Table 14: Quality Risk Management for Cross-Contamination in Multi-Product Facilities

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SCOPE:
Multi-product facilities offer biopharmaceutical and drug manufacturers a multitude of benefits ranging from operational flexibility, efficiency and cost reduction. However, effective control measures must be implemented to prevent cross-contamination to ensure product quality, consistency and patient safety. ICH Q9, which went into effect in 2006, provides a holistic quality risk management (QRM) framework that manufacturers can use to systematically identify, assess, control, communicate and review risks associated with the potential sources of cross-contamination for multi-product facilities. Effective adoption and implementation of QRM principles is increasingly expected and required by global regulators.
This table will discuss current hot topics, including challenges, best practices and other topics of interest, related to the implementation of QRM to address and manage of cross-contamination risks for multi-product facilities.

QUESTIONS FOR DISCUSSION:
What would be our biggest risks associated with cross-contamination and multi-product facilities?
How does the implementation of QRM principles help with the management of these risks?
How does the implementation of QRM principles insure the management of these risks? What are the challenges and barriers in implementing QRMS to address cross-contamination risks? How do we overcome these barriers and challenges?
What do we see as QRM best practices to manage cross-contamination risks in multi-product facilities? Any lessons learned to share?
What additional considerations should be given to assess and include the manufacture of gene and cell therapy products?

DISCUSSION NOTES:

Highest Risks

- Cross-over of products through products, people and equipment
- Introduction of new products
- Highly potent products such as antibody drug conjugates
- Management of the viral vectors, e.g., adeno-associated viral (AAV) vectors, in gene therapy
- Waste disposal – liquid, solid and air born
- What is an appropriate cleaning regime? Needs to demonstrate cleaning efficacy and efficiency while considering cost and downtime to a viable state. For a clinical manufacturing multi-product facility, cleaning processes are typically qualified to ensure that they are effective and efficient every time.

-Virus contamination controls considerations:
- contaminations are usually detected too late
- won't be eliminated by filtration
- Hand-filling of clinical supplies – consider appropriate facility design and equipment (biosafety hoods with proper classification), aseptic techniques, and personnel training
- Compounding of several sub-lots of API into a batch – potential for contamination of the whole batch

QRM Principles

- Industry practices: new product introduction evaluation process to capture of best practices and mitigation of risks-associated with other products – evaluate similarities, i.e., easier or harder to clean compared to other products in the facility
- Capture and mitigation of risks associated with changes or a trend in the data
- Regular update to the risk assessment to reflect gained knowledge and experience
- Internal audits. 'aseptic auditors' and QP
- In one case, all principles of risk identification and management associated with multi-product facilities is documented in a 250-page document

Management and Mitigation of the Risks
- Appropriate facility design and utility set-up
- Waste management set-up
- Single path air
- HVAC dedicated systems
- Functionally closed areas or closed systems (virus)
- Single use components or entire facilities
- Laminar flow helps containment and cross-contamination as well
- Atmosphere in the room: Grade A vs grade B for the different manufacturing operations

- Segregation and control creations
- Product change over SOPs
- Training of operators
- Signs to signal
- Gown and re-gown procedures
- Building of knowledge through the manufacture of the clinical batches

- Cleaning regimen
    - VHP or no VHP?
    - Alternating cleaning agents
    - Lots of sampling to verify cleaning

- Analytical methods and testing
- Ensure that the control strategy allows to detect contamination as early as possible in the process
- Include verification of parameters such as conductivity, pH, TOC are back to normal after cleaning has taken place
- Intense sampling and testing

- Process: multiple filtrations and final downstream 0.2 micron filtration

Additional Considerations

- In context of rare diseases indications and new product modalities, e.g., cell and gene therapy products, it was noted that in one case that although the use of single-use components in a multi-product facility increased drastically the cost of manufacturing of clinical API batches, however given a commercial API batch took a year to manufacture, this was a very effective way of preventing cross-contamination.
- Cell and gene therapy products are opening up new ways of working
- Consider the use of plug and play technology and modular facilities