, biosimilars can positively impact on the financial sustainability of healthcare systems, according to ESMO.

They – like the BBA – are opposed to automatic substitution but positive that interchangeability is assured by European regulation and that switching should be permitted if the physician is well-informed about the products; the patient is fully briefed; and a nurse is closely monitoring the changes and tracking any adverse events.

In our view, it is clear that biosimilar medicines approved for use in the same clinical indications are interchangeable with their reference products based on the regulatory science and real world evidence. The same understanding underpins advice from NICE, NHS, MHRA and stakeholders including professional bodies and patient groups, and this and the currently available evidence will help bridge the gap between the clear EU regulatory policy and decisions, prescribing and medical practice in the UK.

This assurance from a wide group of stakeholders will give healthcare providers and patients confidence in their medicine to ensure the necessary savings for the NHS and provide the opportunity to expand patient access to biological medicines.

PHARMACOPOEIAL COMPACTION!

by Michael Gamlen

The United States Pharmacopoeia (USP) does a fine job of using experts to make the complex understandable. In the solid materials area, Chapter <1062> explains the principles of particle size measurement by laser light diffraction, and covers the measurement of powder flow properties. Readers may not have seen Chapter <1062> entitled "Tablet Compression Characterization". The authors Gregory Amidon and Calvin Sun have excelled in setting out and explaining important properties of materials in the context of the compaction triangle. The key measurements proposed in this monograph can be used to help you understand relevant tablet properties that are essential to the tableting process. In this article, I will explain some applications of the three compaction triangle relationships – tabletability, compactibility and compressibility, and how the data presentation can be applied to the optimisation of tablet formulations.

Michael Gamlen studied for a PhD with Professor JM Newton at Nottingham University and was Head of Solid Dosage Form Development at the Wellcome Foundation Ltd for 15 years. He is the inventor of the Gamlen Powder Compaction Analysis System, and works as a consultant and trainer. He is a regular contributor of articles on tableting and powder compaction.

The compaction triangle (see **Figure 1**) proposed by Gregory Amidon uses measurements of tablet compaction pressure, tablet tensile fracture stress (TTFS), and tablet solid fraction or density. It is simple to visualise compaction pressure, it is the load applied to the tablet divided by the tablet area. The tablet area normally used is the simple cross-sectional area of the punch without adjusting for punch tip shape.

TTFS is a more complex concept. Fell and Newton (1968)[1] proposed the use of TTFS for the characterisation of simple cylindrical tablets. Its application has been extended to other shapes by Pitt and Heasly[2] (see **Figure 2**). The TTFS is calculated from the tablet breaking load measured in tension, the dimensions of the tablet, and a stress factor which is dependent on the shape of the tablets. Breaking load is normally measured in tension using the diametral compression test identified by Newton. For a cylindrical tablet this is straightforward. Capsule shaped tablets are tested by measuring the breaking load of the tablet in the lengthwise direction. The stress factor for this calculation is dependent on tablet shape, which for a cylindrical tablet is $2/\pi$; the formula for alternate shapes is conveniently documented in USP Chapter <1217>. Tablet thickness is the final element needed for a breaking load calculation – regardless of tablet shape.

Newton's 1968 publication[1] showed the value of TTFS measurement. In it, he was able to distinguish between two samples of lactose differing only in particle size by comparing their TTFSs – and clearly demonstrated that TTFS is an extremely discriminating material property. Another important observation in the same paper was the linear relationship between TTFS and tablet compaction pressure. This turns out to be a fundamental material property independent of tablet size, which means that tablets produced at one size can be used to predict the properties of a tablet of a completely different size and shape. For example, Pitt and Heasly in their 2013[2] publication showed that 100mg round tablets produced on a Gamlen Tablet Press (GTP-1) correctly predicted the properties of an 800mg capsule-shaped tablet made on a Fette 2090 rotary press under actual production conditions. Newton's earlier work demonstrating that tableting data generated on a small-scale using a simple cylindrical shape can, therefore, be used to predict the compaction force needed to make tablets of any particular hardness and shape using the same formulation under production conditions, and gives us our first application of the tabletability concept.

Returning to **Figure 1**, we can see that the relationship between TTFS and tablet compaction pressure has been assigned the name "tabletability". Pharmaceutical production prefers to operate in the compaction pressure range up to 200MPa, in which many materials exhibit a linear relationship between compaction pressure and TTFS. Linearity is retained beyond 200MPa for some materials – to 300MPa or even higher; but for other materials the TTFS can level off or even start to fall rapidly. Non-linear TTFS results from the inability of a material to compact further. Instead, the additional pressure generates defects in the tablets resulting in reduced hardness which often translates into capping and lamination problems. Tabletability profiles for a good, and a poor, tablet product are seen in **Figure 3.**

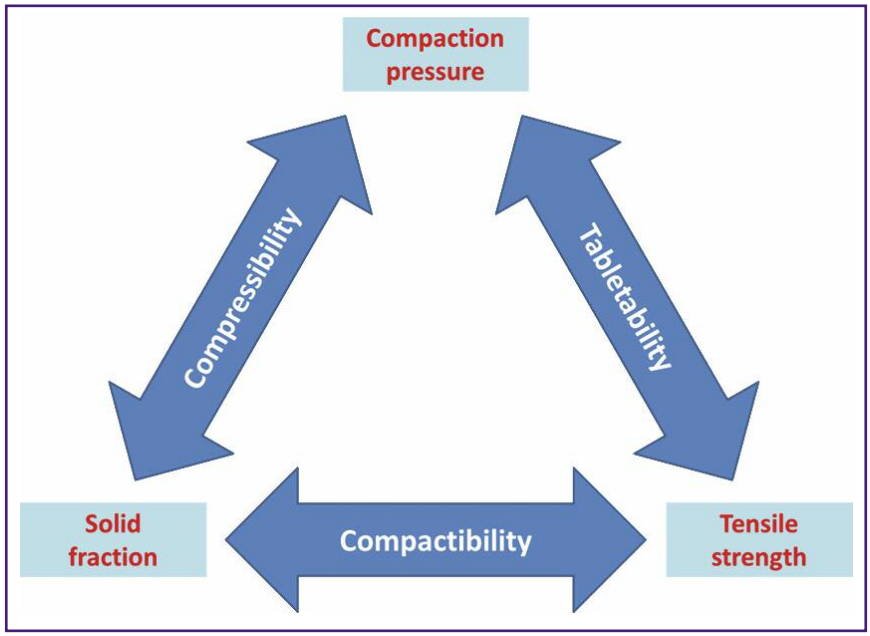

Figure 1. The compaction triangle.

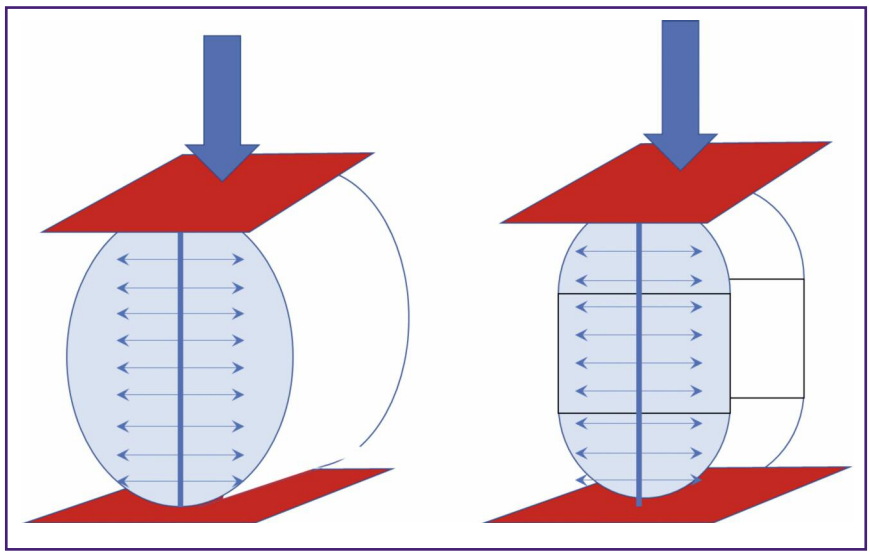

Figure 2. Tensile fracture testing of cylindrical and caplet-shaped tablets.

The good product shows a regular linear increase in TTFS in the pressure range to 250MPa, whereas the poor product shows that if the product is compressed beyond 150MPa, the TTFS is reduced.

