Contamination Control

In Standards Development

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- AAMI: Radiation, Ethylene Oxide, Dry Heat, Microbiological Methods, Aseptic Processing, BIs, Moist Heat, Sterility Assurance

Objectives

- Briefly, this is not a cataloguing of all the standards that address contamination control
- It is intended to show how discussions of contamination control influence the standards development process which draws on global points of view to outline the approaches that are possible.
- Specifically, three standards/technical reports are briefly highlighted to discuss the ways in which the thought process affects the development of the standard.
- Finally, examples are included where the contamination control practices were effective when used, and problematic when not used.

Disclaimer

- All three documents discussed are in development
- Information in them will change
- The concepts within were developed by national and international participants in the standards development process
- Ideas presented here are for consideration, they are not normative
- Any microbial contamination control program must be individually tailored to your specific situation.

Definitions

- Microorganism:
  - entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

    -ISO 11139 (2017)

- Contamination control:
  - Refers to chemical, particulate, and biological (bioburden) contamination events associated with the manufacture of healthcare, pharmaceutical, biological and combination products.
    - Note: Not an official definition

Contamination Control Mindset

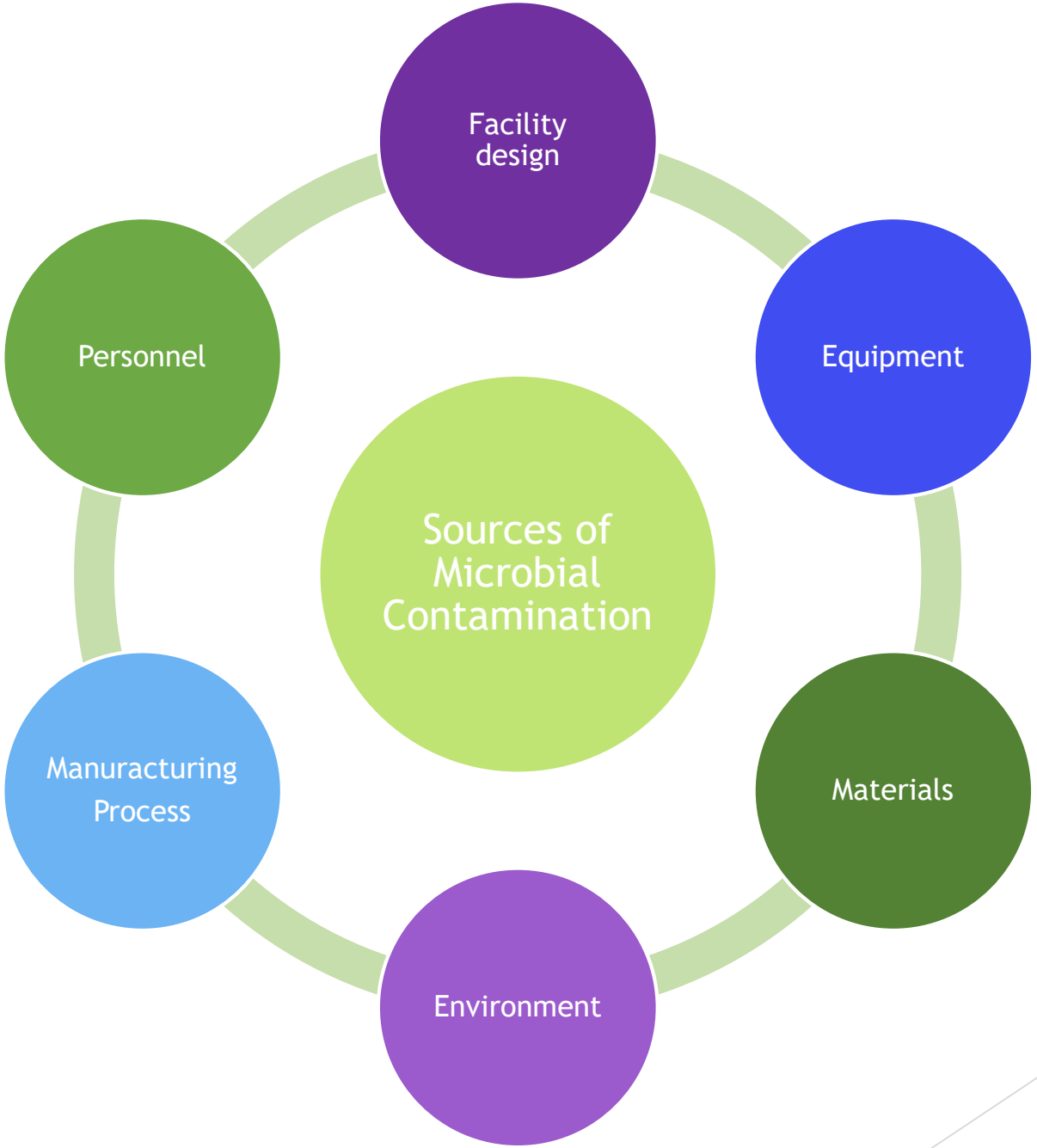
- Contamination Control CANNOT be attained unless:

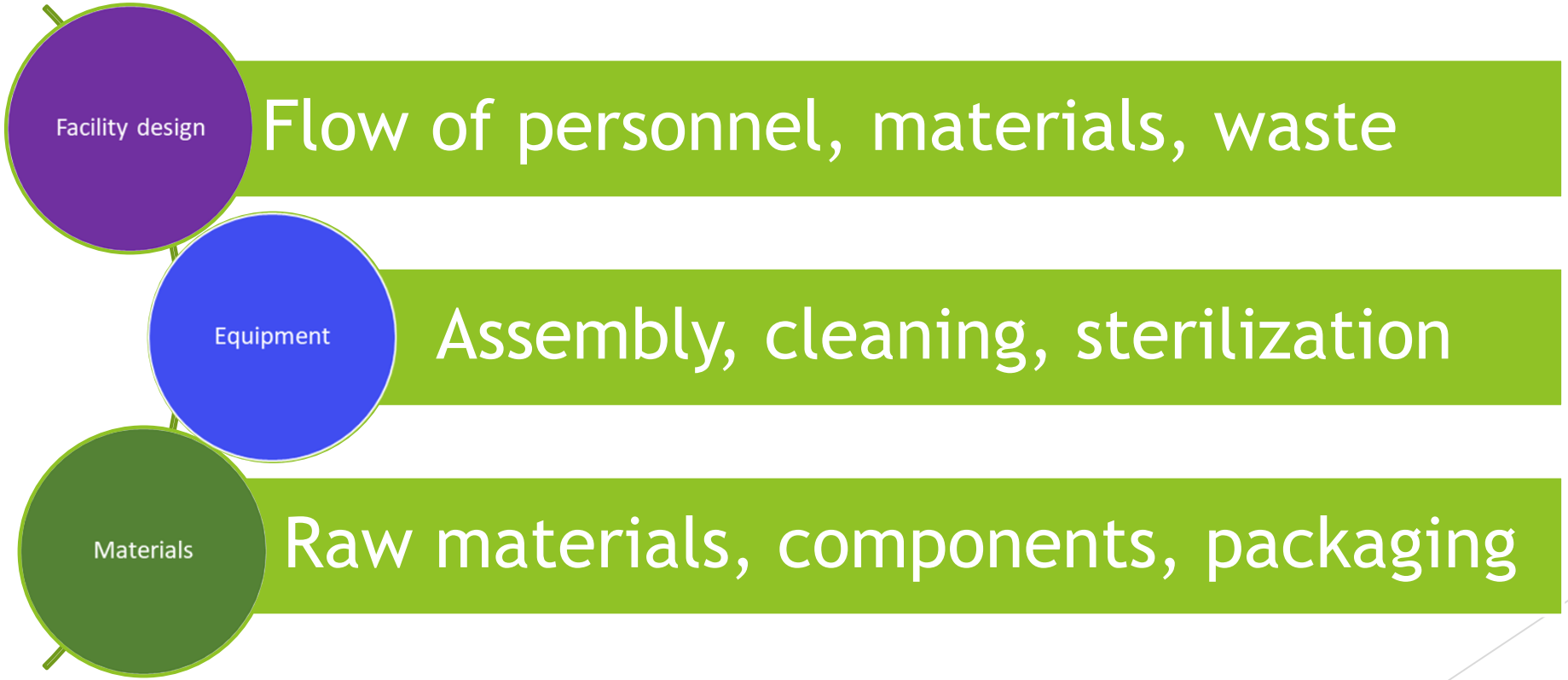
- Product requirements are set based on patient risk
- Real risk not perceived risk must be known
- Experts with the knowledge base to assess these risks are involved
- The facility, process and testing are designed from a risk perspective

