Challenges in Biological and Advanced Medicinal Therapeutic product ATMP manufacturing with GMP compliance

Biological products and ATMPs: Advanced Therapeutic Medicinal Products are challenging in manufacture to meet GMP requirements and regulatory expectations and often require adaption of generic GMP guidance with a QRM: Quality Risk Management approach. Biological products and therapies that interact with biological systems have challenges in testing and biocompatibility of disinfectant residuals used in bio-contamination control. With such interconnected challenges QPs are faced with challenges in certification and release.

This conference has a focus on Biological product and ATMP manufacturing with contamination control in GMP compliance and following QRM principles together with testing challenges and shared experience from QPs on certification and release.

PHSS-UCL Q3P ANNUAL CONFERENCE
10 September 2019
Kensington, London UK

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Over the years Euromed Communications has consistently produced a good quality journal (PDF and paper format) for the PHSS members. But we are now changing the format of the EJPPS. From Volume 24 Number 3, the EJPPS will be an online, open access journal. The only part of the journal that will not be open access is the regulatory update, the details of which will be restricted to PHSS members. The new format journal will be easy to navigate, contain the same research papers, science and technology articles, editorials, regulatory updates and PHSS news. As with the previous format, we will contain limited advertising to help finance the journal.

We feel that this format change will give a wider reader base, help recruit new members and still give a real member benefit. The change will bring us inline with many other similar publications.

The other big change is that the journal will be published by the PHSS. We have not taken the decision lightly. The PHSS values the EJPPS and believe that this is a positive move for the journal in terms of access and readability. The PHSS will be self-publishing using an online software application, we feel we have the skillset in-house in order to complete this. Other than the platform, there will not be any changes, the ISSN number (ISSN: 0964-4679) and registration at The British Library will remain the same. We will continue to submit the quarterly edition to the British Library.

We thank Euromed Communications for the many years of consistently good journals and support. But as the PHSS has now got the capability and software for self-publication, we are moving on with the online open access format journal. I hope you will continue to enjoy the journal in its new format. Please give any comments or suggestions to the Editor or to the PHSS office.
Contamination risks evaluated with the LR-Method in unidirectional airflow at different air velocities

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Operating rooms for patients undergoing infection-prone surgery often have unidirectional flow supply air systems. Many systems installed in Europe have low air velocities, i.e. equal and below 0.3 m/s, while other supply air systems have velocities about 0.4 m/s. The velocity, given by the supplier, is mostly the inlet air velocity just below the filter screen of the unidirectional flow system. The purpose of this paper is to describe contamination risks in unidirectional airflow without obstacles at different air velocities. To evaluate contamination risks, the method for limitation of risks, the LR-Method, has been used. The results show that the convection flows and arm movements from a person standing in the unidirectional airflow system have a great impact on the contamination risks at air velocities below 0.4 m/s and that the air velocity should at least be 0.4 m/s to achieve a good protection efficacy.

Key words: Unidirectional airflow, risk assessment, air velocity, LR-Method

Introduction
The number of airborne bacteria-carrying particles, colony-forming units (CFUs), in operating rooms is considered as an indicator of the risk of infection to the patient undergoing surgery susceptible to infections. An international accepted level of the mean concentration during surgery measured close to the wound is less than 10 CFU/m³. The main source of microorganisms in an operating room is the personnel and the patient.

Operating rooms for patients undergoing infection-prone surgery often have unidirectional flow (UDF) supply air systems. In the past 25 years, many UDF supply air systems installed in Europe have low air velocity, i.e. equal and below 0.3 m/s. It should be noted that Whyte1,2 in his review paper in two parts states that the UDF system, to be able to work effectively, shall have a minimum average velocity of 0.38 m/s for a partial-walled system (0.3 m/s for a full-walled system) when velocity readings are taken 2 m above the floor and minimum average velocity 0.2 m/s taken 1 m above the floor. This agrees with results presented by Nordenadler3.

In this paper, microbiological risk assessment with the method for limitation of risks (LR-Method) is used for the evaluation of contamination risks in UDF without obstacles at different air velocities at laminar as well as turbulent airflows.

Materials and methods
The LR-Method
The LR-Method provides a reliable procedure for assessing potential microbiological risks of airborne contamination in clean zones in a systematic way. The LR-Method is performed in three steps.

- The first step is to visualise (e.g. by using isotherm smoke technique) the main air movements and identify turbulent regions and critical vortices where contaminants can be dispersed or accumulated in an unpredictable way. The illustrative technique of smoke studies provides a useful technique for visualising air movements and the dispersal of contaminants. This technique requires that isothermal smoke is released continuously and almost momentum free using a diffuser. The smoke pattern can be recorded by means of still photography and video. Visualising the air movements improves the understanding of potential risks of airborne contamination.

- The second step – the challenge test – is to identify potential risk situations. The particle challenge test
involves placing the probe of an airborne particle counter in the critical area where, during normal operations, the process/product is exposed, and taking continuous total particle counts (sampling flow 1 cubic foot/min) while generating particles in the close surrounding air (e.g. by using Air Current Test Tubes) to a challenge level of more than 300,000 particles equal to and larger than 0.5 µm per cubic foot (approximately 10^7 particles per m^3). These measurements must be carried out during simulated process activity. At least three samples of 1 minute are sampled at each location or during each process step.

- The third step is to evaluate the risk situation by calculating the risk factor, which is defined as the ratio between the maximum measured particle concentration (number/cubic foot) in the critical region and the challenge level in the surrounding air. Due to limited measurement accuracy at high concentrations, a value of 300,000 particles per cubic foot is used as a challenge level in all risk factor calculations.

When the risk factor is less than 10^{-4} (0.01%) during the challenge test, there are no risks of airborne microbiological contamination during normal operational conditions according to experimental findings from more than 50 studied aseptic production lines. Experiences from the use of the LR-Method have been presented by Ljungqvist et al.\(^4\)–\(^7\).

**Performed tests**

The tests have been performed in a specially designed clean zone test chamber with a UDF-system of 1.2 m x 1.5 m, where the supply air is high-efficiency particulate air-filtered. The vertical air velocity is adjustable from 0.1 m/s to 0.6 m/s. To stabilise the airflow, the test chamber is equipped with partial side walls. Temperature and relative humidity are not controlled but have, during the tests, been in the range 20–26°C and 25–55%, respectively.

**Figure 1** shows the principal arrangement of the tests with a person present in the test chamber. The probe of the particle counter (HiacRoyco 245) is, in all tests, situated...
on the table in the test chamber at 60 cm from the test person. Figure 2 shows the principal arrangement of the particle generation regions in the test chamber.

The particle generation regions A and B were situated at floor level at the outer edges of the clean zone and the particle challenge was performed without a test person in the clean zone of the test chamber. The particle challenge in particle generation region C was performed below the table without a test person in the clean zone. In particle generation region D, the particle challenge was performed in the clean zone in front of a cleanroom dressed test person, who was standing still, or calmly moved his arms in standardised cycles, moving the arms forwards and back, see Figure 3.

The supply air filter screen creates a low turbulence airflow, which in practical situations should often be called laminar. By using a turbulence generating grid placed just below the filter screen a turbulent airflow should be achieved.

The turbulence generating grid was made of tubes with a diameter of 20 mm and the tubes were situated at a distance of 55 mm. A Reynolds number of about 400 and 660 was achieved at velocities of 0.3 m/s and 0.5 m/s, respectively, at normal room temperature. According to photographs presented by Schlichting, it is to be expected that a change to turbulent flow principally consisting of interfering Karman vortex streets will occur at a Reynolds

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*Note: The value of the Reynolds number is an indicator of the degree of turbulence in the parallel flow.*
number of approximately 100. This gives that in the described tests with the turbulence generating grid that turbulent flow is well established and is in the following called flow with high degree of turbulence.

The velocity measurements were performed 0.2 m below the filter screen according to ISO 14644-3\textsuperscript{10}, which gives that the readings were taken about 2 m above the floor.

