Getting it Right Microbial Quality Risk Management

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Programme
- Strategic Background (MAO)
- The Problem (LM)
  - Impact of Environmental microbial contamination on the quality of aseptically prepared products
  - Understanding the process – process mapping
- Trending Approaches (MAO)
  - Immediate Trending
  - Long-term Trending
- Risk Management Processes (MAO)
  - Potential Outcomes (MAO)

Strategic Background 1
Aseptic processing is a high risk activity
Contaminated parenteral products are potentially life threatening and there are reported cases of deaths from such contamination e.g.
- Johannesburg, 1990
- Manchester incident, 1994 (Farwell)
- Tokyo, 2002

Strategic Background 2
- Risks from microbial contamination
- EU GMP standards
- Impact of contamination:
  - Resources required for investigation
  - Destruction of product
  - Reduction of shelf life
  - Closure of workstation/facility
  - Preparation moved to wards/clinical areas
- Application of a Quality Risk Management approach to supplement Quality by Design

Objectives of Environmental Monitoring Processes

Patient Safety

Aims and objectives
Aims:
- Identify the elements of risk associated with microbial contamination in critical zones

Objectives
- Establish the standard level of contamination in critical zones and compare to failure rates from testing:
  - Sterility tests, process validation, operator kits, end of session media fills
- Determine the effects of low levels of contamination on the product
- Develop a quality risk management (QRM) approach to determine the impact of contamination
**Methods - 1**
- Process mapping of aseptic preparation
- Identification of critical control points
- Introduction of control measures

- Evaluation of data from finger dabs and Grade A plates
  - 20 units chosen
  - Data from Jan 2007- end March 2012

**Methods - 2**
- Calculation of failure rates for:
  - Sterility tests
  - Process validation
  - Operator kits
  - End of session media fills

- Comparison with failure rates for finger dabs and Grade A plates

**Results - 1**

<table>
<thead>
<tr>
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<tbody>
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<td>4*</td>
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<td>Operator kits</td>
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**Results - 2**

**Summary of tests performed 2007 – end March 2012**

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* All failed tests from R/P Units
**Broth bottle only contaminated

**Results - 3**

**Results - 4**

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<td>Total tests</td>
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Results of tests of products prepared in critical zones with low levels of contamination

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* All failed tests from R/P Units
**Broth bottle only contaminated
Discussion

- Published data does not provide any evidence of a direct link between contamination in the critical workzone and contamination in the product.
- Evaluation of the data from 2007 - 2012 from 20 NW Units:
  - Failure rates for finger dabs and sessional monitoring of up to 5.7%
  - Probability of a non-sterile unit (PNSU) - aseptic units only is 1 in 10^5
  - Additional testing – products prepared in workzones with low levels of contamination - 0% failure
  - Study in a NW hospital 7,561 PN bags – 0% failure.

Summary

- Use of a risk-based approach to evaluate the impact of contamination can provide confidence that the product is of the correct quality and informed decisions can be taken to reduce the need to destroy products, shut down facilities or to prepare products on the wards.
- Cost Factor:
  - Destroying batches
  - Doing RCA and CAPA
  - Confidence of service
  - Legal / regulatory aspects

Methods of assuring sterility

Dilemma

What do we do when we get positive results?

Trending Methods

A. Immediate Trending

Primary Investigations 1

- Validity of results
  - Operator:
    - Rate of incidents in last 4 weeks
      - ACTION
  - Operator: Transfer disinfection into isolator
    - Rate of incidents in last 4 weeks
      - ACTION
  - Operation: Transfer disinfection into room
    - Rate of incidents in last 4 weeks
      - ACTION
  - Operator ID:
    - Same organism recurring
    - Unidentified organism
  - Growth in sessions before/after
  - Growth on other parameters - same session.
**A. Immediate Trending**

Secondary Investigations 1
- Check physical parameters
- Continuous particle monitoring
- Quarterly EM reports
- Isolator leak tests
- Isolator integrity
- Glove
- Pressure differentials
- Room
- Isolator
- Equipment logs
- Cleaning records
- Process deviation
- Other potential root causes