The impact of over-compaction at high product densities can also be seen in the second important measure from the compaction triangle (**Figure 1**), which is compressibility – the relationship between compaction force and tablet density. A compressibility plot as per USP Chapter <1064> uses the calculated solid fraction of the tablet. Solid fraction is the density of the sample relative to the true density of the material. If the true density of the material is not known, and the solid fraction cannot, therefore, be calculated, the actual tablet density can be used instead as long as comparisons are made with a material of the same composition. As a material reaches its compaction limit, the application of additional compaction force does not result in any further increase in density. In some cases an apparent decrease in density is seen, although this probably results from damage to the tablet. The limit is observed as a levelling off in the compressibility plot.

Designing a tablet in a density regime in which the tablet density can no longer be increased is highly inadvisable for a number of reasons. If an operator cannot achieve the target hardness value for the tablet for any reason, their normal response will be to increase the compaction pressure. Under normal conditions, this additional pressure will increase tablet hardness. However, for a material which has reached its compaction limit, this simply makes the tablet weaker, and causes confusion to the operator (who may further increase pressure instead of reducing it).

The third element of the compaction triangle is the compactibility plot, which is TTFS versus tablet solid fraction (or simple density). As a general principle, it is best to make a product using the highest possible porosity (lowest density) at the required hardness (TTFS). This is for two reasons. Firstly, doing so keeps the product away from high density regimes associated with over-compaction. Secondly, higher porosities will normally show increased dissolution properties of the product by enhancing water penetration rates. So, all other things being equal, a higher porosity product would be selected in preference to a lower porosity product.

To demonstrate the application of the compaction triangle, I have included compaction triangle data on the impact of particle size on tablet properties. Particle sizes of both drug substances and excipients have been demonstrated to affect compaction behaviour and tablet properties. However, the direction of these changes cannot be readily predicted. In most, but not all, cases, smaller drug substance and/or excipient particle size will produce a stronger tablet at a given compaction pressure, thus it is very important to characterise this relationship early and often during the formulation process

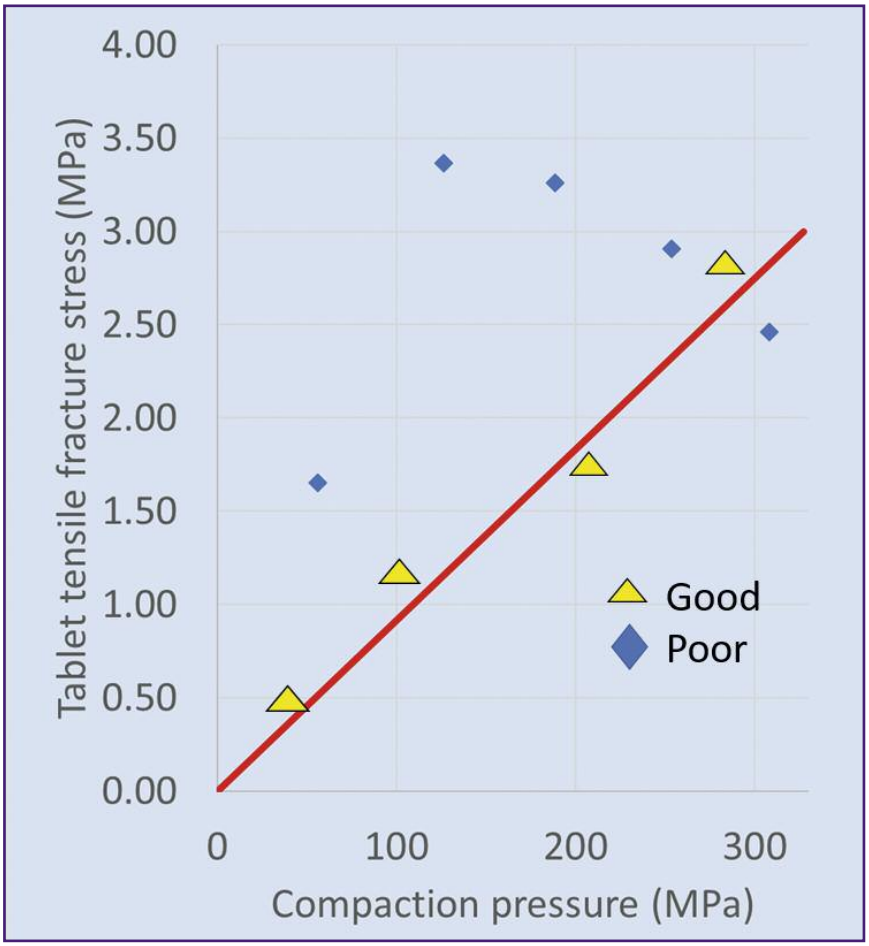

Figure 3. Tabletability profile.

Tabletability, compactability and compressibility are brought together in **Figure 4**, which compares the compaction triangle plots of a coarse and a fine material. The effect of particle size can clearly be seen. In the compactibility plot (**Figure 4A**), the TTFS of the fine material is substantially higher than the TTFS of the coarse material at any given tablet density. The fine material also achieves a much higher TTFS demonstrating that it is inherently much more suited to tableting. The maximum density of the fine material was also higher than the maximum density of the coarse material, most likely as a result of better packing.

In the tabletability plot (**Figure 4B**), where the red line indicates the recommended lower limit of tabletability (TTFS of 2MPa at a compaction pressure of 200MPa), the effect of particle size is also seen. Most of the points for the coarse material lie below the recommended tabletability limit, whereas all of the points for the fine material lie on or above the limit. This shows that the fine material makes better tablets than the coarse material at any given compaction pressure.

Finally, in the compressibility plot (**Figure 4C**), the coarse material is shown to reach a limiting density of 1.3g/mL, whereas the fine material has a continual increase in density up to the maximum pressure. This shows that the coarse material has reached its limit of compressibility, whereas the fine material may have some additional scope for compaction.

The consistency of the data and the clarity of the findings would appear to make size selection in this case a simple matter, but, unfortunately, this is not the case. Although the compression properties are key, but rarely measured, critical quality attributes of a powder blend and the impact

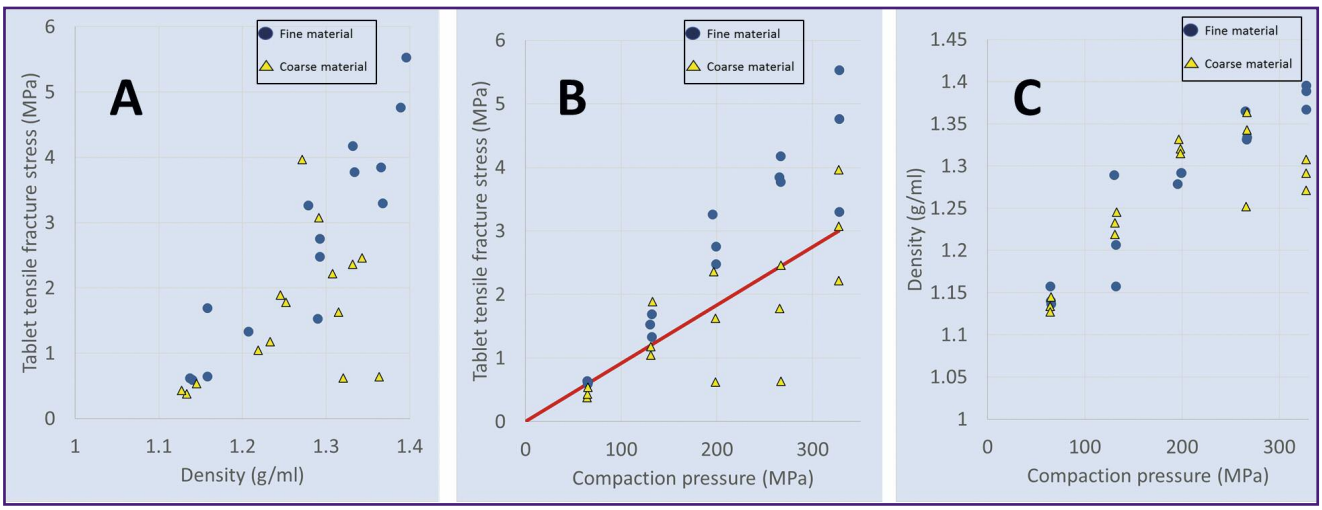

Figure 4. Particle size effects. A: Compactibility; B: Tabletability; C: Compressibility.

of particle size extend well beyond their effect on compression. Particle size affects mixing, flow and electrostatic properties, which would also require evaluation before a decision could be made on the best particle size for the product. Lubrication properties (not considered in this article) are also impacted by particle size differences, as one of the particle size effects is on powder surface area. Content uniformity, production speed, process robustness, and many other particle size-related phenomena also impact on the particle size selection decision. Particle size selection has to be done on the basis of the whole quality profile of the product. Compression studies provide an essential element in the decision-making process and the new USP Chapter <1062> provides an excellent framework for evaluating critical quality attributes of solid-state materials and formulations in the context of tableting and the all-important compaction triangle.

