Microbiological Contamination Control in Aseptic Processing: A US perspective

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Acknowledgements

I would like to extend a massive thank you to the Winston Churchill Memorial Trust for allowing me the opportunity to carry out my research in the USA. I had an amazing experience and have returned with fresh ideas for my work place. I’d particularly like to thank the WCMT staff for answering all my questions! In addition, I was fortunate enough to visit a number of amazing places, though I am unable to name my favourite city visited as I enjoyed each one and they were all so different! I feel very lucky and humbled for the experience.

I would also like to thank all my hosts in the USA for kindly allowing me to visit their institutions and answering all my questions. I met some excellent individuals whom were more than happy to share their knowledge and expertise. In addition, I’d like to say thank you to my hosts that gave me recommendations for great places to visit/eat whilst travelling! I hope that one day I may be able to extend a welcoming hand to those overseas so that we may continue to share knowledge and best practice.

A huge thank you to all my loved ones for their continued support!

“To improve is to change; to be perfect is to change often.”

- Winston Churchill
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My Background

I am currently a trainee clinical pharmaceutical scientist for the National Health Service, about to complete the Scientist Training Programme (Sept 2017). As part of my training I am based within technical hospital pharmacy services, with rotations completed in aseptic services, radio pharmacy, production, quality assurance and quality control. As a biologist by background (Msc Biological Sciences) I have developed a specific interest in pharmaceutical microbiology.

Whilst completing an Msc in Clinical Science (Pharmaceutical Science), I undertook a research project looking into analysing the microbiological impact of incorporating a sporicidal wipe into the transfer disinfection process within NHS aseptic units in the North West. As a result, I became very interested in the prevention of microbes into the pharmaceutical cleanroom and wanted to ascertain how other regulatory bodies were managing this.

I have been lucky enough to experience working and studying internationally, and have learnt the value of gaining an international perspective on ideas and issues. I wanted to try and find novel approaches to preventing microbial ingress in the cleanroom by exploring this issue at an international level, in addition to networking and discussing this field with global experts.
Executive Summary

I wanted to make a comparison between aseptic preparation (IV compounding) between the UK and USA, specifically with respect to the prevention of microbiological contamination in pharmaceuticals. I specifically chose the USA as I was interested in the differing regulations surrounding this topic, in addition to being aware of contamination incidents occurring in the US. I was able to spend 4 weeks on both East and West coasts visiting multiple compounding sites.

At each visit, the disaster occurring at the New England Compounding Center in 2012 was mentioned as a pivotal step in the changes to pharmacy compounding practices. This disaster resulted in over 800 individuals contracting fungal meningitis, with the deaths of 64 of these individuals. The Centers for Disease Control and Prevention (CDC) initiated a large multi-state investigation, with the results concluding the manufacturing site in Framingham, Massachusetts not fit for purpose due to many faults/negligence with the aseptic manufacturing process. Contaminated preservative-free steroid injections were cited as responsible for this outbreak.

Initially, it took a while to understand the different terminology and differing regulatory structure. For example “beyond use dating” which is abbreviated to BUD in the US, or shelf life in the UK. Another example is the term “garbing” instead of “gowning”. However it was interesting to learn and understand the alternative terms, and learn of the differences between regulatory bodies between states. For example, in New York, only pharmacists are able to compound patient specific doses, whereas in California this is carried out by registered technicians.

Key Recommendations arising from this Fellowship

1. Greater focus on the training of aseptic services personnel and implementation of more robust training programmes defining aseptic technique, pharmaceutical microbiology etc.
2. Implementation of a “play-book” type document in order to define the scientific reasoning behind microbiological monitoring environmental samples and strategies
3. Greater application of quality risk management strategies to microbiological monitoring
4. Reduce the amount of paper entering the critical work zone and cleanroom
5. Greater emphasis on the importance of correct sampling and packaging of sampling methods
Report in Context

What is aseptic processing and preparation?