For velocities between 0.3 m/s–0.5 m/s, measurements have been performed in the test chamber with the LR-Meth-od of flows with a low degree of turbulence (almost laminar) as well as with flows with a high degree of turbulence. Figure 4 shows these two types of flow visualised with the aid of smoke.

Results

Results from the measurements with the LR-Method at UDF with low and high degree of turbulence at different air velocities are shown in Table 1 and Table 2. The results in Table 1 and Table 2 show, independently of the turbulence degree of the UDF, that the air velocity should exceed 0.4 m/s to achieve a good protection efficacy, i.e. a risk factor less than 10\textsuperscript{-4}.

Indicative measurements have also been performed at air velocities of 0.25 m/s, 0.35 m/s and 0.45 m/s. The values for the air velocity 0.25 m/s are, for particle generation regions A, B and C, in the same range as the values given for the velocity 0.3 m/s, while the values in particle region D (person present) become higher than those given for the velocity 0.3 m/s.

The values for the air velocity 0.35 m/s are in a level between the values for the velocities 0.3 m/s and 0.4 m/s. The values for the velocity 0.45 m/s are close to the values for the velocity 0.5 m/s.

The results show clearly that the convection flows from the test person and arm movements have a great impact on the particle dispersion at air velocities below 0.4 m/s.

Discussion and conclusion

When the test person is within the UDF region, the results show, when the air velocity is 0.3 m/s or less, that the airflow pattern occurs in a disordered manner in the region around the table and the test person. However, when the air velocity exceeds 0.4 m/s, the airflow pattern more closely resembles undisturbed airflow, and the sweeping action seems to be significantly improved.

UDF vertical downwards airflow has been used for decades in industrial cleanrooms as well as in many ultraclean air operating rooms worldwide. If the main

<table>
<thead>
<tr>
<th>Velocity m/s</th>
<th>Region</th>
<th>Challenge</th>
<th>Number of particles ≥0.5 (\mu)m/cubic foot</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>A</td>
<td>Without person – with particle challenge</td>
<td>8839</td>
<td>(2.9 \times 10^{2})</td>
</tr>
<tr>
<td>0.3</td>
<td>B</td>
<td>Without person – with particle challenge</td>
<td>3625</td>
<td>(1.2 \times 10^{2})</td>
</tr>
<tr>
<td>0.3</td>
<td>C</td>
<td>Without person – with particle challenge</td>
<td>18,469</td>
<td>(6.2 \times 10^{2})</td>
</tr>
<tr>
<td>0.3</td>
<td>D</td>
<td>Person still – without particle challenge</td>
<td>&lt;10</td>
<td>–</td>
</tr>
<tr>
<td>0.3</td>
<td>D</td>
<td>Arm movements – without particle challenge</td>
<td>1138</td>
<td>–</td>
</tr>
<tr>
<td>0.3</td>
<td>D</td>
<td>Person still – with particle challenge</td>
<td>&gt;100,000</td>
<td>(&gt;3 \times 10^{3})</td>
</tr>
<tr>
<td>0.3</td>
<td>D</td>
<td>Arm movements – with particle challenge</td>
<td>&gt;100,000</td>
<td>(&gt;3 \times 10^{3})</td>
</tr>
<tr>
<td>0.4</td>
<td>A</td>
<td>Without person – with particle challenge</td>
<td>0</td>
<td>(&lt;10^{4})</td>
</tr>
<tr>
<td>0.4</td>
<td>B</td>
<td>Without person – with particle challenge</td>
<td>0</td>
<td>(&lt;10^{4})</td>
</tr>
<tr>
<td>0.4</td>
<td>C</td>
<td>Without person – with particle challenge</td>
<td>0</td>
<td>(&lt;10^{4})</td>
</tr>
<tr>
<td>0.4</td>
<td>D</td>
<td>Person still – without particle challenge</td>
<td>&lt;10</td>
<td>–</td>
</tr>
<tr>
<td>0.4</td>
<td>D</td>
<td>Arm movements – without particle challenge</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>0.4</td>
<td>D</td>
<td>Person still – with particle challenge</td>
<td>&lt;10</td>
<td>(&lt;10^{4})</td>
</tr>
<tr>
<td>0.4</td>
<td>D</td>
<td>Arm movements – with particle challenge</td>
<td>1623</td>
<td>(5.4 \times 10^{3})</td>
</tr>
<tr>
<td>0.5</td>
<td>A</td>
<td>Without person – with particle challenge</td>
<td>0</td>
<td>(&lt;10^{4})</td>
</tr>
<tr>
<td>0.5</td>
<td>B</td>
<td>Without person – with particle challenge</td>
<td>0</td>
<td>(&lt;10^{4})</td>
</tr>
<tr>
<td>0.5</td>
<td>C</td>
<td>Without person – with particle challenge</td>
<td>0</td>
<td>(&lt;10^{4})</td>
</tr>
<tr>
<td>0.5</td>
<td>D</td>
<td>Person still – without particle challenge</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>0.5</td>
<td>D</td>
<td>Arm movements – without particle challenge</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>0.5</td>
<td>D</td>
<td>Person still – with particle challenge</td>
<td>0</td>
<td>(&lt;10^{4})</td>
</tr>
<tr>
<td>0.5</td>
<td>D</td>
<td>Arm movements – with particle challenge</td>
<td>0</td>
<td>(&lt;10^{4})</td>
</tr>
</tbody>
</table>
concern in an operating room is to achieve an almost bacteria-free environment by the sweeping action of the air in a region around the operating table during ongoing surgery, a UDF-based room air distribution system with an inlet velocity about 0.4 m/s is needed. This is in agreement with results presented by Whyte\textsuperscript{1,2}, Nordenadler\textsuperscript{3} and Gandra\textsuperscript{11}.

While most UDF-based room air distribution systems for operating rooms, such as those which have been installed in Europe in the last 25 years, have air velocities below 0.3 m/s, the air movements during ongoing surgery just above the operating table become partly turbulent mixing.

For operating rooms with UDF systems with air velocities below 0.3 m/s, one can assume that the dilution principle starts to become valid in the operating zone during ongoing surgery. In such cases, the number of people in the operating room and chosen clothing system should be taken into consideration when the microbial air cleanliness is of importance.

### References


Introduction

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

Europe
- European Pharmacopoeia 10th Edition 10.0-10.2
- European Directorate for the Quality of Medicines (EDQM) inspections and trends of good manufacturing practice (GMP) deficiencies: overview 2006 to 2018
- European Union (EU)–USA Mutual Recognition Agreement (MRA) questions and answers (Q&As)
- EU Authorities Working to Avoid Shortages of Medicines due to Brexit – Questions & Answers
- The role of regulators in establishing added benefit of novel therapies
- European Medicines Agency (EMA) facilitates early engagement with medicine developers to combat antimicrobial resistance
- 20 years of sampling and testing programme for EU medicines
- New EudraVigilance system improves reporting of side effects and detection of safety signals
- EMA now operating from Amsterdam
- Medicines and Healthcare Products Regulatory Agency (MHRA) good distribution practice (GDP) Office Based Evaluation and Risk Assessment (OBERA) programme
- What does qualification of suppliers mean to you? Risks to patients and to your business

USA
- Considerations in Demonstrating Interchangeability with a Reference Product – Guidance for Industry
- Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations – Guidance for Industry
- Submitting Documents Using Real-World Data and Real-World Evidence to FDA [Food and Drug Administration] for Drugs and Biologics – Guidance for Industry
- Framework for the Regulation of Regenerative Medicine Products
- REMS [risk evaluation and mitigation strategies]: FDA’s Application of Statutory Factors in Determining when a REMS is Necessary – Guidance for Industry
- FDA not objecting to losartan with N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) below 9.82 parts per million (ppm) remaining on the market and updates on angiotensin II receptor blocker (ARB) recalls
- Bispecific Antibody Development Programs – Guidance for Industry
- Center for Biologics Evaluation and Research (CBER) FY 2018 Report

International

Australia
- Therapeutic Goods Association (TGA) instructions for disinfectant testing
- Risk Management Plans for Medicines and Biologicals: Australian Requirements and Recommendations
- Medicine shortages in Australia: reporting obligations and the TGA's compliance framework

Canada
- Changes regulations to help prevent illegal production and trafficking of controlled substances

Pharmaceutical Inspection Cooperation Scheme (PIC/S)
- PIC/S meeting April 2019 (Geneva, Switzerland)
- Bangladesh applies for PIC/S pre-accession

Russia
- Compliance Deadline for 12 Nosologies (diseases) Products must be Compliant by October 2019

Switzerland
- Switzerland now also uses EudraGMDP

World Health Organization (WHO)

Products
- Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic USA Stockpiles
- EU withdrawal of marketing authorisations for fenspiride medicines
- EU Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs
Europe

EDQM

European Pharmacopoeia 10th Edition 10.0-10.2
The 2020 subscriptions are now available for sale on the EDQM webstore. They comprise of either a new electronic version, (with the possibility to install the application to one computer and to one USB stick, for online or offline use [Windows and Linux compatible, Mac said to be coming soon]) or a conventional print version. Both comprise the first three volumes (10.0) and two non-cumulative updates, 10.1 and 10.2, and are available in English or French.