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[1] Fell JR, Newton JM. The tensile strength of lactose tablets. *J Pharm Pharmacol* 1968;**20**(8):657–659.

[2] Pitt K, Heasly MG. Determination of the tensile strength of elongated tablets. *Powder Tech* 2013;**238**:169–175.

START-UP OF CLEANROOMS, INITIALLY AND AFTER A WORST-CASE EVENT

by Jim Polarine and Beth Kroeger

Environmental control of classified areas within a biopharmaceutical facility is maintained by systems controlling humidity, air temperature, air exchanges, filtration and pressure differentials, and by practices such as room cleaning, limited access and facility flow. The failure of any of these systems has the potential to impact the clean state of a classified area. Many facilities have procedures in place to conduct the day-to-day operations but fail to have procedures in place to handle catastrophic or non-routine events. These disturbances should be defined as part of the Facility Cleaning Procedures in order to provide guidance to operators in the event they occur during off-shift or to provide a routine response to a non-routine event. The information in this article will provide an understanding of how these events may affect the cleanroom, so measures may be taken to prevent issues leading to shutdown, costly discrepancy investigations, and potential lost product.

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Introduction

Environmental control of classified areas within a cleanroom environment is maintained by systems controlling humidity, air temperature, air exchanges, filtration and pressure differentials, and by practices such as room cleaning, limited access and facility flow. When any of these systems or practices fail, it is considered a "worst case event" which has the potential to impact the clean state of a *classified area*.

Response

Responding to these issues demonstrates how robust the systems are in place to correct these events, and are frequently an area of focus for regulatory agencies since they demonstrate how well, or not well, the systems and management react while under stress.

Understanding areas where issues may arise and having a plan in place for prevention as well as corrective action keeps the events as routine as possible with minimal impact to the environment, the process stream and the schedule.

It is important that those responsible for the environment understand how the area is controlled. Air handling units (AHUs) are the main environmental control for cleanroom environments and are part of the heating, ventilation and air-conditioning (HVAC) system used to provide particulate, temperature and humidity control along with the air flow required to exchange the air in the cleanroom with recirculated air and fresh or make up air. AHUs force the air through high-efficiency particulate air (HEPA) filters to control the level of non-viable and viable particulates in the cleanroom environment. HEPA-filtered air should be supplied at a velocity sufficient to sweep particles away from the area where work is being performed and maintain unidirectional flow at the critical zone during operations.

When cleanrooms are operational, AHUs may occasionally shut down due to mechanical issues or power failures or may be shut down intentionally for routine maintenance, calibration or construction. When these shutdowns occur, procedures should be in place to bring the classified areas back to a state of control. The most probable disturbances to occur, aside from planned shutdowns for maintenance and certification, are power outages, pressure differential excursions and wet conditions. The most probable causes are summarised in **Table 1**. Power outages can impact the AHU control. Pressure differential excursions are primarily caused by human error or mechanical failure. Wet conditions typically occur resulting from mechanical, process or human error.

Many facilities have procedures in place to conduct the day-to-day operations, but fail to have procedures in place to handle catastrophic or non-routine events. Recovery from these disturbances

Most probable causes for disturbances	
AHU	• Power outage • Planned shutdown for maintenance • Damper issues • Temperature excursions • Humidity excursions
Room pressure excursions	• Human error – holding doors open • Mechanical failure
Wet conditions	• Mechanical failure with AHU/humidity control • Mechanical failure with process equipment • Fire suppression system failure • Spill • Human error
Reverse flow	• Equipment • Personnel • Raw materials
Planned shutdown	• Construction activities • Calibration activities • Preventive maintenance • Implementation of CAPAs (corrective and preventive actions)
General	• Entry into an area without proper gowning • Weather causing interruption to power • Exceeding alert/action limits

Table 1. Issues leading to a worst case event.

should be defined as part of the Facility Cleaning Procedures in order to provide a routine response to a non-routine event. It is also valuable to draft procedures to provide guidance to operators in the event that issues occur during off-shift. Procedures should define the most probable excursions and place acceptable criteria around such incidents, so that when an event does occur, there are some parameters in place to provide alternative responses that have been thought out and verified in advance.

When AHUs shut down, or the environment encounters a disturbance for any reason, the recovery measures may involve significant cleaning, limited access and additional environmental monitoring, all of which can reduce manufacturing time and increase costs. An AHU shutdown may last minutes, but require time to restart, time to perform maintenance work, time to clean the impacted area and time to perform additional environmental monitoring. The overall potential start-up time after a planned shutdown may take up to 12 hours per shutdown, with the disruptive impact being even longer for unplanned outages[1].

When the environment is disrupted for any reason, the immediate actions should include the following.

- If open processing, suspend processing operations when safe to do so. Any in-process material should be reviewed by quality and a formal risk assessment or investigation performed to determine impact to the process/product and final disposition.
- Isolate the area (tag the area out-of-service).
- Notify appropriate personnel (Operations Management, Quality Assurance, Quality Control Microbiology, Environmental Cleaning Support, Technical Services, etc.).
- Limit personnel working in the area. If access is required, change shoe covers when exiting the area, to avoid contaminating the adjacent area.
- Clean or cover equipment and materials as they are transported out of the area.
- Clean the area impacted by the event by first clearing any spill or debris using a HEPA wet/dry vacuum or other appropriate means, such as wipes, mops or squeegees, if applicable.
- Triple-clean the area.
- Carry out environmental monitoring for both viable and non-viable particulates.
- Release of the room.

Is action always necessary?

Not always. AHU shutdowns and pressure differentials excursions should have procedures in place for when events occur to avoid unnecessary investigations. A short power outage may only require limited action, such as a single disinfection step, before it is permitted back into operation. Facilities should determine the amount of time a door may be open before pressures are adversely impacted. Facilities should also establish a time limit that pressure differentials are allowed outside of the established range along with how long an AHU shutdown is acceptable without requiring an assessment of product impact, a major clean and environmental monitoring.

The decision to release a room without action should include conditions, such as no traffic in the room (or defining the acceptable number of personnel and movements in the area), if doors need to remain shut, no open product, and time limit for pressure excursions or AHU shutdown and recovery time. Most facilities should be able to withstand an AHU shutdown of 1–2 hours without having to clean and monitor as long as no personnel were in the area during the event and the environment was not breached, i.e. the doors remained closed. This would have to be demonstrated by an environmental study.

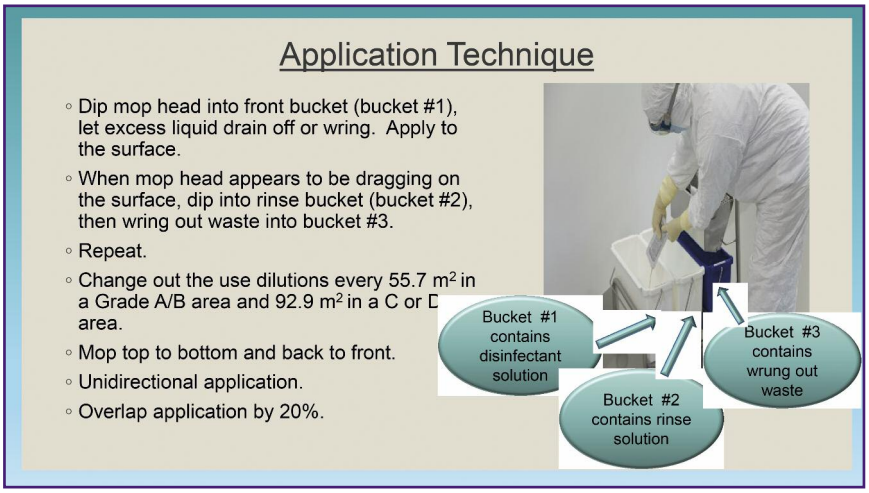

Figure 1. Disinfectant application technique.