Secondary Investigations 2
- Product correlation
- Capacity data
- Additional investigation data
- Sterility tests
- End of session/batch broths
- Validation
- Transfer disinfection
- Cleaning
- Operators
- Process

**B. Long term Trending**

Basic approaches
- Frequency of monitoring – 1 month, weeks/months - ROLLING
- Increasing monitoring period – dampens out peaks

Parameters
- % +ve plates on a rolling 4 week basis/isolator or unit
- Consecutive +ve plates from same operator/same area
- High count on single plate – session or hand
- Presence of unusual microbial flora outside the norm including microbes of concern e.g. coliforms, Pseudomonad spp, moulds, yeasts

**Factors influencing the system**
- Facility design
- Processes are heavily operator dependent
- Sanitisation is heavily biased to alcohol disinfection cf. VHP sanitisation
- Products essentially have short shelf lives
- Little or no environmental monitoring information is available before release (Section 10)
- Little or no traditional QC of products
- Many plates are subject to transportation
- Non-pharmaceutical microbiology
- Resource (personnel, equipment and quality systems)
- Expertise (general, non specialised)

**Trending Approaches Summary**

As the disinfection of components and consumables using alcohol and physical wiping is by nature imperfect, a low level of background Grade A contamination is unavoidable

**Risk Management Process**

1. Validity of Growth
2. Potential Product Challenge
3. Process Risk Factors
4. Unfavorable Consequences of contamination
5. Severe Risk Management Measures to Consider
6. Process Controls
7. Potential follow up
**Initial Risk Management Process 1**

**Validity of Growth**

- Have the plates been exposed and handled appropriately?
- Have the plates been transported appropriately?
- Condensate, temperature fluctuations and extremes
- Have the plates been incubated appropriately?
- Are there any effects from the use of vented plates?

**Initial Risk Management Process 2**

**Laboratory investigation**

- **Monitoring Material**
  - Batch details of monitoring medium, expiry, release, storage conditions, sample transfer conditions
  - Stability of sampling equipment/ aids e.g. sampling device, maintenance records (Disinfectant lot validity)
- **EM Sample Personnel**
  - Performance history – other positive results with this sample taker/ analyst
  - Interpretation of colonies found – transposed colonies, edge of plate
  - Training records
  - Record of sampling activities
- **Conditions**
  - Occurrences during sample taking and transfer to analyst?
  - Analysis conditions: Contamination during immediate read out?
  - EM results of sample processing bench? Negative controls?

Minimised by the use of closed systems

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**Potential Product Challenge**

**What has grown on plate?**

- **Bioburden level** – interpretation of Orange Guide
  - Absolute values on each plate
  - Mean values during session
- **Identification**
  - genus level
  - species level
  - One of characterised high risk group of microorganisms?
  - Recurrence of organisms?

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**Potential Product Challenge**

**What has grown on plate?**

A review of Cleanroom Microflora: Types, Trends, and Patterns

9000 isolates – UK sites

**Limitations**

- Differences in areas (Grades A, B, C, D)
- Phenotypic vs genotypic identification

**Sources**

- Gram +ve cocci – human skin
- Gram +ve rods – environment
- Gram –ve rods – water
- Miscellaneous

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**New England Compounding Centre**

- Fungal contamination – 3 batches of epidural steroid injections
- 44 deaths - 700 patients diagnosed with meningitis
- Recall of all NECC products (shut down)

**Organisms**

- Exserohilum rostratum
- Aspergillus fumigatus
- Cladosporium spp.

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**Initial Risk Management Process**

**Supporting evidence**

- Do other results from adjacent monitoring support this result?
- What is the influence of growth in supporting areas?
**Process Risk Factors**

**Potential of organism entering the product**

- Facility Design
- Pressure cascades
- Decontamination processes

- Process flows
- Personnel
- Starting materials
- Products

- Type of device used
- Laminar flow vs. unidirectional flow vs. turbulent flow
- High change rates (>1000 ACH) vs. lower change rates (550 ACH)
- Flushing efficiency

**Process Controls**

**Potential of organism surviving aseptic process**

- Was disinfectant used during the process session? What disinfectant?
  - Alcohol - high risk of transfer
  - VHP - lower risk of transfer

- