Good Aseptic Manufacturing and New Technologies

Advancements in manufacturing environment and personnel training

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Aseptic manufacturing of medicinal products has evolved rapidly over the last number of years, as a result of the development of numerous new applications and technologies. All of this is with the purpose of increasing the assurance of a safe medicinal product to reduce the risk to patients. Some examples of this development are the high-levels of automation and use of isolator technology, reducing the need for operator interventions, the use of automated systems to enhance repeatability and reliability of processes, real-time monitoring of processes or the environment to allow for direct data processing and interpretation, and the use of Virtual Reality (VR) for operator training purposes. To keep up with these technological advancements, regulations must also be updated or adapted to provide adequate guidance to manufacturers of new technologies and producers of pharmaceutical products and outline regulatory expectations when using novel technologies. One prime example of this was the publication of EudraLex Volume 4, Annex 1 "Manufacture of Sterile Medicinal products" [1] in Aug 2022.

Despite all of the technology developments, one cannot omit the human factor in designing, programming and operating these technological marvels. This article will go through some of the key topics that were presented during the Parenteral Drug Association (PDA) event in Leipzig about Good Aseptic Manufacturing.

On 23 and 24 May 2023, the Parenteral Drug Association (PDA) held its Annual Conference in Leipzig. The topic for discussion was Good Aseptic Manufacturing. With a fully packed program addressing different topics that relate to Good Aseptic Manufacturing, it promised to be a great opportunity to share efficient and sustainable solutions in implementing the requirements of EU GMP Annex 1.

Various experts from the industry, along with (ex) EU and FDA regulators shared their knowledge and insights on developments within the arena of Aseptic Manufacturing. These presentations culminated with interactive questionnaire sessions, where participants had the opportunity to ask the panel of experts about the topics on which they presented. The conference also provided the opportunity to speak to the various vendors, seeing and hearing about industrial advancements in new methods, innovative tools, and developments in emerging technologies and equipment. Above all, it gave the attendees the opportunity to share their interpretation, challenges, and possible solutions for the compliant implementation of the new revision of Annex 1 with their peers from industry. The event was deemed a success based on the high level of interaction and engagement with the presenters and the number of questions asked during the interactive questionnaire sessions. The

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following are the key takeaways from the event.

EU GMP Annex 1

The published Annex 1 proved to be a high point of discussion during the 2-day conference. Following the publication of the final version of Annex 1, companies needed to be compliant with the requirements no later than 25 Aug 2023 – which was less than a 100 days away from the date of the conference.

It was surprising to hear from the responses shared at the conference that there are still organisations who are at the early phases of preparing a gap assessment and have not started implementing remediation actions to ensure compliance at the end of Aug 2023. For these companies, it will be difficult to implement all the requirements within the expected timeframe. Knowing that the clock is ticking, and implementation is imminent, companies are urged to identify the gaps and create a realistic remediation plan with tangible actions.

The interactive questionnaire session revealed that 56 % of the participants indicated that the main source for the information needed to comply with the EU GMP Annex 1 came from the company's own subject matter experts. Another question referred to the top-3 Annex 1 topics that companies still found to be subject to interpretation, and where they felt further clarification from regulatory authorities would be helpful. Top of the list was Pre-Use Post Sterilisation Testing (PUPSIT), followed by Contamination Control Strategy (CCS) and First Air Principles.

Current and former regulators present all re-emphasised the importance of using the principles of Quality Risk Management (QRM) correctly, as it enables organisations to understand their products' characteristics and the processes to manufacture these products, along with the facilities and utilities that support the manufacture of same.

It was highlighted that QRM is not to "risk-out" good practices or Annex 1 expectations such as PUPSIT, nor to justify bad practices or to justify a predetermined outcome.

A solid Risk Assessment facilitates to prioritise and action the identified risks.

New Technologies

The EU GMP Annex 1 repeatedly emphasises the need for companies to consider the use of appropriate technologies, such as Restricted Access Barrier Systems (RABS), isolators and robotic systems to increase the protection of the product from potential extraneous sources of contamination. It also reiterates the use of rapid and alternative methods to assist in the detection of potential contaminants in the environment and product.

Within the pharmaceutical world of sterile manufacturing, this is not new and expressing these expectations in the Annex 1 should not come as a surprise. In 2004, the FDA published its final report "Pharmaceutical CGMPs for the 21st century – a Risk-Based Approach" [2] where it lays out the basis for science-based policies and standards to facilitate innovation. The guidance document recommends building quality into products through science-based facility, equipment, process, and system design, ensuring robust product protection.

Much of the PDA's conference agenda covered topics regarding developments in new technologies, equipment, and utilities, in addition to the use of new methods and innovative tools.

In 2018, approximately 50 % of the aseptic filling lines in the EU and US were of conventional design, meaning a Grade A filling enclosure with a Grade B background that was manually disinfected and open-door interventions, where the operator physically had to engage with the critical Grade A environment. Since then, an increase has been seen where companies upgraded their existing equipment, availing of RABS or isolator technology.