Aseptic processing is the manipulation of raw materials in a controlled environment using strict techniques to ensure the pharmaceutical product is free from micro-organisms and other contaminants. Aseptic processing is required to decrease the risk of micro-organism entry into parenteral preparations. The intended route of administration of such pharmaceuticals means the risk of an adverse event occurring from microbiological contamination is high. Aseptically prepared products in NHS aseptic units are not subject to terminal sterilisation prior to release. Therefore, when compared to terminally sterilised pharmaceuticals the risk of a non-sterile product is greater. Products prepared within hospital pharmacies in the UK are parenteral therapies including chemotherapy, parenteral nutrition and miscellaneous injectable medicines deemed “high risk” if prepared at ward level.

A carefully controlled environment with a high level of cleanliness is required for aseptic preparation of the aforementioned products. Laminar air flow cabinets (LAFCs) and isolators situated within monitored "cleanrooms" are used by pharmacy aseptic units to create and maintain such environments. These act to ensure pharmaceuticals are suitably protected from both microbiological and particulate contamination. Aseptic manipulations take place within isolators and LAFCs, and this area is often termed the “critical work zone” (CWZ). Environmental control and microbiological monitoring strategies are required by regulation in the cleanroom and CWZ. The European Union’s (EU) GMP directive states the recommended limits for microbial counts present in controlled areas. These are classified as Grades A through to D. Isolators and LAFCs used in aseptic processing must be monitored to Grade A standards since this is where the highest risk operation of aseptic manipulation takes place.

Regulation & the UK

The Medicines and Healthcare products Regulatory Agency (MHRA) are the governing body responsible for the regulation of medicines in the United Kingdom (UK). The MHRA ensure all licensed pharmaceutical manufacturers adhere to good manufacturing principles as defined within the MHRA’s Rules and Guidance for Pharmaceutical Manufacturers and Distributors, or “orange guide” as it is known. Unlicensed pharmaceutical preparation, whilst striving to meet the MHRA standards, must meet the standards set out within “Quality Assurance for Aseptic Preparation Services”, to which NHS
aseptic units operating under the Section 10 exemption of the Medicines Act 1968 are audited against.

In January 2015, the MHRA issued the MHRA Guidance for Specials manufacturers’ document. This serves to provide clarification and guidance on the application of good manufacturing practice (GMP) requirements during pharmaceutical manufacture for holders of an MHRA issued specials (MS) licence (MHRA, 2014). The document includes new requirements for preventing microbial entry into the cleanroom, with the sanitisation of items carrying out the transfer sanitisation process within licensed aseptic units. Transfer sanitisation is the process of removing microbes from the surfaces of items entering the clean working environment, e.g. syringes, vials etc.

Specifically, the new regulations require a two-stage spray and wipe process, with a sporicide applied at the first stage. Previously, most hospitals in the UK only used 70% alcohol in spray and wipe formats. Therefore, the requirement to implement this may impact on National Health Service (NHS) aseptic units holding specials licenses. The potential impact to costs, capacity, resources, and health and safety must be considered.

Since this is a requirement set by the UK’s regulatory body, I was interested to determine how the USA was managing the risks of microbial, and more specifically, spore entry into the cleanroom environment.

The regulatory environment in the USA

In the USA, hospitals involved in aseptic preparation are typically referred to as “IV compounding” rooms/units, and follow the guidelines set out within USP 797 (Pharmaceutical compounding – sterile preparations). Different states set out different requirements that hospitals must follow and adhere to. The Food and Drug Administration (FDA) is the national regulatory body in the USA, however hospital sites and audits are usually controlled by the relevant pharmacy board at state level. Prior to the New England Compounding Center disaster, hospital IV compounding sites were not required by states boards to follow USP 797 implicitly. However, the disaster called for major changes to practice. Hospitals partaking in IV compounding are now required to register for, and obtain a sterile compounding license.
Purpose & Aims of Fellowship

The purpose of the Fellowship was to visit industry sites conducting aseptic processing and hospital pharmacy IV compounding facilities conducting aseptic preparation in the USA. I wanted to learn:

1) How does the USA prevent microbial contamination in aseptically prepared/processed products?
2) How does the USA apply current regulations in this field and translate these into the hospital pharmacy setting?
3) What challenges does the USA face with preventing microbiological contamination control in aseptically processed products?
4) Does the USA use any automated technologies in the hospital pharmacy to prepare aseptic products?

The aim was to determine:

- If NHS aseptic units can learn from USA hospital IV compounding facilities
- If there are any different/novel approaches to the prevention of contamination incidents
Fellowship

Endotoxin & Bioburden Summit

I was lucky enough to be invited to attend the first endotoxin and bioburden summit at the biopharmaceutical company Amgen’s headquarters in Thousand Oaks, California. The summit was sponsored by Amgen’s Contamination Control Network and was run across two days. Firstly, I have to mention how amazing the campus is – it resembles a university campus! The summit was attended by personnel working within pharmaceutical microbiology (e.g. quality assurance, microbiologists, production leads) across Amgen’s global sites. It was a great experience meeting individuals from Dublin, Puerto Rico, Rhode Island and Thousand Oak sites whom are all experts in this field. I really enjoyed listening to the discussions by all those attendees and learnt a lot from it. In addition, Amgen’s value of being a science-based pharmaceutical company led by patient’s outcomes was visible throughout the conference. Although the summit was focused specifically on the biopharmaceutical industry, the principles of microbiological contamination control are applicable across pharmaceuticals and a number of ideas discussed would be useful to the hospital cleanroom setting. Further, I personally learnt a lot about biologics manufacture.

Specific issues focused upon at the summit were brought about by recent inspection challenges across the pharmaceutical industry in the USA. In particular, it was noted that regulators were focused upon bioburden and endotoxin control for incoming starting materials and the strategies to maintain this. The inconsistencies between products, suppliers, and the microbiological limits and acceptance criteria applied were noted. In addition, inspectors have focused upon standardisation of documentation across all areas and sites.

Additional difficulties discussed included applying bioburden limits to ready to use equipment, consumables, and sample test volumes. The setting of limits must be consistent across products/sites. It was interesting that not only were alert and action limits set, but also specific “reject” limits. That is, if microbiological results exceed in-house reject limits the batch is automatically rejected, and an investigation is undertaken. This allows for clear, defined criteria for batch rejection.

It was discussed that sampling strategies for each product have a “playbook” type document to define the rationale behind sampling and the methods used. Although this was defined for each product made by the company, this could be applicable to the hospital aseptic cleanroom. This would be an excellent idea for the microbiological monitoring strategies in the aseptic cleanroom, in order to define exactly which locations are sampled and the scientific reasoning behind this. The document
would provide a quick reference to enable staff to learn of the rationale behind each sampling point and location, and may also provide materials to be presented to an inspector during audit.

The use of statistics for microbiological monitoring trending and analysis was also highlighted as being crucial to their monitoring strategies. This is becoming increasingly important for setting action and alert limits in the UK aseptic cleanroom. Another interesting idea which was discussed at the summit was the implementation of a process map to determine exactly where microbiological samples are taken. This is rationalised to enable an understanding of what exactly the samples are testing for. The inspectors in particular in the USA have supposedly favoured this approach. Although this may not be applicable to aseptic preparation, this idea may be useful in hospitals undertaking sterile/non-sterile classical manufacturing production. Further, risk assessments should be included to determine if sampling poses a risk to sterility.