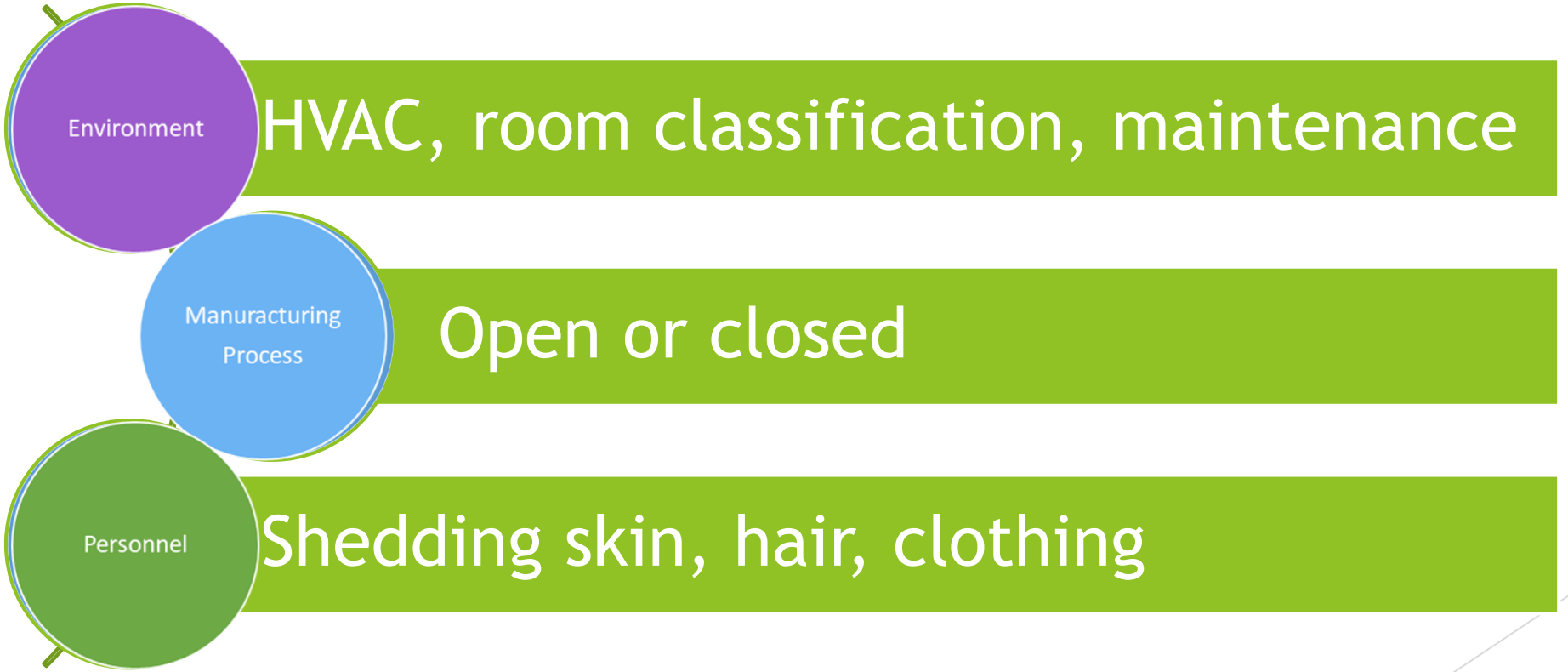
Zeva Abraham, Microrite, Inc.

PDA West Coast

June 2019


Facility design
Equipment
Materials
Environment
Manuracturing Process
Personnel
Sources of Microbial Contamination


Facility design
Flow of personnel, materials, waste
Equipment
Assembly, cleaning, sterilization
Materials
Raw materials, components, packaging


Environment
HVAC, room classification, maintenance
Manuracturing Process
Open or closed
Personnel
Shedding skin, hair, clothing

Applying Knowledge

- Important to understand the entire lifecycle of the product or process, and also consider the requirements of the products – pharma/device/biologics/combination products/sterile (aseptic/TS, desired SAL)/non-sterile
- Standard organisms may not be the only consideration – need to evaluate the product and risk of contamination.