EDQM inspections and trends of GMP deficiencies: overview 2006 to 2018
A review of data from active pharmaceutical ingredient (API) inspections conducted by the EDQM between 2006 and 2018 is now available. This document summarises the trends of deficiencies observed during EDQM inspections with reference to EU Guidelines to GMP and to the corresponding Certificate of Suitability dossiers.

EMA

EU–USA MRA Q&A
The EMA has published an updated Q&As on impact of EU–USA MRA on marketing authorisation applications and relevant variations. There are three Q&As.

- Q1: How does the EU–USA Mutual Recognition Agreement (MRA) affect marketing authorisation applications or variations? (Revised January 2019)
- Q2: Where can I find more information on the MRA?
- Q3: Shall I discuss with the regulatory authorities the possibility of inspections when planning to file an EU marketing authorisation or variation? (NEW January 2019)

EU Authorities Working to Avoid Shortages of Medicines due to Brexit – Questions & Answers
This latest version of the Q&As explains that in case of a withdrawal agreement, there will be a transition period during which EU law will continue to apply in the UK. This means that access to medicines will not be affected.

If the UK leaves without a withdrawal agreement or deal (‘no-deal scenario’), EU law will cease to apply in the UK. In this case, in order to be able to continue to supply medicines in the EU, companies carrying out certain activities in the UK will need to make changes to comply with EU law.

The EMA, the European Commission and EU/European Economic Area (EEA) Member States have been working closely together since May 2017 to advise companies on how to apply for the necessary changes in order to minimise the impact on the supply of medicines, if the UK leaves the EU without a withdrawal agreement.

The document underlines that Brexit will not impact the safety of medicines, nor the way they are evaluated. The EMA and the Member States will continue to monitor the safety and efficacy of medicines without any changes. This document applies to both human and veterinary medicines and will continue to be updated as necessary.

In view of the 22 March conclusion of the European Council to extend the date of withdrawal of the UK from the EU, the EMA calls on all pharmaceutical companies in the EU to continue their preparedness activities, taking into account all possible outcomes. Based on the European Council conclusions, the deadline of 29 March referred to in the EMA’s published Brexit related guidance should be understood to be replaced by 12 April 2019 until further notice.

[As the situation remains fluid, readers should regularly check for updated guidance on the consequences of Brexit – MH.]

The role of regulators in establishing added benefit of novel therapies
The main conclusions of an article entitled Added Therapeutic Benefit and Drug Licensing (which is available through open access in Nature Reviews Drug Discovery) are that regulators have a role to play in ensuring that there is a solid evidence base to support the assessment of added therapeutic benefit of novel treatments compared with existing and potentially cheaper therapies. To help health technology assessment bodies, payers, clinicians and patients to separate merely new from truly better medicines, the regulators, firstly, should provide explicit reasoning on a medicine’s added benefit compared to other treatments at the time of approval. Secondly, they should insist on ‘evidence by design’. This means they must make companies aware of the need to plan the development programmes of medicines upfront, so that they are suitable to address the evidence needs of all relevant healthcare decisions-makers.

EMA facilitates early engagement with medicine developers to combat antimicrobial resistance
The EMA is opening up the early dialogue available through its Innovation Task Force (ITF) to all medicine developers who work on therapeutic approaches for the treatment or prevention of bacterial and fungal infections. The ITF is a forum for dialogue between regulators and developers of innovative emerging therapies, methods and technologies, in the early stages of research and development. The ITF is usually reserved for innovative medicines.

Given the growing threat to public health caused by antimicrobial resistance and the need for new treatments, the EMA is inviting all developers working on medicines for the treatment or prevention of life-threatening microbial infections to enter into early dialogue with the Agency to help strengthen the drug development pipeline for new antimicrobials.

20 years of sampling and testing programme for EU medicines
The number of centrally authorised medicines tested every year has steadily increased and now totals over 700
products. Most of the issues identified during the testing resulted in the EMA requiring companies to amend the registered manufacturer’s control methods for their medicines. In a small number of cases, the tested samples were not compliant with the authorised quality specifications for the medicine and required other regulatory actions such as re-testing (hopefully following a documented/formal out-of-specification procedure – MH), inspections, recalls or suspension of supply.

The programme is an important part of the supervision of the quality of centrally authorised products (CAPs) for human and veterinary use in all parts of the distribution chain. The tests are aimed at verifying the compliance of medicines with their authorised specifications and ensuring that the manufacturer’s control methods are satisfactory.

The selection of medicines for sampling and testing follows a risk-based approach and considers specific criteria, such as products with a narrow therapeutic range, a complex manufacturing process, poor stability or a high exposure, as well as the pharmaceutical forms and patient profiles.

The programme will be expanded from 2019 to include testing of biosimilars, and testing of CAPs from the parallel distribution chain. Additionally, the generics programme started in 2011 will be expanded to increase the coverage of market surveillance. Finally, a new ad hoc programme for APIs will allow the testing of APIs for CAPs sampled during GMP inspections.

New EudraVigilance system improves reporting of side effects and detection of safety signals

The new and improved EudraVigilance, the European system for managing and analysing information on suspected adverse reactions to medicines that are authorised or being studied in clinical trials in the EU, received more than 2 million reports of suspected side effects in 2018. This is an increase of 37% compared to 2017 which largely reflects that, from November 2017, the national competent authorities and the marketing authorisation holders (MAHs) were required to report non-serious cases of suspected adverse reactions to EudraVigilance, having previously only reported serious cases.

This was also a key driver for the increase in the number of reports received from European patients and consumers through national authorities and MAHs, which almost doubled between 2017 and 2018. Improvements in patient reporting also reflect efforts at national level to encourage patients to share information on side effects through information campaigns.

EMA now operating from Amsterdam

The EMA is now operating from Amsterdam after leaving its London premises on 1 March, for the Spark building in Amsterdam Sloterdijk. Close to 350 staff members have already relocated to the Netherlands. A number of EMA staff will telework from London to allow them and their families a smooth transition to Amsterdam in the second half of 2019. Overall, the EMA still anticipates losing approximately 25% of its total workforce (of around 900 staff members) as a result of the move.

MHRA

GDP OBERA programme

The GDP Inspectorate is embarking on a pilot of a new inspection approach that will impact holders of a Wholesale Dealer’s Licence whose main activities operate from a head office supplied from a number of ‘satellite’ facilities. For the companies selected, their satellite sites will be assessed remotely using information provided by the company in a standardised format. Who will be affected?

- The OBERA is targeted at companies that operate from a single head office location, where the majority of the wholesale activity takes place, with a number of satellite sites which perform a very limited range of GDP activity.
- Inclusion in the programme will be dependent upon the head office of the company passing an on-site ‘Gateway Inspection’.
- For the purposes of the pilot, companies with over 100 sites on their Wholesale Dealer’s Licence will be allocated a Gateway Inspection first. These companies will be contacted shortly, with the Gateway Inspections scheduled to commence during Spring 2019.