Another interesting point made was the microbiological limits applied to products/processes. It is often easy to simply look at limits and confirm that microbiological counts are within these limits; however it is important to understand when the process is leaning out of control. An idea is to set appropriate in-house control limits, to enable quality assurance personnel to be alerted to a potential change in the process. Unusual low level counts that are within set alert and action limits still indicate that something about the process is unusual.
On day two, the group was separated into five groups to undertake a workshop to define the location, volume and acceptance criteria for different samples taken throughout the manufacturing process. Again, although I was unfamiliar with the manufacturing procedures (though I ended up learning a lot!) the microbiological principles could be applied. I was placed into the group discussing sampling and testing of resins and membranes.

Key ideas presented included providing a justification for each sample taken (as aforementioned) and considering the bioburden and the potential for microbial proliferation over time. The initial bioburden of the equipment should be established by the vendor (if possible). Considerations must also include endotoxins, and the potential for their increase in concentration following filtration steps (ultra-filtration). The process capability for the clearance of endotoxins (and all micro-organisms) should be determined when microbial limits are being established.

A concept which I liked was the terms “out of place” and “in-place” to define the validation state of the process. If the process has been microbiologically validated, then no additional microbiological samples are required (other than the usual routine samples). If the process is different from the validated process, for example longer product hold times, then this is “out-of-place” and additional microbiological samples are required to prove the microbiological integrity of the process.
Contamination Control Network – Conference days

Following the endotoxin and bioburden summit, the contamination control network conference took place, again at Amgen Thousand Oaks. This was attended by personnel involved in microbiological monitoring across Amgen’s global sites, as well as those responsible for other contamination, e.g. pest control.

The need for risk based decision making was again highlighted as important when making decisions about microbiological monitoring strategies. I undertook the “Wellness to Walk” initiative around the campus, which sees employees log how many steps/laps they have undertaken, which lowers health insurance premiums. I was able to chat with the director of quality sciences and chief microbiologist for Amgen, whom held a wealth of international experience in pharmaceutical microbiology whilst completing the walk. I was interested to learn what the problematic micro-organisms for the biotech industry were, and those which are a recurring problem. *Bacillus spp.* were noted as one of the most problematic, amongst others (including viruses). Typical microbiological monitoring yields nothing out of the ordinary, with *Micrococcus luteus* and *Staphylococcus spp.* found. Interestingly, *Micrococcus luteus* is noted to be more “hardy” than *Staphylococcus spp.*

The next day focused upon Quality Risk Management strategies and their application to microbiological monitoring and contamination control strategies. A discussion was started about the use of “risk icons” within standard operation procedures (SOPs). This is used throughout the SOP to denote that a risk assessment has been carried out for this step in the SOP. The risk assessment is then referenced within the document. The use of HACCP (Hazard Analysis and Critical Control Points) was employed to determine microbiological environmental monitoring locations. This provides quality risk management as applied to monitoring strategies, and it is recommended that this is employed to all monitoring strategies in aseptic units. This would provide greater information about how a unit is performing environmentally and ensure all sampling locations are appropriate.
Hospital Pharmacy - IV Compounding

IV Compounding Sites visited

The hospitals I was lucky enough to visit included:-

- University of California San Francisco (UCSF) – Mission Bay Campus Hospital (San Francisco)
- University of California San Francisco (UCSF) – Mount Zion Campus Hospital (San Francisco)
- Stanford Healthcare (California)
- El Camino Hospital – Silicon Valley (California)
- Kaiser Permanente – Santa Clara (California)
- NYU Langone Medical Centre (New York)
- Winthrop University Hospital (New York)
- Veterans Association Boston (Boston)

Additional

I was also able to arrange a trip to the Parenteral Drug Association’s Global Education Headquarters (Washington DC), a national training centre dedicated to personnel working within IV processing/IV compounding.