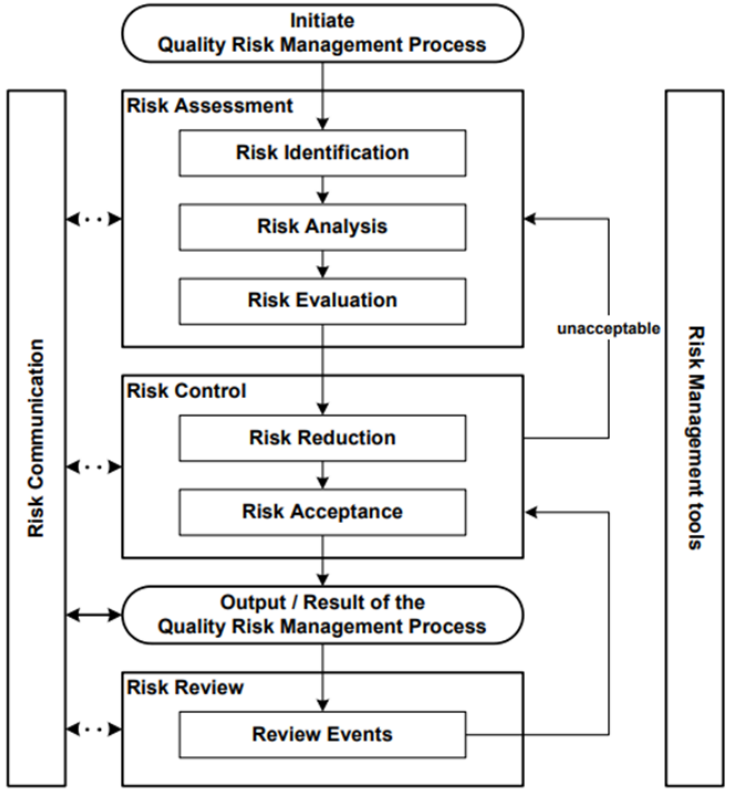
Because….

- Microbial contamination can lead to product variability
- It can cause changes in impurity profiles
- The levels of bacterial endotoxins can increase
- The degradation or modification of product by microbial enzymes can lead to loss of potency
- Essential drugs/devices can be in short supply when there lengthy shutdown periods or recalls, and delays in manufacturing operations during the process of investigations of microbial contaminations.

Microbiological Risk Considerations

- Scientific approach to methods critical to understand contaminants and contamination risks and manage appropriately
  - Microbial and endotoxin contamination considerations
  - Trained personnel
  - Appropriate sampling methods/locations
  - Sample handling pre- & post- sampling
  - Validated test methods
  - Acceptable recovery
  - Objectionable organisms

Risk Management (ICH Q9)



Risk Management

- Risk assessment consists of identifying potential hazards, analyzing hazards and risks associated with exposure to those hazards.
- Risk control consists of developing a plan to reduce and/or accept risks. The purpose of risk control is to reduce risk to an acceptable level.
- Risk communication - Communication of risks between decision makers may be done formally or informally, as appropriate for the risk level of the product and process.
- Risk review is a periodic review of risks as part of the ongoing quality management process.

Reminder about Questions

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PDAMW8

ISO 13408-1 Aseptic processing of health care products: General requirements

- More control allows more flexibility in the approaches delineated in standards requirements
- Introduction of the document includes the following:
- Acknowledges different geographical regulatory approaches and also acknowledges that new approaches are transforming classical aseptic processing
- The effort to move forward:
  - Recognizing risk-based process design
  - Microbiological contamination control
  - Risk management

- Thorough risk management can be used to justify alternative approaches to:
  - Demonstrating ongoing process effectiveness and
  - Product release
- Example given:
  - Automated process conducted in isolator
  - No operator in critical processing area
  - Continuous monitoring of critical control parameters, non-viable and viable particulates
  - OOS result capable of being identified immediately