Cleanroom start-up

When starting up a new cleanroom, it should be certified following International Organization for Standardization (ISO) 14644-1:2015 Cleanrooms and Associated Control Environments, Part 1: Classification of Air Cleanliness by Particle Concentration[2]. This standard states "At-rest or operational classification may be performed periodically based upon risk assessment of the application, typically on an annual basis." ISO 14644-2:2015 Cleanrooms and Associated Control Environments, Part 2: Monitoring to Provide Evidence of Cleanroom Performance Related to Air Cleanliness by Particle Concentration[3] is now a monitoring standard. This standard states "Periodic classification testing shall be undertaken annually in accordance with ISO 14644-1. This frequency can be extended based on risk assessment, the extent of the monitoring system, and data that are consistently in compliance with acceptance limits or levels defined in the monitoring plan." In the absence of monitoring, it is considered good practice for ISO Class 5 environments or stricter that airborne particle counts for classification and test measurement of cleanrooms and clean air devices should be performed every 6 months.

Certification of the cleanroom is performed after the HVAC system has been commissioned to ensure the integrity and efficiency of the HEPA filters and air handling system. "Clean" construction work may still be in progress, which means no invasive work is being performed, such as cutting drywall, flooring, grinding, machining, etc. If remaining work will generate particulates, hold off on certification.

Damage to the filter or seal is a risk during installation and start-up. To avoid delays, plan to purchase extra filters in case of damage. Most third party companies providing certification services will offer training to the mechanical contractor prior to HEPA filter installation to give them an overview of how to install the HEPAs to mitigate the risk of damaged filters or seals during installation. After HEPA filters are installed, if the return vents do not have filters to protect them, consider temporary filters. These will prevent dust, paper and construction debris from getting sucked into the system. They can be installed by tacking or taping into place.

It is recommended to certify while construction personnel are still on site to remediate any issues discovered during certification. At this time, it is not necessary to have the cleanrooms 100% operable with full gowning and routine cleaning and environmental monitoring implemented; however, procedures for work flow, gowning, monitoring, etc., should be prepared and some level of protective gowning should be implemented at this stage. Gowning during this phase can be less restrictive than final gowning requirements, but once the HVAC system is operable, some environmental controls should commence. A thorough "triple-clean" may be performed; however, unless the cleaning regime is to be continued, it is not necessary. When the facility is operable, a more intensive clean or non-routine cleaning procedure is recommended to bring the facility back to baseline. Regulatory agencies expect facilities to have this type of remedial cleaning outlined in their cleaning and disinfection program as indicated in PDA Technical Report 70[4], where "Facilities should strongly consider having special start-up cleaning and disinfection programs in place following "shutdowns" or when significant construction is performed." A triple-clean in this case refers to an application of a disinfectant, followed by another application of a disinfectant using fresh solution and bucket/mop assemblies, followed by an application of a sporicidal agent. A "9X" clean consists of performing a triple-clean each day on 3 consecutive days. There are numerous interpretations defining what a triple-clean consists of; therefore, ensure to provide detailed information for the technique utilised in your facility cleaning program. Proper technique is depicted in **Figure 1**. A triple clean, as per the authors' definition above, was used during the start-up of an aseptic facility. Environmental data for surface sampling prior to and post cleaning is listed in **Figure 2**.

The goal of the initial cleaning, in order to certify, should be to remove particulates to prevent obstruction of the filters when the system is in operation and to classify the system, which confirms the airborne particle count in the cleanroom, not necessarily microbial control. Further invasive mechanical work may be required if there are issues with the integrity or performance of the

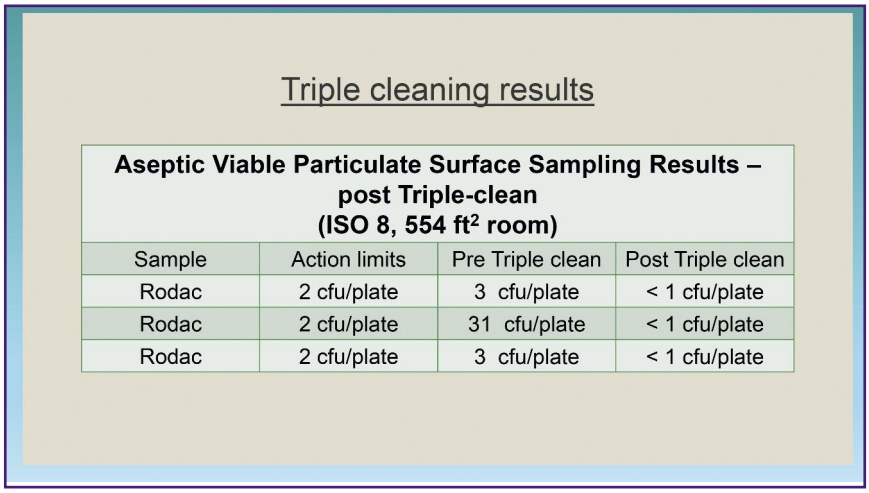

Figure 2. Triple cleaning effectiveness demonstrated by viable particulate surface sampling.

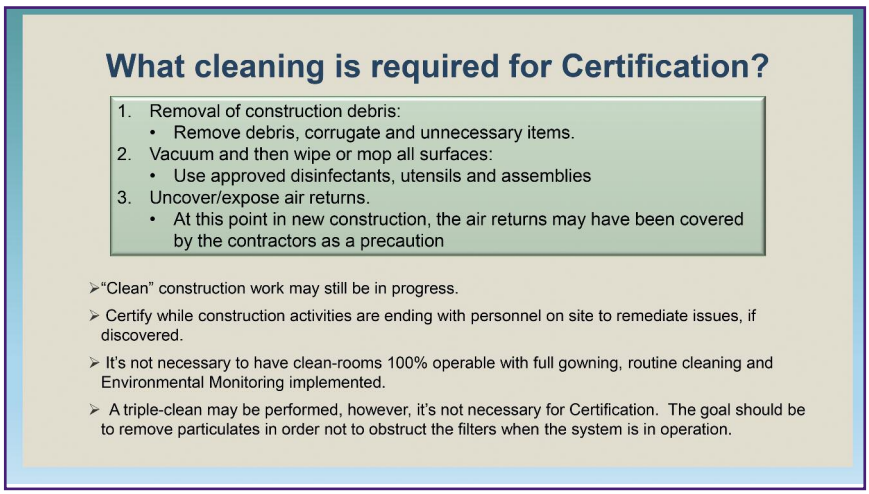

Figure 3. Cleaning required for certification of new build.

system, so a thorough procedural cleaning and maintenance of the cleanrooms may be preemptive. A cleaning consisting of removal of construction debris, corrugated cardboard and unnecessary items followed by vacuuming and a wipe or mop of all surfaces using approved disinfectants, utensils and bucket assemblies should be sufficient. A summary is provided in **Figure 3**. For more information, refer to ISO 14644-5:2004 Cleanrooms and Associated Controlled Environments, Part 5: Operations[5]. Annex F, Table F.1. shows the stages of a construction-related cleaning program. Once the cleaning program is established, it is important to follow the recommendations below to maintain the environment during routine operations.

- No cleaning should take place in an area during open operations and/or during environmental monitoring.
- Rooms divided by lines of demarcation, separating two classes in the same room, should be cleaned and monitored as per the stricter classification.
- Solutions and equipment for a less strict classification should not be used to clean a stricter classification of room.

Tests prior to certification and classification by particle concentration

ISO 14644 Part 1 states "Prior to testing [i.e. certification/particle counting], verify that all relevant aspects of the cleanroom or clean zone that contribute to its integrity are complete and functioning in accordance with its performance specification." What this means is that, at a minimum, the following tests, described in ISO 14644-3:2005 Cleanrooms and Associated Controlled Environments, Part 3: Test Methods[6], should be performed.

- Airflow volume or airflow velocity, which confirms the volume air change rate per hour[6].
- Room differential pressure or air pressure difference test[6].

The following tests are also recommended to certify that the HEPA filters are performing as expected.

- Installed [HEPA] filter leakage test using an aerosol photometer[6].
- Airflow visualisation testing or "smoke studies" as part of validation[6].
- Unidirectional airflow hood or Biological Safety Cabinet Certification, if applicable.

