Roundtable Session 2 - Table 20: Navigating the Complexities of EU EMA Annex 1: Overcoming Challenges in Sterile Pharmaceutical Manufacturing

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Abstract:

The implementation of the revised EU EMA Annex 1 has introduced new expectations. This regulation, brought forth a myriad of challenges that companies must adeptly navigate to maintain compliance.

- Risk-Based Approach: places a stronger emphasis on a risk-based quality management system. Companies are expected to identify, evaluate, and control risks throughout the manufacturing process to ensure sterility.
- Contamination Control Strategy (CCS): A comprehensive contamination control strategy is now required. This strategy must be holistically designed and implemented, encompassing all aspects of manufacturing, environmental monitoring, and personnel practices.
- Environmental and Process Monitoring: There are more detailed requirements for environmental and process monitoring to provide ongoing assurance of the operational conditions and manufacturing process control.
- Aseptic Process Simulation (Media Fills): includes more detailed guidance on the design, frequency, and evaluation of media fill trials to simulate aseptic operations and validate aseptic process control.
- Personnel Qualifications and Cleanroom Behaviors: Enhanced requirements for personnel training, gowning, and behavior in clean areas to minimize contamination risks, including more stringent gowning qualification and monitoring.
- Utilities: increased expectations for the design, maintenance, and monitoring of utilities such as water, air, and gases that come into contact with sterile products or product contact surfaces.
- Single-Use Systems: provides guidance on the use of single-use systems, which have become more prevalent in sterile manufacturing, addressing their validation and the risks associated with their use.
- Quality Control: emphasizes the role of quality control throughout the manufacturing process, including the need for robust methods and systems to detect contamination.
- Premises: more detailed guidance on the design and maintenance of premises to prevent contamination, including the flow of materials and personnel.

This discussion will be an interactive dialogue, encouraging participants to share their experiences and learn from the collective insights of industry peers. We will discuss the implications of these challenges on the global pharmaceutical landscape, including the potential impact on international markets and supply chains. The session aims to foster a collaborative environment where professionals can discuss the nuances of regulatory inspections and the evolving expectations of Health Authorities.

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Discussion Questions:

These questions are designed to prompt detailed discussions, facilitate the sharing of the best practices, and help identify areas where further guidance or clarification from regulatory bodies might be necessary. The goal is to collaboratively address the challenges of implementing the revised EU EMA Annex 1 and to ensure a smooth transition to the new requirements while maintaining the highest level of sterility assurance.

1. How are companies addressing PUPSIT?
2. How have QRM principles been accepted throughout the guidance? Has appropriate level of leeway been given when an alternative or existing condition is utilized?
3. How are companies applying Annex 1 to low bioburden drug substance manufacturing?
4. How are companies assessing Annex 1 compliance readiness for CMOs?
5. How have you integrated the risk-based approach mandated by Annex 1 into your existing quality management system?
6. What strategies have you employed to develop and maintain a robust Contamination Control Strategy (CCS)?
7. What challenges have you faced with the enhanced environmental and process monitoring guidelines, and how have you addressed them?
8. Can you share your experiences with the design and execution of media fill trials under the new guidance?
9. How have you adapted your training programs to ensure personnel are compliant with the heightened cleanroom behaviors and gowning procedures?
10. What modifications have you made to your facility design to meet the revised premises guidelines?
11. How are you validating and controlling the risks associated with single-use systems as per the updated Annex 1?
12. What steps have you taken to enhance your utilities to ensure they meet the revised quality and monitoring expectations?
13. In what ways has your approach to sterilization processed changed with the updated Annex 1 requirements?
14. What impact has the revised Annex 1 had on your quality control and batch release processes?

Notes:

- The discussion table comprised of members across CMO, Biologics manufacturing, Regulatory CMC, Policy etc.
- There were general discussions regarding the impression that the revised Annex 1 Implementation has on the overall Industry. The table members were interested in understanding the application of the revised EU Annex 1 and its impact and potential resulting modifications that may be required.