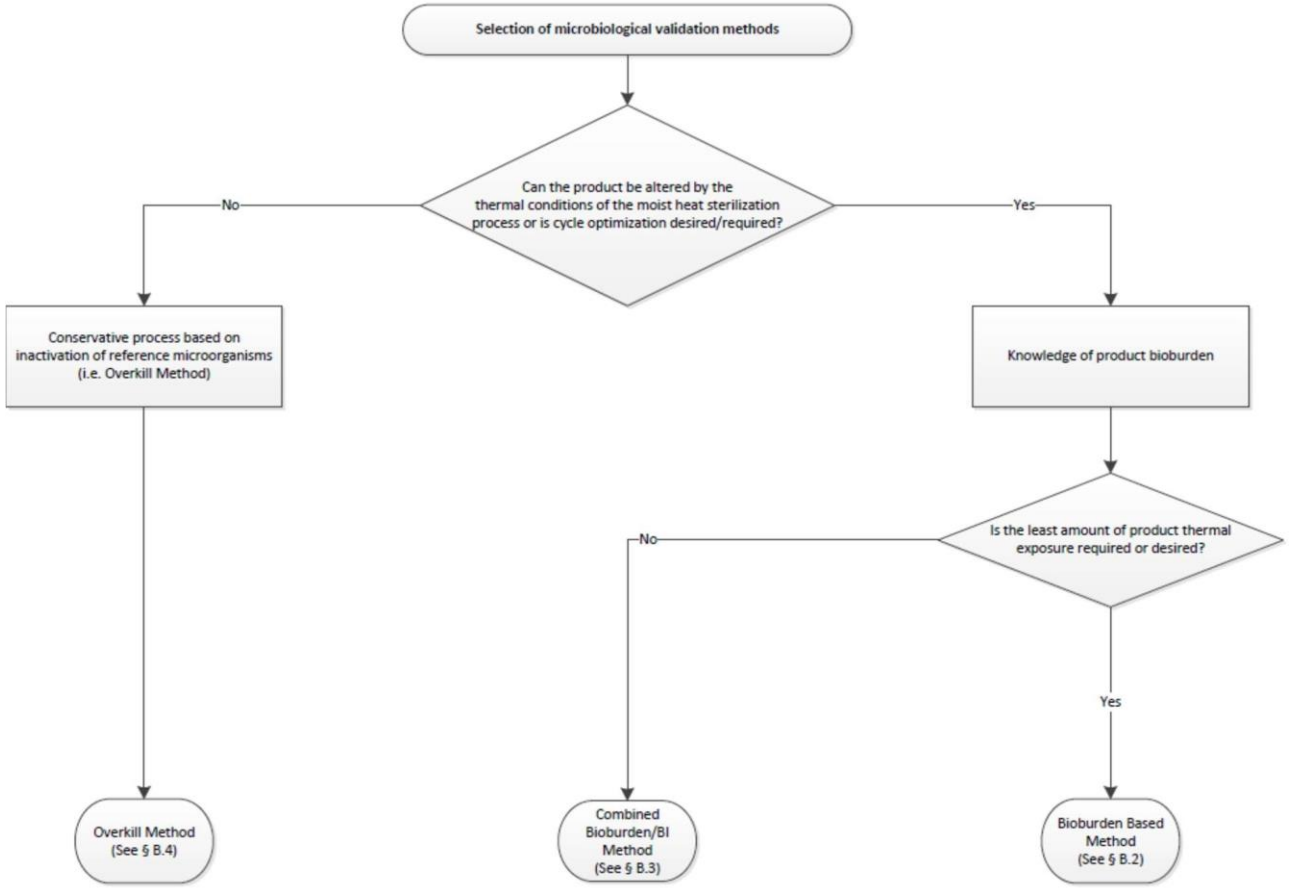
- Could this continual monitoring provide an opportunity for
  - Reduced frequency of process qualification?
  - Reduced sampling?
  - Real time release of product?
- Basis: greater assurance of sterility, thus patient safety

ISO 17665, Sterilization of Healthcare Products, Moist Heat

- Attention is given to the following in order to properly validate a sterilization process:
- the microbiological status of incoming raw materials and/or components;
- the validation and routine control of any cleaning and disinfection procedures used on the product;
- the control of the environment in which the product is manufactured, assembled and packaged;
- the control of equipment and processes;
- the control of personnel and their hygiene;
- the manner and materials in which the product is packaged;
- the conditions under which product is stored.

- Evaluation and discussion about what is really necessary in the moist heat process with respect to microbiological kill.
- Approaches to development of sterilization processes:
- Bioburden based approach
- Bioburden-BI based approach
- Overkill based approach

Draft Decision Tree



- Microbiological contamination control more important than ever
  - In consideration of product presented to sterilization
  - Ensure sterilization process effectivity is not compromised
- Tests for sterility……. “Such tests have little statistical relevance and will only be capable of determining high levels of microbial contamination, indicative of a major process failure”
- Microbial contamination control and risk management, reducing variability, all support a parametric release strategy
- Historically, the overkill approach was used in sterilization, more rare to see other approaches
- Now with biological, tissue based and other temperature sensitive products, it’s important to subject products to “as necessary” sterilization processes, and not to excessive treatments.