Once the OBERA process has been proven through the pilot, it is anticipated that it will be applied to other companies operating applicable business models. The MHRA will publish a follow-up blog post towards the end of 2019 on the findings from this pilot phase.

What does qualification of suppliers mean to you?

Risks to patients and to your business

The MHRA continues to note concerted efforts to falsely obtain stock by some parties from suppliers, and has undertaken targeted inspections of supply chain integrity, resulting in cases of regulatory and enforcement action. Further emerging trends have been observed by the MHRA around criminal attempts to sell falsified and stolen stock into the legitimate supply chain by a variety of methods. This creates the prospect of patients being supplied with substandard medicines, by way of gaps in the qualification processes of suppliers.

Several recent cases have exposed weaknesses in some supplier qualification processes, with individuals stealing the identity of legitimate companies and purporting to be someone they are not. In this instance, validation via EudraGMDP and Competent Authority sources would not detect a fraudulent supplier. There have been further examples of fake websites created in order to mimic legitimate companies, with the intent to deceive prospective businesses into purchasing from them. Obtaining a licence and checking on EudraGMDP may not be enough in these instances to protect licensed entities from fraudulent approaches.

There have also been instances of companies’ wholesale dealer licences being purchased outright and new directors and personnel appointed. Such cases are hard to spot as the licence details do not change. Here the newly purchased company supplies falsified medicines to customers who do
not notice that contact details have changed or that the company is now offering product types not previously seen.

USA

FDA

Considerations in Demonstrating Interchangeability with a Reference Product – Guidance for Industry

This final guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product is interchangeable with a reference product for the purposes of submitting a marketing application or supplement under Section 351(k) of the Public Health Service (PHS) Act (42 U.S.C. 262(k)). Although the 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic protein products and gives an overview of important scientific considerations in demonstrating interchangeability of a proposed therapeutic protein product with a reference product.

Section 351(k) of the PHS Act, as amended by the Biologics Price Competition and Innovation Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(k)(4) of the PHS Act further provides that upon review of an application submitted under Section 351(k) or any supplement to such an application, the FDA will determine the biological product to be interchangeable with the reference product if the FDA determines that the information submitted in the application or the supplement is sufficient to show that the biological product “is biosimilar to the reference product” and “can be expected to produce the same clinical result as the reference product in any given patient” and that “for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”

Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations – Guidance for Industry

This draft guidance describes the Agency’s recommendations on the design and evaluation of comparative analytical studies intended to support a demonstration that a proposed therapeutic protein product is biosimilar to a reference product licensed under Section 351(a) of the PHS Act. Additionally, this guidance is intended to provide recommendations to sponsors on the scientific and technical information for the chemistry, manufacturing, and controls portion of a marketing application for a proposed product submitted under Section 351(k) of the PHS Act.

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics – Guidance for Industry

This guidance document is being distributed for comment purposes only. Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance.

This guidance is intended to encourage sponsors and applicants who are using real-world data (RWD) to generate real-world evidence (RWE) as part of a regulatory submission to the FDA to provide information on their use of RWE in a simple, uniform format. The FDA will use this information for internal tracking purposes only. This guidance applies to submissions for investigational new drug applications, new drug applications and biologics license applications that contain RWE used to support regulatory decisions regarding safety and/or effectiveness.

For the purposes of this guidance, the FDA defines RWD as data relating to patient health status and/or the delivery of healthcare that are routinely collected from a variety of sources. Examples of RWD include the following.

- Data derived from electronic health records.
- Medical claims and billing data.
- Data from product and disease registries.
- Patient-generated data, including in-home use and/or other decentralised settings.
- Data gathered from other sources that can inform on health status, such as mobile devices.

RWE is defined as the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated, for example, by collecting information about effectiveness or safety outcomes from an RWD source in randomised clinical trials or in observational studies.

Framework for the Regulation of Regenerative Medicine Products

The FDA has published four final guidance documents that are part of a comprehensive policy framework to address how the Agency plans to support and expedite the development of regenerative medicine products, including human cells, tissues, and cellular and tissue-based products. These guidance documents build upon the FDA’s risk-based, flexible regulatory framework, and underscore the Agency’s commitment to help bring new and innovative treatment options to patients.

REMS: FDA’s Application of Statutory Factors in Determining when a REMS is Necessary – Guidance for Industry

This final guidance is intended to clarify how the FDA applies the factors set forth in Section 505-1 of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 355-1) in determining whether a REMS is necessary to ensure that the benefits of a drug outweigh its risks. This guidance fulfils one of the performance goals that the FDA agreed to satisfy in the reauthorisation of the Prescription Drug
User Fee Act V.

If the FDA determines that a REMS is necessary, the Agency may require one or more REMS elements, which could include a Medication Guide, a patient package insert, and/or a communication plan. The FDA may also require elements to assure safe use (ETASU) as part of a REMS. ETASU may be required if the drug has been shown to be effective, but is associated with a specific serious risk and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate a specific serious risk(s) listed in the labelling of the drug. ETASU may be required for approved drug products that were initially approved without ETASU when other elements are not sufficient to mitigate a serious risk.

FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market and updates on ARB recalls

As well as updating the list of products recalled, the FDA has posted new testing methods which can help manufacturers and international regulators detect and identify multiple nitrosamine impurities. The FDA and international regulators have identified N-Nitrosodimethylamine, N-Nitrosodiethylamine and NMBA in ARBs. These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

To ensure patient access to losartan, the FDA will not object to certain manufacturers temporarily distributing losartan containing NMBA above the interim acceptable intake limit of 0.96 ppm and below 9.82 ppm until the impurity can be eliminated. The Agency expects many companies will be able to manufacture losartan without nitrosamine impurities and replenish the USA supply in approximately 6 months.

Agency scientists evaluated the risk of exposure to NMBA at levels up to 9.82 ppm and determined that it presents no meaningful difference in cancer risk over a 6-month time period when compared to a lifetime of exposure to NMBA at 0.96 ppm. Distributing losartan containing NMBA up to 9.82 ppm, will help maintain adequate losartan supply while companies obtain approval for manufacturing processes that produce nitrosamine-free losartan for patients.

Bispecific Antibody Development Programs – Guidance for Industry

This draft guidance provides recommendations to assist industry and other parties involved in the development of bispecific antibodies. Discussion includes general considerations and recommendations for bispecific antibody development programs, as well as regulatory, quality, non-clinical, and clinical considerations in the context of bispecific antibody development programs. This guidance does not discuss development considerations for other multitarget therapies that are combinations of monoclonal antibodies or are antibody cocktails or polyclonal antibodies. Although this guidance is specific to bispecific antibodies, the principles discussed in this guidance may also be applicable to the development of other types of bispecific protein products.

Since the first therapeutic monoclonal antibody was commercialised in 1986, monoclonal antibodies have become a vital component of therapy for various diseases and conditions including, but not limited to, cancer, autoimmune and infectious diseases, and inflammatory conditions. The regulatory pathway for evaluation of monoclonal antibodies is well established, but additional guidance is needed regarding antibody-based products that target more than one antigen. Advances in technology and an interest in novel therapies that combine targets have led to the development of bispecific antibodies, which are genetically-engineered recombinant antibodies that consist of two distinct binding domains capable of binding two different antigens or two different epitopes of the same antigen.

There is often a strong scientific rationale for engaging two targets in the therapeutic strategy for a specific disease. Bispecific antibodies can target multiple disease-modifying molecules with one drug, with possible advantages over combination therapy or the use of antibody mixtures. The possibility of immune cell retargeting through the delivery of an effector or effector cell to a specific target or the possibility of synergistic efficacy through engagement of multiple targets gives bispecific antibodies the potential to advance the development of antibody-based therapies. There are a number of challenges in developing bispecific antibodies, one of which may be significant immunogenicity caused by novel epitopes. This guidance addresses these considerations and provides recommendations regarding the type of data necessary to support the approval of bispecific antibodies.

This guidance focuses on general regulatory and scientific considerations for bispecific antibodies, not on development of a particular bispecific antibody. Industry and other stakeholders are encouraged to engage the FDA to discuss their individual bispecific antibody development program.