Training

I was told that the California State board governing hospital pharmacy and IV compounding held the strictest standards when compared to other states so I was interested in making the comparison throughout my trip. On my first visit to UCSF’s Medical Center Mission Bay Campus, I met with their head of quality assurance/training/microbiology. I was shown their induction programme for all new staff entering the aseptic cleanroom environment. The programme included a pre-questionnaire for new starters to determine their prior experience and knowledge, to enable the trainer to determine how to pitch the induction. The induction lasts one week, and the new employee is shown videos on aseptic technique, the cleanroom, and gowning, dependent on experience. After a few days of lectures and tours, the trainee is then given an exam to sit to enable the trainer to ascertain their knowledge. If a pass is achieved, the employee can progress to the next stage of the induction. If they fail they complete more training. Following this, the new employees receive on-the-bench practical training for aseptic manipulations and are able to make a number of products which are compounded.
in the IV room. They also gown up with the trainer so that they can be taught the ideal way to gown whilst minimising outer contamination. This is a great training technique, as it combines both theoretical and practical training and allows the new employee the chance to practice their technique prior to entering the cleanroom. The exam also allows the trainer to assess how much information the new employee has taken in, and if they are ready to be placed into the cleanroom. This would be an excellent tool to implement into hospitals in the UK, if not already doing so. Although a dedicated “trainer” is required, the benefits can be observed in hospitals in the USA when the new employee quickly adapts to the IV room. Whilst speaking with operators in IV compounding cleanrooms, all have an excellent understanding of the reasons why they must adopt such behaviours in the cleanroom, and the impact this will have on the product. In the UK, at my host trust I have observed that often the theoretical understanding behind cleanroom behaviours and carrying out specific tasks is lacking, and changes are often made against procedures due to a lack of understanding.

In addition, an online in house training tool has been set up to enable competency assessment and re-assessment. Each employee has their own login and must pass all online activities and quizzes. Annually, staff are required to re-take activities and quizzes specific to their role. The trainer is then able to logon and determine pass rates and who requires re-training/due for re-assessment. This allows management greater control and oversight of training programmes, and determination of which staff members are competent for which tasks. The trainer stated that this has saved a lot of time and paperwork, and is a more efficient system than previously employed paper based systems.

At the hospitals visited on the East Coast, electronic training programmes were also employed to manage operator competency assessments. A tool called “Simplifi 797®” was used to compile all required operator competencies and monitor progress. Winthrop hospital was kind enough to share all the competencies which are uploaded onto the Simplifi system. The electronic database allows selection of whether each task is in progress, complete, or incomplete. Notes can be added to highlight areas of strength/weakness as appropriate. Each area for competence is separated into different chapters, e.g. cleaning and disinfection; material handling, gowning. The competencies test theoretical knowledge in addition to practically being able to carry out the tasks. This is tested through observations, questioning and written tests. Training is also cited by the MHRA as a major deficiency observed during MHRA inspections of pharmaceutical manufacturing units. The use of an electronic training tool would provide additional evidence to present to an auditor, and ensure training records are complete and up to date.

In addition to assisting with training, the Simplifi 797® is used for alerting personnel to the need for cleaning and additional ancillary tasks including recording environmental monitoring results (pressure
differentials, temperatures etc). As well as providing an alert to operators so that the task is not missed, the system also permits contemporaneous recording of when the task was undertaken and by whom. This allows for electronic recording and the creation of an electronic audit trail for all activities undertaken. If a task is not undertaken within the allotted time-frame, the system administrators are alerted, enabling timely rectification and investigation into why the task has not been completed. This would be an excellent system to adopt in the UK and would allow compliance to regulatory requirements for data integrity, in addition to ensuring no data entries are missed. Initial validations and costings to run this system would potentially be a barrier to implementation in the U.K.