From the interactive questionnaire session, 31 % of the respondents indicated that their organisation planned to implement isolator technology in the next 5 years, with 20 % specifying this would be within the next year.

Robotics

Over 25 years ago, in 1997, the first robotic assisted surgery took place, and the FDA approved the Da Vinci system for general robotic surgery in 2000. Gloveless robotic systems within aseptic filling also emerged as a more frequently seen technology. Options are available for open-isolator settings where automated systems or robots reduce the need for glove handling by automation of certain process aspects like automated line start-up and line clearance at batch end, automated in-process weight checks and completion of environmental monitoring, to name a few. The pinnacle is a design where robot technology fully replaces the need for operator intervention in a closed isolator setting.

The latter comes with the big advantage that human interaction is completely removed from the process but, regardless of the extend of automation and technological capabilities, it comes with some challenges as well.

Firstly, the design of robotics and their movements. Annex 1 emphasises that Grade A conditions should be ensured with first air protection, preventing obstruction of the path of the unidirectional airflow. This principle also applies to an automated process. Replacing old concepts with robots could even worsen the practices of aseptic assurance. Correct design and adaptation of the robot's movement to prevent moving parts

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above the critical process are important to protect first air. Maintenance of unidirectional airflow must be demonstrated and qualified across the whole of the Grade A area by air visualisation studies. The use of Computational Fluid Dynamics (CFD) studies is a helpful technology in the design of robot systems and to visualise the impact such a system has on the airflow within the isolator before physically designing the robot.

Secondly, any automated system or robot will only perform as well as it has been instructed to do. Process understanding and how the system is programmed to perform activities in the correct sequence at the exact right time can be time consuming, with a lot of trial and error before getting it right.

Thirdly, the design must allow for full decontamination in the isolator and prevent the risk of any surface exposure during operations that may not have been decontaminated.

Such concepts can work and are accepted by regulators when implemented in the correct way. This was demonstrated by examples presented, such as semi-automated filling of Advanced Therapy Medicinal Products (ATMPs), and gloves filling of drug product, including automatic installation of the filling path.

This indicates that the opportunities are endless with much more to be expected as technology evolves.

Real-time Microbial and Particle Detection

Having robotics performing environmental monitoring within an isolator is one aspect, but it still requires a number of days of incubation before the final results are obtained. The same applies for sampling and testing of utilities, mycoplasma testing of biological products and sterility testing of the final drug product; these all require incubation of samples to detect microbial contamination.

European legislation has already highlighted its expectation to use modern technologies. Article 23 of EU Directive 2001/83 [3] states: *"After an authorization has been issued, the authorization holder must [...], take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. This has now been further emphasized in Section 9.28 of Annex 1 where it is described, 'that suitable alternative monitoring systems such as rapid methods should be considered to expedite the detection of microbiological contamination issues'".*

Rapid microbiological detection systems can be an option to consider to reduce the time to results, with different technologies available that end users can choose from. Applications utilising ATP-bioluminescence, measuring changes in metabolic activities, such as pH and CO_2 changes, Polymerase Chain Reactions and DNA sequencing are examples of the gamut of technologies available. Their suitability depends on what one wants to achieve, with some critical points to consider:

- Time to result
- Sample preparation and overall complexity
- Limit of detection
- Presentation of results, Colony Forming Units (CFU) or units
- Destructive or non-destructive
- Known and accepted technology
- Commercially available and support
- Reference standards available
- Test capacity
- Validation
- Comparability to the compendial method
- Cost of equipment and tests

Presentations were given where real-time monitoring of air quality within an isolator was applied in support of conventional air sampling using biofluorescent particle counting. The equipment used was capable of generating results for total-particulate counts and viable particulate counts based on the measurement of fluorescence signals emitted by viable particles. The benefits described were that results are presented in real-time, which allows for a direct reaction to an alarm. As no media is used, there is also no requirement for changing samples thus preventing necessary interventions.

Annex 1 presents the maximum permitted microbial contamination levels in Colony Forming Units (CFU) and expects the manufacturer to scientifically justify the limits applied and, where possible, correlate these to CFU. Challenges presented themselves with the real-time air sampler as results were reported in Auto-Fluorescent Units (AFU) and not in CFU. Study results from the presentation given showed that AFU counts were significantly higher than CFU counts. Besides false positives from interfering factors, the higher levels of AFU were explained by the fact that all living microbes emit intrinsic fluorescence. However, this does not mean that these microbes are culturable as they could be damaged, dormant or stressed. Furthermore, the broad limitations of the traditional environmental monitoring media like Tryptic Soy Agar (TSA) and sampling methods may hinder the microbes cultivability.

As the Annex 1 encourages the use of Rapid Microbial Methods (RMMs) and science is evolving with technologies emerging that detect the presence of microorganisms differently than the traditional cultivation methods, there is a clear requirement from all parties involved – end users, manufacturers, and regulatory bodies – to stay informed about developments in the world of RMMs. In an open dialogue, all involved can educate each other about the benefits RMMs can bring, but also appreciated the limitations and an understanding of the differences compared to the traditional methods. This will help adjust expectations and clarify the requirements for both the industry and regulatory agencies when

considering the implementation of an RMM.

The Human Factor

Despite promising new technologies that are already available and more to come in the future to help the manufacture of sterile medicinal products, the human factor remains one of the most important elements in the success or failure in the manufacturing of quality products.

A solid training and qualification program for both new and existing personnel is one of the cornerstones for achieving compliance and product safety. Many of the training programs we see across the industry are focusing on the need to comply and demonstrate compliance to, and with, relevant procedures and regulations. Focusing on the compliance element alone brings the risk that personnel are merely following the procedure, demonstrating the "how" and "what" to do, but do not understand the "why". Embedding scientific thinking in a training and qualification program stimulates the trainee to think about the why element, as it provides the reasons for executing manufacturing steps in a certain way – why a specific temperature must be maintained or the importance of wearing cleanroom clothing of the right size, to name a few examples. It allows personnel to understand the scientific reasons behind procedures and what the impact could be in the case of deviations. It motivates personnel to challenge the status quo and, therewith, achieve continuous improvement.

Equipment Design and Commissioning

Early involvement of operating personnel, along with the team of engineers, in designing and testing of a new filling line can potentially prevent many issues and setbacks. What might look good on paper, meeting all technical specifications, is not a guarantee that the end users can work with what was designed and agreed upon. Once a line is built, making fundamental changes is very difficult, or even impossible, and from that point onward, operators have to live with what is available. This can lead to sub-optimal situations that pose a risk to the process – for example, when gloves on the isolator are positioned incorrectly making it hard to reach all areas. It can potentially result in non-compliance situations, when environmental sample locations for total particulate and viable particulates are randomly selected, and not based on the actual process risks and principles of Quality Risk Management, leading to regulatory observations.

When end users and other personnel with specific technical and regulatory expertise, such as microbiologists, are involved from the beginning and having their input taken seriously, it can prevent longer term issues. It also promotes ownership and allows for early development of sound procedures based on gained experience and not on theory.

Augmented and Virtual Reality

Besides emerging manufacturing technologies as described previously, new applications in delivering training programs are also surfacing. Augmented Reality (AR) is one of these. It guides the operator through a step-by-step workflow, where the person is learning by doing the actual tasks. Rather than just reading and following a procedure, the new trainee actually operates a virtualised machine, where the trainer can follow the activities via a computer screen and give direct feedback.

With Virtual Reality (VR), situations can be created where the trainee is asked to perform specific tasks, e.g. transfer of materials within an isolator from Grade A to B. The training software allows for a realistic presentation of the impact the operator has on the environment and direct feedback is given. The benefits of both AR and VR are that the training is done in a safe environment, where there is no risk to the actual cleanroom, equipment or product, and the trainee can build confidence and competence before participating in a real qualification.

These digital innovations can be tailored to a company's unique processes or equipment, giving a realistic picture of the actual situations that the person is going to face. This approach not only covers the "how and what" aspect, but also the "why", as it instantly shows the impact if something goes wrong.

Applications were seen where video technology was used in support of risk profiling of ATMP manufacturing, where the entire process was dissected into small individual tasks. These microtasks were analysed further, identifying what could go wrong in these individual steps. Subsequently, work instructions were written with emphasis on these risks, while providing clear instructions on how to perform the task and what to avoid. It then also helped in the development of the training module, where the video recordings demonstrated the correct ways of working and areas of risk.

Conclusion

As per Annex 1, organisations are expected to have their facilities, equipment and processes appropriately designed to increase the protection of the product from potential extraneous resources of contamination. Considerations for the use of new technologies must be made to facilitate reducing the contamination risk or increase the detectability if such contamination should occur. There are already many options available – all with their benefits, challenges and limitations that must be considered and understood before availing of such technology.

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Whether it is at the design and implementation phase of new equipment, or routine operation of a well-established process, the human factor still remains and must not be overlooked. A robust training program is paramount to provide personnel with the right level of qualifications and experience for the manufacture of a safety quality product. A well-designed program promotes scientific thinking and provides personnel the "why" behind processes and procedures.

Technological advancements are seen in both the manufacturing environment and personnel training and are expected to be considered with the purpose to improve product quality and, ultimately, patient safety.

REFERENCES

[1] EudraLex Volume 4 Good Manufacturing (GMP) Guidelines – Annex 1, Manufacture of Sterile Medicinal products (2022). *https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf*

[2] Department of Health and Human Services U.S Food and Drug Administration – Pharmaceutical CGMPs for the 21st Century – a Risk Based Approach, Final Report. *https://www.fda.gov/media/77391/download*

[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use (2001). *https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf*

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