CBER FY 2018 Report

One of the highlights of FY 2018 was the approval of two gene therapies: Luxturna, the first directly administered gene therapy for a specific genetic disorder, an inherited retinal disease; and Yescarta, a cell-based gene therapy for certain types of adult large B-cell lymphoma. The CBER also approved Heplisav-B, a hepatitis B vaccine to prevent infection caused by all known subtypes of hepatitis B virus in adults 18–70 years of age; Shingrix, a vaccine for the prevention of shingles in adults 50 years of age and older; and Fluarix Quadrivalent, to prevent influenza disease in children as young as 6 months of age. In addition, the CBER/FDA granted an emergency use authorisation to the Department of Defence to enable the use of freeze-dried plasma to treat haemorrhage or coagulopathy of USA military personnel injured during military combat when plasma is not available or its use is not practical.

The FDA’s ongoing contributions to controlling Zika virus included the CBER’s approval of the cobas Zika test and the procleix Zika virus assay (nucleic acid tests), the first donor screening tests for the direct detection of Zika virus RNA in human plasma from individual donors.
The report highlights these and other CBER accomplishments that reflect its responses to new and ongoing scientific and regulatory challenges, such as those posed by advanced therapies, emerging infectious diseases, and threats to the blood supply.

Nonproprietary Naming of Biological Products: Update Guidance for Industry
This draft guidance is issued for comment only. It describes the FDA’s current thinking on nonproprietary names of biological products licensed under Section 351 of the PHS Act that do not include an FDA-designated suffix. Specifically, the nonproprietary names of these products need not be revised in order to accomplish the objectives of the naming convention described in the Naming Guidance.

For similar reasons, the FDA does not intend to apply the naming convention described in the Naming Guidance to transition biological products. In addition, this draft guidance describes the FDA’s current thinking on the appropriate suffix format for the proper name of an interchangeable product licensed under Section 351(k) of the PHS Act. For interchangeable products, the FDA intends to designate a proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lower-case letters. The FDA is also reconsidering whether vaccines should be within the scope of the naming.

Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling – Guidance for Industry
This final guidance is intended to assist applicants in determining the appropriate placement and content of paediatric information in human prescription drug and biological product labelling as described in the regulations for the content and format of labelling for human prescription drug and biological products.

The goal of this guidance is to provide recommendations to help ensure that information on the use of prescription drugs in paediatric populations (whether positive, negative, or inconclusive) is consistently placed in the proper sections and subsections within labelling so that the information is clear and accessible to healthcare providers.

Until the early 1990s, the majority of drug labelling contained minimal or no paediatric use information to guide safe and effective use in the paediatric population. In 1994, the FDA began the first of several initiatives to improve paediatric use information in drug labelling by issuing a final rule revising the requirements for the Pediatric Use subsection of labelling. This regulation was intended to promote the inclusion of paediatric information from new clinical studies, previously published paediatric studies, and case reports in an effort to provide paediatric dosing and monitoring information in labelling. It also required drug manufacturers to examine existing data and determine whether those data were sufficient to support additional paediatric use information in a drug’s labelling.

Subsequent paediatric legislation included the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The BPCA contains economic incentives for conducting paediatric studies of drugs and biological products, and the PREA establishes requirements for studies of certain drugs and biological products that may be used in paediatric patients. The BPCA and PREA were made permanent in 2012 with the passage of the Food and Drug Administration Safety and Innovation Act.

Special 301 Report on Intellectual Property Protection and Review of Notorious Markets for Piracy and Counterfeiting
The Office of the United States Trade Representative (USTR) has released its annual Special 301 Report on the adequacy and effectiveness of trading partners’ protection of intellectual property (IP) rights and the findings of its Notorious Markets List, which highlights online and physical markets that reportedly engage in and facilitate substantial copyright piracy and trademark counterfeiting. The Special 301 Report identifies trading partners that do not adequately or effectively protect and enforce IP rights or otherwise deny market access to USA innovators and creators that rely on protection of their IP rights.

Trading partners that currently present the most significant concerns regarding IP rights are placed on the Priority Watch List or Watch List. The USTR identified 36 countries for these lists in the Special 301 Report.

- Algeria, Argentina, Chile, China, India, Indonesia, Kuwait, Russia, Saudi Arabia, Ukraine and Venezuela are on the Priority Watch List.
- Barbados, Bolivia, Brazil, Canada, Colombia, Costa Rica, Dominican Republic, Ecuador, Egypt, Greece, Guatemala, Jamaica, Lebanon, Mexico, Pakistan, Paraguay, Peru, Romania, Switzerland, Thailand, Turkey, Turkmenistan, the United Arab Emirates, Uzbekistan and Vietnam are on the Watch List.

These trading partners will be the subject of increased bilateral engagement with the USTR to address IP concerns. Specifically, over the coming weeks, the USTR will review the developments against the benchmarks established in the Special 301 action plans for countries that have been on the Priority Watch List for multiple years. For such countries that fail to address USA concerns, the USTR will take appropriate actions, such as enforcement actions under Section 301 of the Trade Act or pursuant to World Trade Organization or other trade agreement dispute settlement procedures, necessary to combat unfair trade practices and to ensure that trading partners follow through with their international commitments.

[A little surprising to see some EU Member States and countries such as Switzerland and Canada on the Watch List – MH.]

International

Australia

TGA instructions for disinfectant testing
The TGA has made the new TGO 104 to replace the previous TGO 54 which sunset (ceased) on 1 April 2019.
The TGA has incorporated stakeholder feedback from consultation about the proposed new TGO and its associated guidance documents for listed and exempt disinfectants. TGO 104 incorporates the following.

- Updated sections of the previous TGO 54 and clarifies the requirements for hard surface disinfectants.
- The labelling requirements of the previous TGO and TGO 37 ‘general requirements for labels for therapeutic devices’ (which sunset on 1 October 2018).
- Standards and requirements within the guidelines for the evaluation of disinfectants.

As a result, these regulatory requirements are now contained within one TGO.

TGO 104 March 2019 is designed to support the quality, safety and efficacy of therapeutic goods that are disinfectants, sterilants and sanitary fluids and powders.

The Order does so in relation to disinfectants by, in part, specifying a number of important performance requirements. These performance requirements principally require that disinfectants comply with specified microbiological tests, such as the TGA Disinfectant Test, to support the claims for bactericidal activity. Additional testing is required where a claim is made for a disinfectant in relation to the product having a sporicidal, fungicidal, tuberculocidal, virucidal or other biocidal use.

An ‘outcomes from consultation’ document sets out for the purpose of identifying and explaining the testing requirements (TGA Disinfectant Test [Part 1] and specific testing requirements [Part 2]), principally for the purposes of the Order.

Risk Management Plans for Medicines and Biologicals: Australian Requirements and Recommendations

This guidance is for sponsors of prescription medicines and biologicals making applications to enter or vary Australian Register of Therapeutic Goods entries. It describes the risk management plan requirements.

Guidance for TGO 101: Standard for Tablets, Capsules and Pills

This guidance is to help sponsors and manufacturers of medicines understand the role of TGO 101: Standard for Tablets, Capsules and Pills in ensuring that these types of therapeutic goods are of appropriate quality.

The requirements that applied to tablets and capsules under TGO 78 Standard for Tablets and Capsules have been adopted into TGO 101. This means that, generally, a transition period is not needed for these medicines. Sponsors can elect to move to alternative testing requirements, where this is permitted under the Order, at any time. Details on how to request this type of change are provided later in this document.

The TGO 101 requirements that apply to pills commence on 31 March 2021. Pills were not subject to TGO 78. The delayed commencement allows sponsors 2 years to update their manufacturing documentation and ensure that their goods will comply with the new requirements by the end of March 2021.

A 2-year transition period has also been specified in relation to Section 16 of the Order. This allows sponsors time to review the manufacturing documentation for their medicines and update them in line with the requirements for elemental impurities and residual solvents in tablets and capsules. All tablets, capsules and pills subject to the Order and released for supply after 30 March 2021 must comply with TGO 101.

Medicine shortages in Australia: reporting obligations and the TGA’s compliance framework

Medicine shortages have become an increasing problem in recent years for a number of reasons, including a decrease in the local manufacture of prescription medicines, and the increasingly globalised nature of supply chains. A Medicine Shortages Information Initiative (MSII) and website was launched in 2014 by the TGA. This was a voluntary notification scheme where sponsors were encouraged to notify the TGA of medicine shortages, but reporting was not compulsory. Under that scheme, however, a significant number of medicine shortages of critical impact on patients had not been reported, notwithstanding considerable encouragement from the TGA for greater industry engagement.

As such, the voluntary arrangements did not provide a sufficient incentive for sponsors to report when their product would be in shortage, meaning that the information available on the TGA’s website in relation to shortages, notified under the MSII, was not a complete or current source of information about medicine shortages.

In response to the issues experienced with the voluntary scheme, a Medicine Shortages Working Party developed a revised protocol for the management and communication of shortages. This involved mandatory confidential reporting of all shortages to the TGA, the publication of those shortages that are of particular impact on patients, and the development of a more transparent and action-oriented approach to the management of confirmed and serious medicines shortages.

Canada

Changes to regulations to help prevent illegal production and trafficking of controlled substances

The crisis of opioid overdoses continues to be one of the most serious public health issues in Canada's recent history. Illegal drugs tainted with highly toxic opioids, such as fentanyl and carfentanil, continue to be behind the majority of opioid-related overdose deaths.

The Government of Canada has announced new regulatory amendments to help tackle the illegal trafficking and production of controlled substances. The amendments under the Controlled Drugs and Substances Act (CDSA) come into force immediately and control specific chemicals – known as precursors – from being imported and used in the illegal production of fentanyl and amphetamines, such as methamphetamine and 3,4-Methylenedioxymethamphetamine (MDMA – commonly known as ecstasy).

In recent years, law enforcement identified novel chemicals not controlled under the CDSA that were making their way across the border and being used in the illegal production of fentanyl and amphetamines. Before these
regulatory changes, law enforcement could take action only once illegal substances were produced using these chemicals, or if there was evidence that the chemicals were intended to be used to produce an illegal substance.

With today’s changes, the Canada Border Services Agency and other law enforcement officers can now take action against illegal activities involving precursor chemicals, such as benzylfentanyl, derivatives and analogues of 4-anilino-N-phenethylpiperidine and norfentanyl. Specifically, officers can detain and seize these chemicals to prevent them from entering Canada.

**PIC/S**

**PIC/S meeting April 2019 (Geneva, Switzerland)**

The PIC/S Committee met on 9–10 April 2019. The meeting was attended by 45 out of 52 PIC/S Participating Authorities as well as by a number of applicants, pre-applicants, associated partners and guests. The latter including delegations from China National Medical Products Administration (NMPA) and Philippines Fisheries Development Authority. The highlights included the following.

- **PIC/S Inspection Reliance Initiative: PI 048-1.**

  Further to the entry into force of this guidance, members have been invited to collect statistics on desktop assessments as from 1 January 2019, based on a template including metrics. The purpose of these statistics is to document the efforts made by members to rely on existing inspection reports rather than duplicate foreign GMP inspections. Results will be collected at the end of 2019.

  In order to apply PI 048-1, some Members will need to adapt their inspection strategy to a risk-based strategy. In this perspective, the Committee was updated on successful examples of processes used by some of its Members in identifying instances where an on-site inspection of an overseas facility is not necessary. In particular, Australia TGA and Health Canada presented on their active desktop assessment procedures and implementation as well as on current statistics.

  The interest of industry in PI 048-1 and its implementation is key, in particular, as it is up to manufacturers to proactively share reports if they wish to avoid duplicate inspections.

- **Updates on future revisions to PIC/S Guide to GMP for Medicinal Products: Annex 1 (Manufacture of Sterile Medicinal Products); Annex 2 (Manufacture of Biological Medicinal Substances and Products for Human Use); Annex 13 (Manufacture of Investigational Medicinal Products); and Annex 16 (Qualified Person and Batch Release).**

  The revision of Annex 1 will be the focus of the PIC/S 2019 Seminar which will be hosted by Japan Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Device Agency (PMDA).

  The PIC/S Working Group established with the World Health Organization (WHO) on the Revision of Annex 2 of the PIC/S Guide to GMP has drafted a new annex, Annex 2A for Manufacture of Advanced Therapy Medicinal Products (ATMP) for Human Use. This new Annex takes into account the EU Guidelines to GMP on ATMPs while addressing the concerns of PIC/S, as expressed to the European Commission during the drafting process of the EU Guidelines to GMP. Annex 2B for the Manufacture of Biological Medicinal Substances and Products for Human Use will be the revised version of EU Guidelines to GMP Annex 2 for biologics (excluding ATMPs). The Committee also decided to carry out a targeted stakeholder consultation on the development of revised Annex 2.

  The Committee updated the outcome of step 1 of the draft adaptation for PIC/S purposes of EU Guidelines to GMP Annex 16 (Certification by an Authorised Person and Batch Release). One major difficulty in the adaptation of Annex 16 was that neither the PIC/S nor the PIC/S Guide to GMP deal with import or import controls. As a result, there was some discussion on whether to allow for the voluntary implementation for import-related activities. The Committee decided that the question of whether to include or exclude release aspects associated with importation should be further addressed by PIC/S experts of non-EEA Participating Authorities in order to clarify this issue prior to proceeding with step 2.

  The Committee also decided to carry out a targeted stakeholder consultation on the development of revised Annex 1.

- **New working group established to develop a PIC/S Aide Memoire on Tissues and Cellular Therapy Products Inspections (excluding ATMPs).**

  This future Aide Memoire is intended for inspection of minimally manipulated human tissues and cells for human applications (ATMPs will not be within its scope).

- **Progress in amendment of PIC/S.**

  - **PIC/S 2019 Seminar to be hosted by Japan MHLW and PMDA in Toyama and updates on PIC/S Inspectorates’ Academy and future training activities.**

  - **Completion of pre-accession of Saudi Arabia Saudi Food and Drug Authority and new PIC/S pre-accession application received from Bangladesh’s DGDA.**

  - **Bilateral meetings with China NMPA and International Council for Harmonisation.**

**Bangladesh applies for PIC/S pre-accession**

Bangladesh’s DGDA applied for PIC/S pre-accession. The Rapporteurs were appointed at the PIC/S Committee meeting on 9–10 April 2019.

**Russia**

**Compliance Deadline for 12 Nosologies (diseases) Products must be Compliant by October 2019**

Previously, pharmaceutical products sold in Russia would need to be in compliance with the announced serialisation and aggregation regulations by 1 January 2020, but at the
end of 2018, Russia published an update to Federal Law No. 425-FZ. This update included guidance for manufacturers of medicines to treat 12 specific conditions, specifying an earlier deadline of 1 October 2019. This gives manufacturers of these products very little time before they must be in complete compliance with the new serialisation requirements.

The medications are used in the treatment of these 12 rare medical conditions: haemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, myeloid leukaemia, multiple sclerosis, immunosuppressive therapy for organ transplant patients, haemolytic-uremic syndrome, juvenile arthritis with systemic onset and Mucopolysaccharidosis type I, II and VI. All medicines aimed at these medical conditions must be labelled, serialised and reported in order to be compliant.

Switzerland

Switzerland now also uses EudraGMDP

The Swissmedic regulatory authority has started in 2019 to enter information on GMP compliance as well as on manufacturing authorisations related to Swiss manufacturers into the EU’s EudraGMDP database. This applies for all new or renewed manufacturing authorisations and the related GMP-certificates issued using new templates (similar to those of the EMA). This will allow replacing the current practice of issuing paper documents, i.e. GMP certificates for certain regulatory procedures, and therefore should lead to easier information-sharing and efficiency gains for all stakeholders.

The EMA offers ‘read and write’ access to EudraGMDP to the regulatory authorities of all countries with which the EU has an MRA. Since 2013, the Japanese authorities also enter data into EudraGMDP which allows waiving the need for paper GMP certificates for certain procedures.

WHO

The 53rd ECSPP report (WHO Technical Report Series, No. 1019)

The following guidelines, as contained in the Annexes to the ECSPP’s 53rd report, are now recommended for use.

- Annex 3: GMP: Guidelines on Validation
  - Appendix 1 Validation of Heating, Ventilation and Air-Conditioning Systems
  - Appendix 2 Validation of Water Systems for Pharmaceutical Use
  - Appendix 3 Cleaning Validation
  - Appendix 4 Analytical Procedure Validation
  - Appendix 5 Validation of Computerized Systems
  - Appendix 6 Guidelines on Qualification
  - Appendix 7 Non-Sterile Process Validation
- Annex 4: Protocol to Conduct Equilibrium Solubility Experiments for the Purpose of Biopharmaceutics Classification System-Based Classification of Active Pharmaceutical Ingredients for Biowaiver
- Annex 5: Guidelines on Import Procedures for Medical Products
- Annex 6: Good Practices of National Regulatory Authorities in Implementing the Collaborative Registration Procedures for Medical Products
  - Appendix 1 An Example of Information to Applicants for Registration via the WHO Collaborative Registration Procedure
  - Appendix 2 Verification for Product Submitted under the WHO Collaborative Procedure
  - Appendix 3 Abridged/Abbreviated Review for Product Submitted under the WHO Collaborative Procedure
  - Appendix 4 Additional Information to be Included in the Screening Checklist
  - Appendix 5 Example of a National Regulatory Authority Reliance Model Approach: Information, Documentary Evidence and Assessment Activity
  - Appendix 6 Model Acknowledgement or Approval Letter for Variations of Products Registered through the WHO Collaborative Procedure

The newly adopted specifications and general texts will be included in the 9th edition of The International Pharmacopoeia which is currently in preparation.

Products


A number of US government public health and emergency response stakeholders maintain stockpiles of doxycycline tablets or capsules for post-exposure prophylaxis or treatment of inhalational anthrax in the event of an anthrax emergency. States have asked the FDA what would be necessary to provide confidence that stockpiled doxycycline tablets and capsules have retained their original quality (i.e. purity and potency) beyond the manufacturer’s labelled expiration date so the replacement of stockpiled product could be deferred.

This final guidance document provides guidance to government stakeholders on testing to extend the expiration date – under Section 564A(b) of the FD&C Act of stockpiled doxycycline tablets and capsules for public health emergency preparedness and response purposes for an anthrax emergency.

‘Many antidote medicines end up not being used before their expiry date. To my mind, it is a sensible use of quality
risk management to allow expiry date extensions as long as the effectiveness of the antidote is not affected, that the supply chain remains secure and as defined, and that the ability to create new supplies as and when needed is maintained – MH.

EU withdrawal of marketing authorisations for fenspiride medicines
The EMA’s safety committee (Pharmacovigilance Risk Assessment Committee [PRAC]) has recommended that the marketing authorisations for fenspiride medicines be revoked, so the medicines can no longer be marketed in the EU. This follows a review that has confirmed that these cough medicines could cause heart rhythm problems. The recommendation will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human to make a decision about its implementation.

Fenspiride medicines are available as syrup or tablets and used in adults and children from the age of 2 years to relieve cough resulting from lung diseases. In the EU, fenspiride medicines have been authorised via national procedures in Bulgaria, France, Latvia, Lithuania, Poland, Portugal and Romania and are available under various brand names (Elofen, Epistat, Eurefin, Eurespal, Fenspogal, Fosidal, Kudorp, Pneumorel, Pulneo, Еуреспал and Сиресп).

EU restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs
The EMA’s PRAC is recommending that doctors must not prescribe the 10 mg twice daily dose of Xeljanz (tofacitinib) in patients who are at high risk of blood clots in the lungs.

Xeljanz is currently authorised for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis. The new advice means that, since 10 mg is the only recommended starting dose for ulcerative colitis, patients with this condition who are at high risk of blood clots must not be started on Xeljanz. Patients at high risk currently taking this dose for any condition must be switched to alternative treatments.

Further information on these and other topics can be found in recent versions of the "Regulatory Update" on the PHSS website and on the websites of the relevant regulatory bodies and international organisations. In addition, a list of useful websites can be obtained from: info@euromedcommunications.com
The annual PHSS Challenges in Sterile Product Manufacturing in Manchester, UK was a highly successful conference with sold out attendance. The format of four different presentation groups worked very well and covered: 1) Regulatory/GMP (good manufacturing practice) auditor perspectives; 2) Main pharma and ATMP (advanced therapy medicinal product)/biopharma product manufacturing via aseptic processing; 3) New technology developments and strategies for aseptic containment; and 4) Academic research in the area of viable but non-culturable (VBNC) microorganisms and connection with GMP.

The upcoming PHSS Annual Conference in London on 10 September 2019 in collaboration with the University College London School of Pharmacy Q3P course will continue to explore the challenges of biological product manufacture and ATMP processing, regulatory challenges and challenges to qualified persons (QPs) in their role of certification for release.

The PHSS QP Forum continues to develop and provide a connection to QPs to learn and share experiences of challenging areas of GMP, good distribution practice (GDP) and product release.

The PHSS Aseptic Processing Special Interest Group met on 7 June 2019 after the annual Challenges in Sterile Product Manufacturing Conference to discuss the guidance initiative of preparation of Clarity on GMP Guidance Notes. There was a well-balanced discussion group that included three ex-MHRA (Medicines and Healthcare Products Regulatory Agency) senior GMP inspectors, representation from major pharma industry (GlaxoSmithKline, Pfizer Ireland and Belgium, Ely Lilly France and Italy), filling machine manufacturers, barrier technology and environmental monitoring system manufacturers, together with academics involved in GMP.

Schedule of PHSS Clarity on GMP Guidance Notes

1. Assurance of sterility indirect product contact parts: stopper pathway.
2. Environmental classification, qualification, monitoring.
3. Localised unidirectional airflow (L-UDAF).
4. Barrier leak rates and leak integrity applied to isolators.
5. Continuous particle monitoring: compliance and event monitoring with trend predictor.
6. Risk assessment in setting environmental monitoring (EM) sample locations during design.
7. Airflow visualisation in controlled areas: computational fluid dynamics (CFD), smoke studies, limitation of risks (LR).
8. Avoiding wet loads in moist heat sterilisation.
9. Glove management strategy for barrier system gloves.
10. Vapourised hydrogen peroxide (vH$_2$O$_2$/VHP) bio-decontamination of loads: isolators and material transfers.
11. Definitions of ‘open’ and ‘closed’ applied to aseptic processing.
12. No-touch-transfer (NTT) of pre-sterilised containers following GMP and quality risk management (QRM) principles.
13. Aseptic containment strategy (ACS) for processing sterile toxic and biologically hazardous products.
14. Contamination control strategy (CCS) for Annex 1 compliance.
15. Media fill design for aseptic processing.

All sixteen proposed Clarity on GMP Guidance Notes were reviewed in general for scope and proposed content with more detailed discussion focused around the following four guidance notes as issues are current and topical.

Clarity on GMP Guidance Note No.1 Assurance of Sterility in Aseptic Manufacturing of Contact Product Contact Parts – New and Existing Filling Lines.

Clarity on GMP Guidance Note No.2 Rationale for Environmental Classification, Qualification, and Monitoring for Aseptic Process Filling Applications with Barrier Technology.

Clarity on GMP Guidance Note No.6 Risk Assessment in Setting EM Sample Locations for Monitoring During...
Classification, Qualification/ Process Simulations/ Media Fills and During Routine Production Operations.

Clarity on GMP Guidance Note No. 12. No-Touch-Transfer (NTT) of Pre-Sterilized Containers into Barrier Technology following GMP and QRM Principles. Rationale for Qualification.

Outcome of discussions considering Clarity on GMP Guidance notes

- For each guidance document, small focus groups responsible for initial preparation will be provided with a template and guidance scope document – by end of July 2019.
- A wider review of developed draft documents will include the full Aseptic Processing Special Interest Group before guidance finalisation and issue to the MHRA for regulatory review and before publication (PHSS website and EJPPS).
- Two guidance documents, No.1 and No.6, will be developed in collaboration with BPOG (Biophorum) to assure harmonisation.
- Guidance notes will be case study based to prevent being over prescriptive.

Outcome of discussions around guidance note scope and content

Clarity on GMP Guidance Note No.1 Assurance of Sterility in Aseptic Manufacturing of Contact Product Contact Parts – New and Existing Filling Lines

Discussion outcomes
The PHSS has already published a first release of Clarity on GMP Guidance Note No. 1 with MHRA review before publication. This publication was, in part, a response to the MHRA blog on ‘Fragility of VHP’ where vH2O2/VHP only as a surface sterilisation method was challenged by regulatory authorities.

The regulatory challenge followed outcomes from GMP inspections that highlighted, in some cases, a lack of scientific and process knowledge related to the VHP bio-decontamination process leading to poor practice in process operations and over-claiming of VHP efficacy without regard to the limitations of VHP penetration. If the bioburden is high and/or protective contaminants provide an exposure barrier, efficacy of VHP cannot be assured. Too much focus was placed on inactivating biological indicators with 6 log sporicidal efficacy claims but where adjacent surfaces may not be presented or exposed to efficacy to the same extent so assurance of surface bio-decontamination was compromised.

The first published Guidance Note No.1 is considered to be comprehensive for new filling lines where design and procedural controls could be embraced from the outset as assurance of sterility of indirect product contact parts could combine a sterilisation process out-of-place, e.g. moist heat, bioburden control in transfers and assembly, and VHP in-place in a closed barrier.

From feedback on this first guidance after release, there are some areas of the guidance that need more details on expectations to prevent unnecessary over complication, or have performance expectations that are very challenging to meet and add little value.

An example is air flow protection over the stopper pathway (bowl, hopper, chute, track ways) during assembly into the isolator is a bioburden control measure. Requirements are not for full unidirectional air flow (UDAF) over the stopper contact parts and controlled exit of the isolator from the open barrier door at low level protecting from any airborne contamination ingress into the barrier with the isolator door open. This pre-VHP set-up should not be considered the same as assembling
sterilised product contact parts into a restricted access barrier system (RABS) where outward protective airflow would be expected through the open access barrier door through the complete procedure until barrier door is closed.

It is considered that transfer and hold in a Grade C cleanroom of sterilised indirect product contact parts (with a protective covering, e.g. Tyvek®) followed by assembly into the isolator with the barrier doors open as required access for the procedure will not assure sterilised surfaces remain sterile, but with bioburden control measures bioburden maintained below 10 colony-forming units (cfu) is an acceptable challenge to VHP given the limitations on penetration.

The regulatory expectation remains that indirect product contact parts should be sterilised by a recognised sterilisation process. VHP is not a recognised sterilisation process (fully penetrative) as applied to barrier technology. There are some VHP sterilisers that use vacuum and VHP pulses in a vacuum chamber to effect surface sterilisation, and this is in variance to the gaseous bio-decontamination process applied to isolators, closed RABS and cleanrooms.

For existing filling lines that cannot adopt all the requirements as defined for new filling lines, QRM has to be considered on a case by case basis with local inspectors consulted on the approach taken. If an out-of-place sterilisation process is not possible because of line design or complexities in operations and VHP is used as a bio-contamination control measure to assure surface sterility with 6 log sporicidal efficacy (from a starting position of 10 cfu bioburden), this approach has to be discussed with the regulator.

In such a case, cleaning validation (verification of protective soiling, e.g. silicon, fatty acids from skin contact are removed) becomes process critical. In addition, a manual disinfection process would be required in combination with physical removal of bioburden and bioburden control to low level – PHSS guidance will be updated to include points to consider for existing filling lines and not define guidance as a case study indicating direct regulatory acceptance.

Clarity on GMP Guidance Note No.2. Rationale for Environmental Classification, Qualification, and Monitoring for Aseptic Process Filling Applications with Barrier Technology

Discussion outcomes
It was decided this guidance document was required to be detailed as a set of principles for environmental classification taking reference to ISO 14644-1, but guidance on environmental qualification should be set out as a series of case studies with more flow diagrams and graphical examples. Case studies will be considered for the following.

- Isolator filling line and surrounding environment.
- RABS filling line and surrounding environment.
- Hospital pharmacy isolator and surrounding environment.
- ATMP processing safety cabinet and surrounding environment.
- Change rooms for entry to Grade C and Grade B cleanrooms.
- Material transfer airlock: manual disinfection and VHP/vH₂O₂ gaseous disinfection chamber.
- Sterility test isolator and surrounding environment.

Clarity on GMP Guidance Note No.6 Risk Assessment in Setting EM Sample Locations for Monitoring During Classification, Qualification/Process Simulations/Media Fills and During Routine Production Operations

Discussion outcomes
BPOG have already published guidance on setting, including risk assessment, for defining EM locations in controlled areas. The PHSS have reviewed this guidance and made comment, particularly around terminology in risk assessments considering high-risk outcomes so there is clarity.

Risk assessments for setting EM locations that have an outcome of a high risk of contamination should first have control measures applied to reduce risks to acceptable levels before EM sample locations are considered. Risk assessments for setting EM locations should consider process points/areas that would have a high impact if the area/zone was contaminated so detectability is required to inform of such a risk escalation.

The developing PHSS EM location guidance is positioned to apply to the design phase when integrating barrier technology with cleanrooms and considers two successive steps.

1) To consider risks of process ‘risk’ zone contamination from process and operator interventions.
2) To consider detectability of a contamination event from process, corrective and inherent interventions based on EM sample locations set in the considering risk identification of possible contamination routes and sources.

It is considered both BPOG and PHSS guidance can be developed as complementary.
Clarity on GMP Guidance Note No. 12. No-Touch-Transfer (NTT) of Pre-Sterilized Containers into Barrier Technology Following GMP and QRM principles. Rationale for Qualification

Discussion outcomes
No other not-for-profit societies or associations are taking initiative on guidance development for transfer of pre-sterilised containers into Grade A filling environments via an NTT process making the PHSS initiative highly important.

The increase of NTT applications for filling line projects requires an alignment with regulators (on expectations based on QRM as this is an alternative methodology and does not follow generic GMP), pharma/biopharma industry/ATMP community and pre-sterilised container manufacturers as to the qualification methodology.

Pre-sterilised containers assurance of sterility is required at manufacture, through the supply chain and in aseptic processing operations so all must be aligned for GMP/GDP compliance. The pre-sterilised container manufacturers are starting to engage studies to support sterility assurance through the supply chain and support the holistic processing steps.

The PHSS guidance document will be developed for qualification in two parts.

• Part A for pre-sterilised container manufacturers: qualification of pre-sterilised container suitability for NTT application together with supply chain qualification.
• Part B: filling line barrier surface and airborne contamination control qualification with application of the NTT process. Qualification includes CFD studies, smoke studies and LR method particle challenge to verify smoke particles (surrogate for microbe-carrying particles) do not transfer to a higher grade zone in pre-sterilised container de-bagging and NTT transfers.

Next steps in PHSS Clarity of GMP Guidance Notes
Guidance note templates with scope and required content for each guidance document will be issued to the PHSS focus groups by the end of July to facilitate the preparation of initial drafts.

Future developments in the PHSS
The PHSS continue to play an active role in GxP education and guidance development. It has been identified that more needs to be done within the PHSS relating to guidance on non-sterile product manufacturing where increasingly bioburden control is required and much reference is made to sterile manufacturing GMP without clarity, what applies, and where adaption to generic GMP is required.

The PHSS management team has been reinforced with a team that has specialist knowledge in non-sterile manufacture, so initiatives can be started to identify ‘gaps’ where the PHSS can support with education and guidance.

James Drinkwater
PHSS Chairman and Leader of Aseptic Processing and Containment Special Interest Groups
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