There is a major difference between filter leak testing and efficiency testing. The purpose of performing regularly scheduled leak tests is to detect leaks from the filter membrane, the frame or the seal. HEPA filters are challenged with aerosolised droplets having a mean particle size of <1µm but > 0.3µm. The aerosol is introduced upstream of the filter and the filter is scanned on the downstream side at a distance of approximately 1–2 inches from the filter. The downstream leakage is calculated as a percentage of the upstream challenge with any reading equivalent to or greater than 0.01% of the upstream challenge considered indicative of a significant leak. An efficiency test, which is normally carried out at the factory before dispatch, is a general test used to verify the rating of the filter. A HEPA filter has a minimum efficiency of 99.97% retained particles > 0.3 m in diameter[7]. The filter's

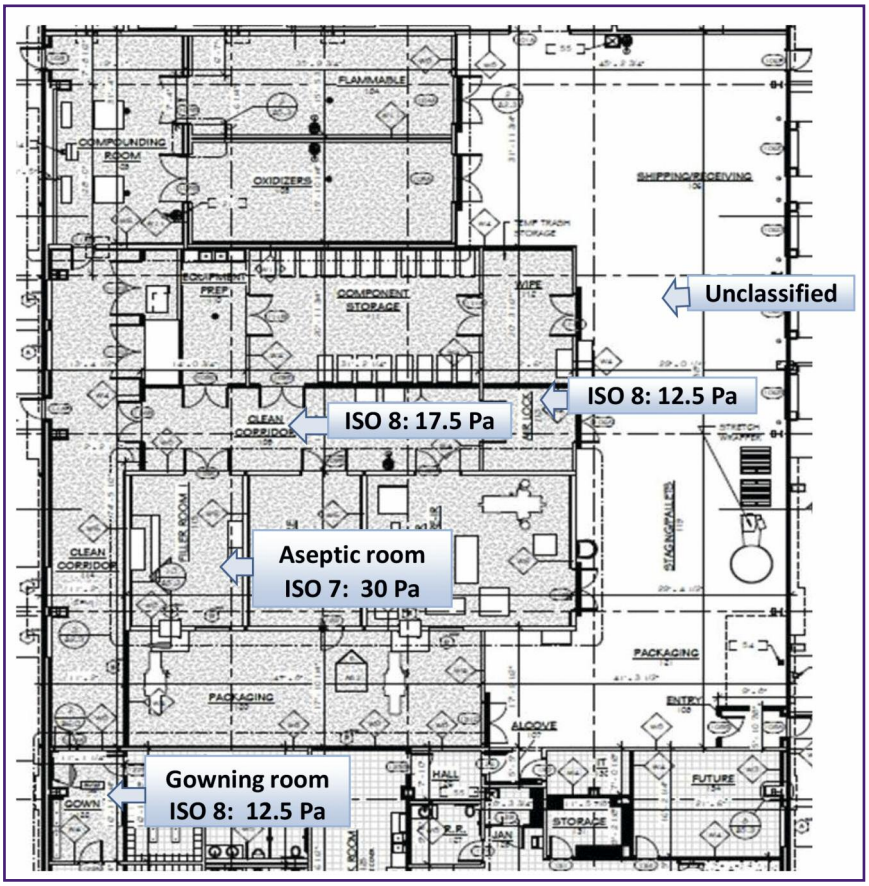

Figure 4. Example of pressure differentials through an aseptic facility.

efficiency will increase as it accumulates particles and will be at its lowest when it is new or has a leak.

Pressure differentials

In addition to moving the air through the HEPAs to reduce the particle counts to comply with room classifications, the system must also be able to provide the pressure differentials required between areas with different classifications. As per the current Guidelines to Good Manufacturing Practices, there must be adequate separation between areas of operation and surrounding areas. This is accomplished by creating a pressure difference between adjacent classified areas in a cleanroom.

In aseptic manufacturing, the intent is to cascade the flow from the most interior or the more critical (stricter) classifications commonly referred to as the "core" by maintaining 10–15 Pascals between adjacent areas of reducing classification through to non-classified areas[7]. There should be enough pressure in the core area to ensure the airflow is flowing out so particles and contaminants will not move inwards into the area through any spaces around or under doors or through doors when they are open. A pressure differential of 5 Pascals is recommended between adjacent areas with the same classification if one of the areas has more stringent cleanliness requirements[8].

The image in **Figure 4** depicts an aseptic facility with an ISO 5 unidirectional airflow hood located in an ISO 7 room used for filling operations. The ISO 7 fill rooms are adjacent to a corridor, classified as an ISO 8 area. The areas adjacent to the corridors are also classified as ISO 8 areas and are considered transition areas. Transition areas are areas designated as pass through areas for equipment, personnel and raw materials and are typically used for gowning and cleaning items into the area. To maintain the pressure differentials outlined in the guidance, the fill room was set to a set point of 30 Pascals. The set point of the adjacent corridors was lowered from that of the fill room to a set point of 17.5 Pascals in order to maintain a pressure differential of 12.5 Pascals between the two areas with different classifications. The transition areas (wipe-down room, equipment pass and gowning rooms) were then lowered another 5 Pascals to a set point of 12.5 Pascals to protect the corridors from air flowing into the "cleaner" ISO 8 area from the unclassified area, yet still adhere to the guidance recommendations.

Figure 4 describes ideal room pressures. As with a lot of things, more is not always better. Increasing room pressure beyond what is described is not recommended. Too high a pressure differential can result in extremely high and uncomfortable noise levels and can make the doors difficult to open or close.

When pressures are set to the recommended set points, there will be times when rooms will lose pressure due to mechanical failure or fall out of specification and experience reverse flow of air, more than likely due to doors not shutting properly or by doors being held open to accommodate equipment movement or facilitate communication. As per the Food and Drug Administration Guidance for Industry Sterile Drug Products Produced by Aseptic Manufacturing, it is critical that the time a door can remain ajar be strictly controlled. The guidance goes on to further state that pressure differential alarms should be documented and deviations from established limits, which include time out of specification, should be investigated[8]. It is important to include a time out of specification, or there can be a maximum number of non-critical out of specifications before a full investigation is required. However, it may be a good idea to trend this information and determine whether corrective

actions need to be taken.

Much like AHU shutdowns, facilities should determine the amount of time a door may be open to not impact the pressures. For lack of a better term, it is referred to as a "close the door" policy. In addition to establishing a time limit in which doors can remain open, it is also suggested to establish a time limit that pressure differentials are allowed outside of the established range without requiring an assessment of product impact. Not having these two time limits could result in a significant increase in the number of investigations required due to spikes, blips and excursions lasting seconds. This places a considerable burden on the person(s) responsible for writing and reviewing these discrepancies.

If the facility is to rely on magnehelic gauges to monitor room pressures, ensure the gauge is located in an area accessible for operators to read the gauge without having to leave the immediate area. Lastly, avoid establishing an extremely tight range if using a non-digital readout. It is simply not possible to read an extremely tight range when using a magnehelic gauge due to the dial format.

Temperature and humidity

Temperature and humidity control is required for manufacturing processes to ensure stable operating conditions, but is also required for personnel comfort, static charge reduction and microbial control. Normally, the temperature should be maintained at 68–72°F (20–22.2°C) and the relative humidity at 30–60%[7], with humidity levels up to 65% as mentioned in the guidance documents[9]. Although a temperature range of 20–22.2°C is recommended, an operating temperature of 16–20°C (60.8–68.0°F) is typical in areas where full gowning in aseptic garments is required, since multiple layers of gowning add stress on the operators. Aseptic gowning requirements may include goggles, face mask, hood, coveralls, booties, sterile sleeves and multiple pairs of gloves when making aseptic manipulations. Increasing operator comfort, by means of keeping the room temperature comfortable when gowned, increases the likelihood for adherence to gowning requirements, as well as decreasing sweating and shivering of the operators, which may increase personnel shedding of particles. Cuffs stay tucked in gloves, goggles/safety glasses do not fog, masks stay on and zippers/buttons stay fastened.