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- CMO understanding risk-based classifications of changes was explored to define implementation within the Quality Management System.
- There have been cases sighted where FDA CBER requested Annex 1 requirements during Inspections; this was called out to knowledge share across Industry. To keep in mind the FDA participated in the drafting of the revised Annex 1 and so will be inspecting with the Annex in mind.
- Manufacturers can expect some key elements of the Annex 1 implementation to be subject to great critiquing, particularly on the risk assessments conducted to determine the specific Annex implementation action plan (with most focus on the CCS).
- Discussions on how to implement the Swissmedic interpretation of the Annex 1 Requirements as few experiences during inspections have shown that the interpretations are different from EMA. Industry must be mindful of this and ensure they use any opportunity to clarify as required.
- There have been insights that few companies are not in agreement with few requirements within the Swissmedic questions posed; so there have been side talks that Swissmedic may retract the requirements for modification due to possible misinterpretation.
- The EU Annex 1 have been referred to by EMA as the CMC GMP document.
- An example was referenced by which sterile intrinsic connectors used by companies for many years have been classified as Grade C and D; whereas the revised Annex 1 now denotes these sterile connectors as the Grade A and B state. Therefore, clarity is required on how to apply the Annex overall as the rationale for the assignment was not clear nor convincing for the respective company. There is a fear of setting precedence if this is accepted (therefore, a push back was attempted; awaiting feedback to date). With regards to preventative maintenance, validation data and reports have supported the use of Grade C and D state for many years as per the companies discretion based on the GMP Guidelines (which doesn't explicitly state). However, now the revised Annex 1 Requirements now explicitly mandates the use of Grade A and B state for the sterile intrinsic connectors.
- Another point to note is that the Annex 1 requirements is not considering this system as a closed system, therefore Grade A and B state is mandated as required.
- The discussion table points are that if Industry would be able to prove the system is a closed system then it may prove successful to maintain Grade C and D despite Annex 1; however, for now the Inspectors will continue to request Grade A state.
- Recommendation is to connect with EMA alongside Advocacy Groups through Trade Associations, attending sessions such as CASSS, and any other forums that allows cross company sharing and even compose Publications may aid to support.
- The questions arose regarding pushing back on the revised Annex 1 Requirements in the Clinical Trial Space, are there any experiences? It was suggested that as the clinical space may be less stringent than the commercial space the requirements may not be as firmly applied. Recommendation to conduct Integrity Tests at the sites and provide any corresponding COAs as Annex 1 may not be heavily required here. This is yet to be confirmed.
- Assumption was that possibly CMOs may not struggle as much to implement the Annex 1 Requirements for the Clinical space as it is more flexible. The Commercial space is more rigid and complex (e.g. Time for transfer, comparability studies, etc.). Hence, the question was raised,

what is your use of the risk-based approach associated? Answer shared: The risk to public health is lower, hence less risk associated. Patient safety is the same across the board so there. Process development with quality discussions.

- Regarding the integration of the risk-based approach mandated by Annex 1 within Companies Quality Management System, it was shared that some companies have already modified trainings, processes, etc. to accommodate Annex 1 Implementation within the QRMs. Companies have also conducted comparison and gap assessment of their PQS and adapted accordingly.
- There are some indifferences sighted regarding PUPSIT introducing more risk. That it adds complexity to pursue more tests that may not be valid. It was said that several companies says it introduces more risks and are not intrigued to pursue PUPSIT. Therefore, Industry has been discussing and reviewing PUPSIT for many years.
- However, companies have been relying on years of data to prove there are no issue at all or situations of concern. Having a contingency plan on hand is always recommended.
- Larger Pharmaceutical companies are currently assessing and have progressed greatly as they possess many years of operational experience with global requirements, CAPAs in audits, new technologies and yearly survey data collected and used to determine push back approaches and responses to findings and citing from Annex 1.
- Training is being conducted to ensure the Annex 1 Requirements are implemented, as there are a lot of specifics around this (such as gowning, socks, etc.), also on the job learnings acquired during site inspections.
- Regarding modifications made to the facility to meet revised premises guidelines the table had no experience to share any sighted out of conformance observations seen.
- Likewise, regarding the impact of Annex 1 implementation on the companies' quality control and batch release processes, no real observations were sighted as well.
- Qualified Person (QP) reads the risk assessments and be adequately trained. It is recommended to include them in the conversations early enough to be comfortable with the adaptations.
- Further to this RoW countries will be affected as PIC/s aim towards global harmonization. Expectations to hear what other PICs members are going through and saying and to collect the observations for the further future outcomes.