**Robotic technology**

UCSF has a RIVA (Robotic IV Automation) robot which compounds IV medication automatically in a closed system and monitored environment. The system utilises a bar coding and photography system to enable all items to be tracked and recorded, as well as multiple weight, height, size and product barcode checks. Each dose is labelled inside the system and the software provides a complete electronic audit trail of the entire compounding process. The system maintains an ISO Class 5 (Grade A) environment during all compounding operations and is compliant with USP 797. All items are sprayed with 70% alcohol into the hatch of the robot and continuous particulate monitoring is performed. If the particle counts exceed limits during production, then the robot automatically stops until a senior member of staff can investigate. The robot is currently used for batch manufacture, and the batch is rejected if the robot stops. In addition, all bags are UV irradiated to provide further sterility assurance. All bags are labelled within the robot. Interestingly, the arm of the robot was actually donated by NASA as it was used for building space shuttles in the past. Currently the RIVA is used only for compounding of non-hazardous drugs. In addition, UCSF is attempting to validate a rapid microbiological monitoring technique, in which CO₂ levels are detected and calculated as an indicator of microbial growth.

I would love to recommend the implementation of the RIVA to UK hospital pharmacy; however I’m not sure that the initial finance costs could be met! The benefits of using this automatic technology were stated by managers in the USA to be efficient pharmaceutical processing, and a greater number of batches that can be processed in a set time compared to manual processing. Use of automated technologies in the UK would also allow for robust audit trails and would address current data integrity issues. Validation of such equipment would prove extremely time consuming and potentially costly, so the benefits of an increased number of batches made compared with these initial costs and the overheads of maintaining the equipment would have to be appropriately costed out. In addition,
the clinical demand for products would have to be established in the U.K, and regional procurement of a robot would be perhaps more realistic. Since NHS England have stated that they wish 90% of chemotherapeutic agents to be dose-banded, perhaps an IV compounding robot is not such an abstract idea for the NHS.

**Microbiological testing**

At Kaiser Permanente, I was able to observe operator microbiological testing – or “operator validation”. The test ascertains if the operator is able to perform manipulations using strict aseptic techniques. The “broth” test was similar to that used in the UK; however finger dab samples are not taken on agar plates. Instead they use finger dab “paddles” which the operator grips whilst the testing operator holds the handle. The paddle is then placed into the protective case to prevent further contamination. Supervision by the testing operator is required, which enables confirmation that the operator being tested is not disinfecting their hands prior to undertaking the test. This method protects the sampler from damage and accidental contamination, and therefore may be suggested to allow for more valid operator microbiological results than is currently achieved by the agar plate method in the UK.

Although microbiological monitoring (environmental and operator) is not undertaken as frequently as is the case in the UK, product shelf-lives are a lot shorter and manufactured products are considered simpler to prepare. For example, operator monitoring (finger dabs) are undertaken annually, comparative to the sessional testing in aseptic units of the UK. The preparation of parenteral nutrition (PN) is considered a very “high risk” activity, and so many units choose to outsource this activity. As defined within USP 797, different shelf lives must be assigned to different products based on their risk classification. During my visit, only 1 hospital manufactured PN in house – and an automated compounder was used to do so.

Automatic handwashing machines were also used in one hospital IV compounding site, in which a standardised amount of sporicidal handwash is dispensed to the operator and hot water is cycled for a set amount of time. This means that handwashing is undertaken in a process controlled manner, ensuring all operators use the same amount of disinfectant to hands. The barrier to implementing this system in NHS hospitals in the U.K will be financial. However a scientific approach would suggest that ensuring all operators are disinfecting hands for a standardised time could eliminate operator variability, and potentially improve microbiological results in the cleanroom.
Paperless systems

Perhaps one of the most interesting observations during my time visiting hospital IV compounding units was the lack of paper that entered the cleanrooms. In the UK, batch manufacturing records/worksheets are transferred into the unit (usually within plastic wallets which are surface sanitised) detailing the product to be made, manufacturing instructions, reconciliation etc. In the USA, I observed that only the product label is transferred into the cleanroom, and attached to the outside of the laminar flow cabinet/isolator. This limits the amount of paper which is transferred into the clean working environment, and subsequently decreases the likelihood of microbes that are of paper/cardboard sources being transferred. It is well established that the transfer of items into isolators/laminar flow cabinets also confers a high risk of transferring microbes on these items.