When a temperature or humidity excursion does occur, procedures should be in place to address the issue, as in the case of pressure differentials and AHU failures. Allow for momentary spikes which may occur due to power outages or equipment interruptions. If possible, build in the amount of time a real excursion is allowed before action is taken. Temperature may not have the same impact on the environment as humidity excursions would. Temperature may impact product or raw materials, however, humidity excursions may cause excessive condensation to form on the floors, walls and ceilings, especially when combined with an increase in temperature. If this takes place, it is imperative the area is treated as if a worst-case event occurred and to clean the area accordingly. The formation of humidity gives microorganisms the media they require and increases the opportunity for exceeding the environmental monitoring alert/action limits.

Worst-case event response should be detailed as part of the Facility Cleaning Standard Operating Procedures. Action is not always necessary provided there are proven acceptable limits and procedures surrounding AHU shutdowns and pressure differential excursions. When an event occurs that requires action, rooms should be isolated with restricted personnel access to the area and additional gowning procedures in place to avoid contaminating adjacent areas. The area should be triple-cleaned after a worst-case event and monitored prior to release of room. New cleanrooms should meet ISO 14644-1 requirements, however, new construction cleaning is more concerned with particulate removal than microbial control for certification. Final triple clean prior to room release is required along with environmental monitoring and quality release of room based on microbiological results.

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This article first appeared in *Clean Air Containment Review* 2017;**31** (July):14–19.

The current review period has seen a number of changes in the regulation of medicines and regulatory guidance in the EU, International markets and the USA.

USA

Contaminated steroid injections – Chief Executive Officer given 9 years prison sentence

Following the 2012 USA fungal meningitis outbreak caused by contaminated steroids, the co-owner of a pharmacy responsible for the deaths of 76 people has been sentenced to 9 years in prison. Besides the 76 people who died, more than 700 were sickened. Illnesses and deaths in 20 states were traced to the contaminated steroids.

Prosecutors said the co-owner and president of the now-closed New England compounding centre in Framingham ran the company in an "extraordinarily dangerous" way, sending out the steroids when he knew there was mould present in the room where the steroids were made and skirting industry standards on cleanliness and sterility to step up production and make more profit.

Jurors acquitted the accused of 25 second-degree murder charges under the federal racketeering law but found him guilty of fraud and conspiracy.

The scandal prompted increased scrutiny on compounding pharmacies, which differ from ordinary drugstores in that they custom-mix medications and supply them directly to hospitals and doctors. In 2013, in reaction to the outbreak, Congress increased federal oversight of such pharmacies.

Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy: Guidance for Industry

The Food and Drug Administration (FDA) issued this draft guidance informing manufacturers/supply chain stakeholders that although manufacturers are to begin including a product identifier on prescription drug packages and cases on 27 November 2017, the FDA is delaying enforcement of those requirements until November 2018 to provide manufacturers additional time and avoid supply disruptions.

The compliance policy outlined in the draft guidance applies solely to products without a product identifier that are introduced into commerce by a manufacturer between 27 November 2017 and 26 November 2018.

Europe

European Medicines Agency (EMA)

EMA prepares for Brexit

The EMA has developed and initiated a business continuity plan to deal with the uncertainty and workload implications linked to the UK withdrawal from the EU and the EMA's relocation. It will help the EMA take the difficult decision to reallocate the available resources as needed to maintain its priority activities over the next years. The plan sets out three layers of priority; it categorises and prioritises tasks and activities according to their impact on public health and the Agency's ability to function.

In May, the EMA started to scale back activities in the outer layer (so-called category 3 activities) to free up 43 staff by the end of 2017 who will focus on the preparations for the UK's withdrawal from the EU and EMA's relocation. To achieve this, the Agency decided to temporarily suspend a number of activities.

- The development of the European Medicines Web Portal, a new publicly available online information source on all medicines marketed in the EU.
- The EMA's contribution to the e-submission project that will allow applicants to electronically submit documents linked to authorisation requests for human and veterinary medicines in a secure and efficient way.
- The development of a transparency roadmap for the EMA that lays out future transparency measures of the Agency.
- Participation in the benchmarking of medicines regulatory authorities in the EU as of 2018.

In addition, the EMA reduced the number of audits as well as some corporate governance and support activities. Participation of EMA staff in external meetings or conferences has been reduced, as has the organisation of EMA meetings and workshops.

Implementation plan – introduction of safety features on packaging of medicinal products

Certain aspects of the implementation of the Falsified Medicines Directive and the new delegated act on the safety features may impact on the product information and the marketing authorisation dossier; in particular the placing of safety features, a unique identifier (UI) carried by a 2D barcode and an anti-tampering device on the packaging of prescription medicines and certain non-prescription medicines. The EMA and the European Commission have prepared this implementation plan to guide applicants and marketing authorisation holders (MAHs) through the regulatory changes necessary to accommodate the new legislative requirements.

First ever EU guidance on sterile manufacturing processes for veterinary stem cell medicines

The guidance addresses concerns raised by manufacturers and authorities in regard to the sterility of allogenic stem cell therapies in

the veterinary sector. (Allogenic stem cell-based veterinary medicines originate from tissues, such as bone marrow or fat, from a donor from the same species of animal, not from the recipient of the cells.) Microbiological contamination can occur at various steps, from the initial sampling of the cells and tissues, up to the final product packaging into containers. The guidance provides answers to eight main issues identified to support manufacturers in ensuring sterile and safe stem cell-based therapies for veterinary use.

Medicines and Healthcare Products Regulatory Agency (MHRA)

Good manufacturing practice (GMP) short notice and unannounced inspections

MHRA is authorised to perform inspections both at short notice (a few days) or unannounced (no notice given). The use of these inspection types allows the MHRA to investigate issues that pose a significant risk to public health without obstruction and to work efficiently.

In a recent blog posting, the MHRA explains the background to such inspections and it specifically notes the following.

- You will need to have available during the inspection the details that would have been completed as part of the pre-inspection compliance report, the inspector will obtain this information from you whilst on site.
- You will be charged for the inspection at the normal daily rate per inspector.
- If you choose to refuse the inspector entry to the site, you will be in breach of the obligations you have as a licence holder. This will result in an instant referral to the Inspection Action Group with a recommendation to suspend or not grant the licence as appropriate.

Use of freezers

In another recent blog post, the MHRA describes the main issues seen when freezers are used by pharmaceutical wholesalers and provides an MHRA good distribution practice inspectors' view on possible ways to address them. Most of the problems seen with use of freezers also apply to refrigerators.

Do wholesale distributors require pharmacovigilance agreements?

In this blog, it is concluded that when deciding if such an agreement between the MAH and the wholesale distributor is required, the MAH needs to consider if the wholesale distributor is a potential source of safety information and/or performing pharmacovigilance tasks on behalf of the MAH, and implement agreements as appropriate.

International

World Health Organization (WHO) Technical Report Series 1003

The WHO has published its 51st report on the Expert Committee on Specifications for Pharmaceutical Preparations. The WHO Technical Report Series makes available the findings of various international groups of experts that provide the WHO with the latest scientific and technical advice on a broad range of medical and public health subjects.

In this document, Chapter 7 Quality Assurance/GMP summarises updates in GMP. The main focus is the guidance on validation and its appendices.

For further information on these and other topics, we suggest you refer to the websites of relevant regulatory bodies and to current and past editions of "GMP Review News" published by Euromed Communications. To subscribe to this monthly news service contact info@euromedcommunications.com

PHARMA IN PLENARY

Decision-making at the European Medicines Agency

by Dr Nicola Davies

With the onset of Brexit, the European Union (EU) is undergoing some structural and administrative changes. A review of the latest questions posed on the European Parliament showcases some concerns of Honourable Members with decisions relating to the European Medicines Agency (EMA), specifically on the lease and relocation of agency offices and advice on the safety of medicines.

Termination of the lease of the EMA

Prior to Brexit, the EMA office was stationed at premises leased in London. With Britain's egress from the EU, National Front Member of the European Parliament, Mireille D'Ornano, pointed out the lack of a termination clause in the lease contract. This would require the continual payment of rental fees until the contract period's end in 2039, costing the EU an estimated €347.6 million. The failure to include a termination clause in a 30-year contract was thus questioned. The inclusion of such a clause in the contracts for other premises leased by the European Commission was also queried[1].

In a response, the Commission said that lease contracts are settled between the agency and the host state on a "case by case basis"[2], and so vary across agencies and over time. Hence, the decision to preclude a termination clause can only be explained by the EMA[2].

