Roundtable Session 2 – Table 4 – Managing Contamination Risks in Cell-Based Products

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Abstract:

Ensuring viral and microbiological safety remains a challenge in the development and manufacture of cell-based therapies. Unlike traditional biopharmaceuticals, many cell-based products have short shelf lives, patient-specific manufacturing processes, and limited opportunities for conventional sterility, mycoplasma, and adventitious agent testing prior to administration. These constraints require risk-based contamination control strategies that maintain product availability while ensuring patient safety.

This roundtable will explore approaches to preventing, detecting, and managing contamination risks throughout the cell therapy lifecycle in the context of evolving regulatory expectations, including the implementation of EU GMP Annex 1 and its emphasis on contamination control strategies (CCS), quality risk management, and holistic oversight of sterile manufacturing. Discussion will include environmental monitoring, in-process testing, rapid microbiological methods, and real-time monitoring technologies. Additionally, we will discuss the extent to which adoption of fully closed and automated systems may reduce contamination risks compared with traditional open processing. Participants will explore whether Annex 1 requirements can and should be applied differently when manufacturing is conducted in fully closed systems, and whether there is scope for a more risk-based approach to cleanroom classification, environmental monitoring, and facility controls while maintaining patient safety and product quality.

Discussion Questions:

1. How should the principles of EU GMP Annex 1, particularly contamination control strategies and quality risk management, be adapted for autologous and other cell-based products?
2. To what extent can fully closed and automated manufacturing systems reduce the need for traditional cleanroom controls, and how should regulators assess and justify any resulting reduction in facility requirements?
3. How should manufacturers and regulators manage residual contamination risks for cell-based products when traditional sterility testing is incomplete at release, and how can rapid testing and real-time monitoring technologies support risk-based release decisions?

Notes:

Implementation of EU GMP Annex 1:

- The adaptation and implementation of Annex 1 requirements for ATMP manufacturing were generally considered challenging.
- The applicability of a risk-based approach was discussed extensively. It was noted that the relevance and implementation of specific requirements may differ across the diverse modalities covered by ATMP definition. Specifically, participants noted the distinction between cell-based therapies and gene therapy products. In vitro gene therapy may be considered, in some respects, more aligned with biological products, potentially easier facilitating the application of contamination control strategies. In contrast, cell therapy manufacturing often presents unique situation that may require a different risk-based justification and control strategy. As a result, the question was posed whether a specific annex for cell therapies is required rather than relying on Annex 1.

Use of fully closed and automated manufacturing systems

- Discussion focused on the expectation for closed systems. In most cases, there are still certain operation steps requiring open handling such as connection of containers with starting / raw materials.
- One of the major issues with closed automated system is limited access to detailed information regarding the system / operating parameters available to manufacturer by the supplier, as such information is often proprietary. In addition, possibilities for additional in-process sampling options are limited. Nevertheless, the main responsibility for product quality remains on the manufacturer.
- Similar limitations may apply to the level of detail that can be shared with regulatory authorities. To some extent, reliance can be placed on comprehensive supplier qualification, system qualification and corresponding quality agreements, which can be verified during inspections.
- Confirmation that the system is truly closed and maintaining aseptic operation can be challenging. It was suggested that aseptic process validation by media fills, in combination with real time environmental monitoring may provide supportive evidence.
- As the highest risk for contamination, combined personnel and environment risk was identified. The first can be ameliorated by e.g. personnel training, qualification and appropriate operating protocols. Further, closed systems are expected to be used within suitably classified areas (Class C).

- Potential concerns were discussed also regarding sterility and quality of the disposables and containers which are difficult to verify. As an example, issues with particles in pre-sterilized plastic containers were noted. Such issues should be addressed as a part of robust supplier qualification.
- The discussion followed on the risk / benefit ratio and how this could be considered, e.g. in the context of an automated system used for point-of-care / decentralized manufacturing. It was noted in the discussion that theoretically high clinical benefit for the patient may in part, support the acceptance of certain justified residual risks, given that these are well understood and managed.
- Other residual contamination risks that are difficult to completely control were briefly discussed, including risks associated with the reconstitution step for cell therapies at clinical site or during the transport of such products. Monitoring of such risks could include periodic collection and testing of samples following reconstitution as part of the overall contamination control strategy.

Managing residual contamination risks

- Two-tiered release approaches especially regarding sterility testing are used for short-lived cell therapy products. In such cases, product release for administration is typically based on a combination of negative-to-date sterility test results, in-process controls, and controls applied to the materials. However, this is approach is seen less now due to improvements in rapid sterility testing.
- Rapid automated growth-based methods are widely used, and in some cases have been accepted with shortened incubation duration (such as 5 or 6 days) provided that the method was appropriately validated. The implementation of rapid sterility methods should be encouraged along with appropriate risk assessment, as these approaches have potential to replace negative-to-date release strategies.
- Use of NGS-based methods for contamination controls was discussed, and these technologies are considered a potentially suitable alternative with potential to cover a broader range of contaminants and under certain circumstances provide information relevant to virus contamination. However, significant issues might be e.g. method validation, implementation and data handling or interpretation of complex sequencing data.
- The group noted also that the challenges related to the sterility control and product release are not completely unique to the cell therapies and similar considerations may apply to other short-lived medicinal products, including radiopharmaceuticals.