The clinical pharmacist will prescribe the required drug, which is verified electronically by a second pharmacist to ensure clinical acceptability. Once accepted, a product label including patient details and product information is printed by pharmacy, which serves as the product worksheet. This is not only better for the environment (!) but also decreases the need for paper transfer. Interestingly, one hospital was using low bioburden reduced particulate (non-rip) labels. This further reduces the potential for microbial bioburden on labels, and also prevents particulates generated in the cleanroom from labels ripping.

In addition, the use of barcoding systems offers an electronic means for traceability of aseptically prepared products at all stages in the process. Once the label is generated by the clinical pharmacy team and sent to the IV compounding room, this is given a unique barcode identifier. Scanning this barcode at multiple steps in the process allows for nurses and other medical staff the opportunity to ascertain when the product will be ready to be sent to the ward for use. This was observed to be a very efficient and streamlined service, mitigating the need for constant communication between clinical and pharmacy teams regarding the status of manufactured products. In a number of hospitals, the barcoding system has been extended to raw materials. Prior to manufacture of a product, the product label and each raw material is scanned into the electronic system. If the wrong raw material is selected, for example wrong diluent, strength or inappropriate expiry, the electronic system will “alarm” and will not allow the operator to proceed. The system also records the operator whom has manufactured the product and acts as an in process check. This is an excellent system to reduce errors during aseptic preparation, and also enables audit trail functionality and fulfils data integrity requirements (another hot topic with the MHRA!).
The use of labels as an alternative to worksheets for product manufacture is both an excellent system to reduce the likelihood of microbial ingress into the cleanroom and also allows for product traceability, and informing all medical professionals involved in the care of the patient the status of an aseptically prepared product. However, it is difficult to establish the exact microbiological implications in the USA, due to different environmental monitoring strategies than those employed in the U.K. For example in the U.K. we may continuously monitor our critical Grade A work zone for microbiological contamination, whereas in the USA there is only a requirement for quarterly monitoring. After discussing quarterly results obtained in the USA with senior managers, and viewing a number of results, no worse results were seemingly obtained than those in the U.K. The barriers to implementing a paperless system in the UK would be an entire change in pharmacy practice, however it is suggested that a reduction in paper entering the cleanroom should be investigated.

The Parenteral Drug Association Global Headquarters

The parenteral drug association (PDA) Education Headquarters in Washington DC is a training site which offers lectures and practical training on all aspects of parenteral drug preparation. It houses its own cleanroom used for practical demonstrations, including monitoring equipment. In addition, there is an autoclave, vial manufacturing room, HEPA filters, isolators, and microbiological identification equipment. The training sessions are mainly attended by industry professionals working in aseptic processing, but a few attendees work in hospital IV compounding also.

I was offered a tour of the education facility and the chance to look around all the cleanrooms. There is a microbiology lab which is used to allow students to partake in microbiological techniques including sample preparation and incubation. The need for appropriate sample handling following exposure was discussed, which is specifically focused upon during operator training. From observations of staff training in aseptic services (UK), this training is deficient. Correctly packaging microbiological samples is a critical step in the monitoring process, as non-compliance to procedures can lead to contamination of samples and the potential for invalid/false results. Plates should be turned upside down to avoid condensation and secured appropriately. Aseptic technique is crucial.

I was also lucky enough to get the opportunity to have a “play around” with the equipment involved in the qualification of cleanrooms – including air samplers, smoke visualisation techniques. There are a number of different equipment types on the market, and the importance of correct use and selection of each was stressed.
Conclusions

Aseptic processing/preparation is a high risk pharmaceutical activity due to the intended route of administration of manufactured products, and the often immunocompromised status of patients receiving parenteral therapy. Previous contamination incidents of aseptically prepared products in both the UK and USA highlight how disastrous contamination incidents can be to patients. In the USA, the fungal contamination of steroid epidural injections in 2012 resulted in major changes to pharmaceutical practice nationally, both to industry and hospital IV compounding. In the UK, contamination of parenteral nutrition (feeding bags) for babies with Bacillus cereus in 2014 also led to review of aseptic preparation practices and preventing micro-organism into the cleanroom.