AAMI TR 100

- New AAMI Technical Information Report in development
- End-to End Sterility Assurance

- Role of microbiological quality and sterility assurance in the entire product process
  - From research and development based on user needs
  - Through planning, sourcing, and manufacturing
  - To delivery, training, instructions for use, and post market feedback.

- Emphasizes the importance of customer needs which involves a consideration of all aspects of the product and how microbiological contamination is controlled throughout, not just in the manufacturing setting.
- Examples in the delivery stage:
- How to aseptically open packaging,
- How to introduce product into the sterile field
- Feedback on the human factors issues
- Modifications necessary for different circumstances
  - Do increased PPE requirements affect ability to work with the product and maintain necessary aseptic techniques?

Microbial Contamination Control Examples – Case Studies 1

- Contract manufacturer contaminated an API with *Bacillus thuringiensis* due to poor cleaning and improper ventilation systems – result was a sterilization dose of 27.5 kGy was needed.
- The client changed to a different contract manufacturer that had proper controls in place. Dose re-establishment has not yet been completed but initial indications are that a lower dose expected.

- *Methylobacterium* present in water used in processing as a result of poor cleaning practices - resulting in radiation doses of 33 kGy or more.
- When the *Methylobacterium* from above was eliminated then doses of 25 kGy were acceptable.

- For gowns and drapes, the original radiation dose was 45 kGy

  (for 10^{-3} SAL)
- By implementing thorough cleaning, supplier controls, personnel controls, radiation dose reduced to 25 kGy (for 10^{-6} SAL)

Case Studies 2

- Best outcome for Microbial contamination control:
  - Reduce variability for most consistent results
  - Purchasing and Supplier Quality communication critical
  - Vendor validates or the receiver tests every lot
  - The point is to take out sources of variability

- Worst outcome
  - Dose audit failure
  - Traced back to tubing from vendor
  - No controls on water troughs
  - No sporicide used in cleaning
  - Resulted in high bioburden on product
  - Discovered through raw material monitoring

- Another learning: Over action for EO sterilized product –
  - Quarterly bioburden testing performed - numbers
  - Evaluate the organisms
  - Perform periodic monitoring of raw materials
  - Rotate testing of incoming commodities (component bioburden)
- Results in more certainty around incoming quality – (risk management)

- Over action – BET on trough water
- Periodic Review
  - Look at frequency of monitoring – and maintain control in that sense
  - Look at volumes produced and adjust frequency of monitoring accordingly

Case Study 3

- Beware: Testing performed on a API supplied to make drug product
- Qualification of vendor and material was completed appropriately
- Example, minimum 10 lots tested (assume this took into account seasonal variation)
- Company went to skip lot testing
- Boom –Over Action Limits caused huge issue
- Ultimately traced back to humans involved; Proprionibacterium identified

Case Study 4

- *What experience or example do you have where some aspect of contamination control had a positive outcome or influence?*

Contamination control is an essential element of aseptic processing, therefore there are many examples:

- to prevent cross contamination in multiproduct facilities
- to protect operators from high potency actives and products
- to maintain sterility
- to prevent the adulteration of product from cleaning and disinfectant agents
- maintain microbiological and particulate control appropriate to the cleanroom and clean zone classification, e.g., reduce the frequency of EM excursions and the presence of spore forming bacteria and mold, and thus time-consuming investigations
- to address non-routine events such as planned or unplanned shut downs
- simply delineating all the elements of contamination control and how they work together to maintain sterility assurance

What about a negative example where lack of control caused a problem/issue?

- Rejection or delayed release of product
- Shut down of line
- FDA citations, FDA shut down
- Resources and time to address and correct contamination issues
- Often with microbial contamination - there isn't a smoking gun or root cause, therefore, the entire operation or specific process is under "suspicion" until the environment and/or process is back in a state of control

Conclusions

- Microbial contamination control is complex
- Critical to understand customer needs and associated risks
- It is greater than your own manufacturing process
  - Product concept through product delivery and use
  - Procurement of goods and services whether internal or external
- Greater control/s allow increased flexibility in product manufacturing requirements
- More control allows more latitude and opportunity in industry standards requirements
- Greater sterility assurance and thus greater patient safety – the ultimate goal!

Questions

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