In addition, the Commission outlined the status of rental contracts throughout Europe with respect to termination clauses. The contracts for rented buildings in Brussels do not account for an early termination clause since the lack of one enables the EU agencies to obtain better contract conditions. Lease contracts for premises in Luxembourg, on the other hand, contain a termination clause to account for the possibility of the agency relocating by virtue of Article 341 of the Treaty on the Functioning of the European Union (TFEU), which conveys that the seat of EU institutions shall be settled by agreement of the Member States governments[2]. The lessee, however, has the option in both Brussels and Luxembourg to transfer the lease to any other EU agency or third party. The buildings hosting the Commission Representations are owned by the EU and most contracts involving them include an early termination clause[2].

Relocation of the EMA headquarters after the UK's decision to trigger Article 50 of the TFEU

In late 2016, when the EMA and the European Banking Authority (EBA) were just preparing to leave London after the results of the Brexit vote, an individual Member representing Croatia enquired about the criteria that a Member State must meet to be considered as a host country. Croatia is the newest Member State and one of the few Member States that do not host any EU agency. Being able to host EU agencies could provide jobs in Croatia, which has the third highest unemployment rate in the EU after Greece and Spain[3].

At that time, however, the European Council had yet to receive a notification from the UK indicating its intention to withdraw from the EU. Under Article 50 of the TFEU, a Member State may choose to remove themselves from the EU "in accordance with its own constitutional requirements" and should notify the Council of such an intention[4]. Without a proper and official notification, the relocation of the EMA and EBA agencies to other countries had not yet been discussed, as explained in the Commission's reply to the Croatian member's question[4].

New headquarters for the EMA and EBA

In 2017, the UK Government triggered Article 50 of the TFEU, necessitating the relocation of the EMA's and EBA's headquarters. The Commission and the Multiannual Financial Framework published a draft of the relocation terms in May 2017. The relocation is expected to affect the EU's 2018 budget and also lead to staff reductions, which the Environment, Public Health and Food Safety (ENVI) subcommittee of the European Parliament has expressed concerns over[5]. In particular, the subcommittee highlights that such staff reductions will almost inevitably negatively impact the EMA.

The procedure and formal criteria for the relocation were queried along with the possibility of considering countries currently without a single EU agency, such as Croatia, Bulgaria or Romania, to become the host country for the EMA and EBA headquarters[6].

The Commission referred the querying individual to the published Procedure leading up to the decision on the relocation of the two headquarters. The document was endorsed by the State or Government Heads of the 27 Member States in June 2017[7]. The Procedure requires the host country to meet six criteria[8].

1. The assurance that the EMA and EBA can be set up on site and take up their respective functions at the date of the UK's withdrawal from the Union.
2. Accessibility of the location.
3. The existence of adequate educational facilities for agency staff's children.
4. Appropriate access to the labour market, social security and medical care for both spouse and children.
5. Business continuity (having an acceptable timeframe to achieve the first four criteria).
6. Geographical spread of agencies' seats.

The Commission said that negotiations with the UK required the exiting nation to fully cover the costs related to the withdrawal process, including the relocation of agencies. With the cost of relocation expected to be high, the possibility of 'having the UK bear the costs' was also raised[6]. However, the exact amount of costs to be covered is yet to be determined[7].

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bottled brown

This is us

The installations in the window of the Wellcome Foundation, London riveted me. Stuart Haygath's artist's eye reimagined the venerable Wellcome collection. The pristine practical world of the science laboratory became the rounded sensual shapes of funnels, molecular structure, organism, petri dishes, pipettes and vials.

The London photographic studio that I attended for a photoshoot also intrigued me. Why I was there amongst the glamorous models who would add glitter to glossy pages? Why was Andrew Hayes-Watkins, photographer of celebrities, taking a hundred photographs of *me*? Astonishingly, I would feature in the British monthly magazine with the highest circulation (420,000). The answer lies not in me but in what I was contemplating. It was my spatula. I had used it as a pharmacy student, industrial pharmacist and DIY home decorator. That rosewood/stainless steel spatula had little commercial value but was priceless, emotionally, saturated with nostalgia. *SAGA* magazine had selected it for their "humble treasure" series.

Both the Wellcome artwork and spatula have close connections with industrial pharmacy. They reflect the hopes, biases and experience of two individuals. That started me thinking. Was there a symbol of not pharmacy but *industrial* pharmacy?

Quest

A symbol is an outward sign understood by those who create and those who witness; if it appears, they know what it means. Symbols have a life span: invention, birth and death; they become stale and dated. For example, today an eagle seldom symbolises the Greek God, Zeus. Symbols for pharmacy include carboy, pestle and mortar, or green cross. The (Royal) Pharmaceutical Society's coat of arms (19th century) included a dove (signifying peace); aloes, representing pharmacognosy; a still and receiver, symbolising the new chemical pure active pharmaceutical ingredients (APIs); scales symbolising weighing ingredients; and exotic bearers, pharmacy's international nature. However, I could not think of a symbol that was unique to the industry, something more than a caricature, some image that nailed what industrial pharmacy was *about*.

I looked in Google Image, YouTube, associated professional and trade bodies, the European Medicines Agency, and so on. Their logo, introduced in 2009, a mortar and pestle, is "one of the most ancient and universally recognised images associated with medicines". However, cooks pound mortars and pestles too, more frequently than pharmacists do, on the television and, perhaps, in public perception. A textbook cover featured an operative wearing an aseptic suite coverall. Iran highlighted gleaming pipes and vessels for API manufacture.

My search for images of industrial pharmacy was not a rigorous research, but jottings for a pilot study in the style of Francis Bacon. That pioneer of the inductive scientific method, in 1620, listed when a phenomenon was present, absent and circumstances. Content analysis is an example of this method that can identify the commonest symbol of industrial pharmacy. It is flawed. It only counts frequency without allowing for the impact of each instance; that may vary with the authority of the user or skill of the artist.

Metonym

Amongst our senses, vision is usually dominant; it involves a third of our cerebral cortex. One *image* combining industry and pharmacy, a motif without words, unlimited by language — a metonym — could confer instant public recognition. Examples are the snake entwined on a staff or stethoscope for medical practitioner. Perhaps, today, for industrial pharmacy, molecular engineering and computers should feature. Any metonym will have critics, but could boost the presence of industrial pharmacy.

I have only considered what already exists and so is familiar. However, perhaps some reader, or medical illustrator/artist colleague, who creates vibrant, memorable images, could suggest some fresh image that hooks the public.

Malcolm E Brown

news from the EIPG

Technical documents and Interested Parties Meeting with GMP/GDP Inspectors Working Group at the European Medicines Agency (EMA)

Documents

A plan for replying to several EMA consultation documents was prepared by Piero Iamartino (Vice-President for Technical Affairs) and information on the documents circulated to delegations.

The EIPG comments on the guideline for the notification of serious breaches of Regulation 536/2014 or the trial protocol were submitted to the EMA in August.

Meeting at the EMA

Following feedback from our members, topics with background explanations of the problems raised were proposed to the EMA. A further joint telecom will be held to develop the agenda for the December meeting and to decide what topics can be handled by correspondence.

Webinar

The next free webinar for members of EIPG to be run in conjunction with PIER and University College Cork will be at 5.00 pm CET (4.00 pm GMT) on Wednesday 1 November. The title of this webinar is "Development and regulatory approval of new medicines for children". The speaker is John Watson, Zogenix International. For further information, contact your EIPG national delegate.

Education and European Pharmacy Students Association (EPSA)

At the end of September, Anni Svala (Vice-President for Education and Careers) will attend a progress meeting in Milan of Moglynet, the European Joint Doctorate programme. Anni Svala has had a telecom with representatives of the new executive of EPSA to discuss joint webinars, the EPSA mentoring project, a potential careers fair and an article for the *european Industrial Pharmacy*.

Meetings

The following national meetings have been endorsed by EIPG:

- 18th Panhellenic Pharmaceutical Congress to be held in Athens, Greece, 6-8 October
- Associazione Farmaceutici Industria (AFI) Conference on the Clinical Trial Regulation to be held in Milan, Italy on 13 October (the meeting is in English and there is a possibility of attendance remotely via streaming)

For further information, contact your EIPG national delegate.

Shortages of medicines

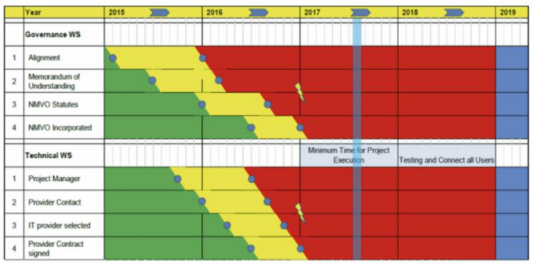
The COST project CA15105 (Medicines Shortages Research Network – addressing supply problems to patients) is now into its second year. Two training schools for young researchers have been held in Portugal, and for the coming year support for short-term visits to research workers in other countries is available to those undertaking research into shortages of medicines. Further information on COST can be found on their website www.cost.eu/COST_Actions/ca/CA15105.

Working Party 3 on shortages caused by provision and procurement disruptions has a list of research projects identified by experts from wholesalers, generic and research-based industry and from community and hospital pharmacy representatives. This group provided their opinions on the causes of shortages and compiled a list of research projects which might assist. Young researchers are sought, such as 4th year pharmacy students with research assignments, and PhD or Pharm D students who could undertake research into shortages. Anyone interested in participating should contact Jane Nicholson.

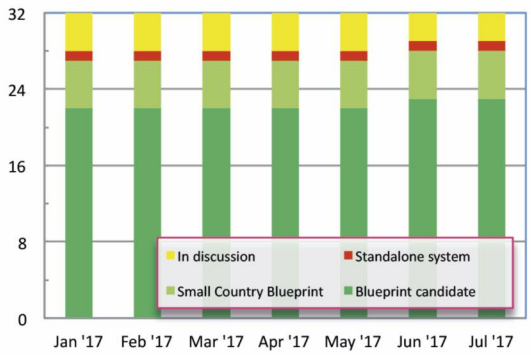
Jane Nicholson
(jane@nicholj.plus.com)

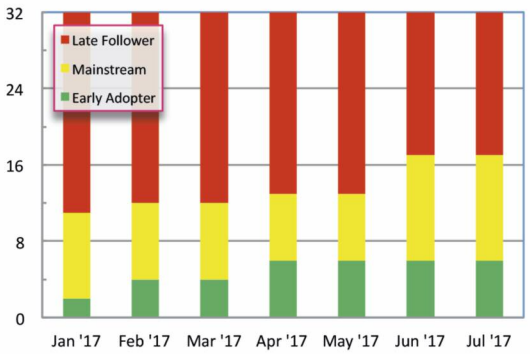
Progress Monitoring Report, July 2017

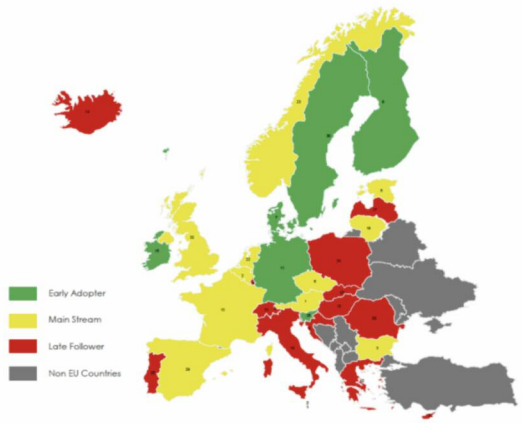
Country Readiness



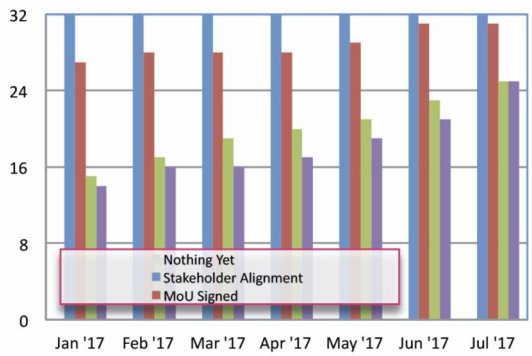
Blueprint Tendency



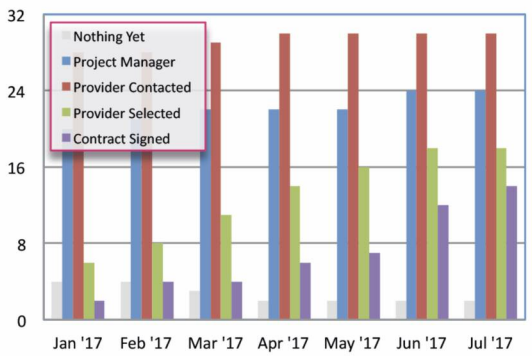




Governance Workstream



Technical Workstream



events

OCTOBER 2017

3–4 October 2017 – Philadelphia, PA, USA
Outcomes-Based Contracting
www.cbinet.com/conference/pc17034

9–10 October 2017 – San Diego, CA, USA
4th Annual Drug Discovery USA Congress
http://www.discoveryusa-congress.com/

10–11 October 2017 – Strasbourg, France
EDQM Symposium on Microbiology
https://www.edqm.eu/en/news/edqm-symposium-microbiology-planned-october-2017

10–11 October 2017 – Prague, Czech Republic
Pharmaceutical Cold & Supply Chain Logistics
www.pda.org

10–12 October 2017 – Barcelona, Spain
World Vaccines Conference Europe
http://www.terrapinn.com/conference/world-vaccine-congress-europe/index.stm

16–17 October 2017 – San Francisco, CA, USA
10th International Conference and Exhibition on Biologics and Biosimilars
http://biosimilars-biologics.pharmaceuticalconferences.com/

16–18 October 2017 – Baltimore, MD, USA
11th World Drug Delivery Summit
http://drugdelivery.pharmaceuticalconferences.com/

16–18 October 2017 – Budapest, Hungary
12th World Pharma Congress
http://world.pharmaceuticalconferences.com/

16–18 October 2017 – Bethesda, MD, USA
12th Annual PDA Conference on Pharmaceutical Microbiology
www.pda.org

19–20 October 2017 – Seoul, Republic of Korea
9th Annual Congress on Drug Design & Drug Formulation
http://drugformulation-bioavailability.pharmaceuticalconferences.com/

19–20 October 2017 – San Francisco, CA, USA
Speed to IND for Biologics
www.cbinet.com/conference/pc17411

23–24 October 2017 – Bethesda, MD, USA
2017 Visual Inspection Forum
www.pda.org

23–24 October 2017 – Philadelphia, PA, USA
8th Annual Internal Audit Summit
www.cbinet.com/conference/pc17265

23–25 October 2017 – Paris, France
International Conference on Biotech Pharmaceuticals
http://biotech.pharmaceuticalconferences.com/

24–26 October 2017 – Prague, Czech Republic
Global Pharmaceutical Regulatory Affairs Summit
https://lifesciences.knect365.com/global-pharma-regulatory-affairs/

29 October–1 November 2017 – San Diego, CA, USA
2017 ISPE Annual Meeting and Expo
www.ispe.org

31 October–1 November 2017 – Basel, Switzerland
World Biosimilar Congress
http://www.terrapinn.com/conference/world-biosimilar-congress/?utm_source=terrapinn&utm_campaign=listing&utm_medium=link&utm_term=AF

NOVEMBER 2017

1–2 November 2017 – Basel, Switzerland
HPAPI World Congress
http://www.terrapinn.com/conference/hpapi-world-congress/index.stm

2–3 November 2017 – Cambridge, UK
BioData World Congress 2017
http://www.terrapinn.com/conference/biodata/index.stm

7–8 November 2017 – Vienna, Austria
The Universe of Pre-filled Syringes and Injection Devices
www.pda.org

9–11 November 2017 – Vienna, Austria
4th European Biopharma Congress
http://biopharmaceutics.pharmaceuticalconferences.com/europe/

13–15 November 2017 – Barcelona, Spain
World Orphan Drug Congress
http://www.terrapinn.com/conference/world-orphan-drug-congress/?utm_source=terrapinn&utm_campaign=listing&utm_medium=link&utm_term=AF

16–17 November 2017 – Berlin, Germany
European Pharma Summit
https://www.gtcbio.com/conferences/european-pharma-summit-2017/

16–17 November 2017 – Vienna, Austria
European Biopharma Congress
http://biopharmaceutics.pharmaceuticalconferences.com/europe/

21–22 November 2017 – Munich, Germany
Outsourcing and Contract Manufacturing
www.pda.org

DECEMBER 2017

4–6 December 2017 – San Francisco, CA, USA
2017 Biopharmaceutical Manufacturing Conference
www.ispe.org