Although the principles of pharmaceutical microbiology are the same globally, the application of monitoring strategies and regulatory requirements are not. In the USA, there are vast differences in the requirements for microbiological monitoring strategies, and a different regulatory structure. Visits to hospital IV compounding sites across different states have enabled an appreciation of the requirements of different state boards in the US, and how different these can be.

Similarities between the UK and USA were observed, including stricter requirements for the use of sporicides in the IV compounding room (USP 800 coming into force July 2018), the requirements for no cardboard in the cleanroom, and strict requirements for disinfectant contact times and validation of microbiological efficacy. The increasing emphasis on pharmaceutical microbiology practices in the USA is also highlighted by the fact that the FDA are reportedly training recently qualified microbiologists to perform cGMP inspections.

I observed that the training of staff is a major element of microbiological contamination control in the USA. Training programmes in hospital pharmacies appear more advanced and technology based in the USA, compared to those I have observed in the UK. The theoretical knowledge of the operator in basic pharmaceutical microbiology is a critical aspect to contamination control.

In addition, compounding technologies in a number of hospitals are very much more advanced, and provide greater process control and additional barriers to micro-organism entry. The lack of paper in the cleanrooms in the USA is also suggested to reduce the likelihood of micro-organism (specifically spores) entry in the manufacturing environment.
Recommendations

1. Greater focus on the **training** of aseptic services personnel and implementation of more robust training programmes defining aseptic technique, pharmaceutical microbiology etc.
   a. Decrease the reliance on methods such as the “spray and wipe” transfer technique and equipment
   b. Creation of training programmes incorporating electronic elements – allow personnel the opportunity to complete competency based-assessments at their own pace – availability of information in one place
   c. Induction training incorporating both theoretical and practical elements – “on-the-bench” training of material transfer techniques, aseptic manipulations and gowning, Prior knowledge of aseptic services/aseptic technique assessed via survey
   d. Competency to be re-assessed by theoretical knowledge/understanding electronically

2. Implementation of a “play-book” type document in order to define the scientific reasoning behind microbiological monitoring environmental samples and strategies
   a. Provide a rationale based on risk for each microbiological sample
   b. Greater understanding of what sampling is aiming to tell you
   c. Provides work to be presented during inspection/audit

3. Greater application of quality risk management strategies to microbiological monitoring
   a. Risk analysis for samples (documented e.g. HACCP)
   b. Process map where samples for microbiological analysis are to be taken to enable an understanding of what each sample is aiming to tell you (more appropriate perhaps for sterile/non-sterile manufacture)

4. Look at ways to reduce the amount of paper entering the critical work zone and cleanroom
   a. Decrease the risks of organisms with a known source of paper/cardboard entering the cleanroom e.g. *Bacillus spp.*

5. Importance of correct sampling and packaging of sampling methods
   a. Improve training techniques in this area
   b. Include in operator competency assessments/re-assessments
Future

So far, I have presented my Fellowship and findings at the Manchester Academy of Healthcare Science Education (MAHSE) research day (June 2017) to healthcare scientists across the country. The findings and recommendations were well received.

I will share this report and findings with the other Clinical Pharmaceutical Scientist trainees working in this field at multiple hospitals in the UK, as well as senior pharmacy staff in my host technical pharmacy trust. I am planning to discuss ways to implement my findings, particularly improving training programmes within aseptic services.

Following completion of my training programme, I am hoping to pursue a role within pharmaceutical microbiology, in order to begin implementing my recommendations.
References


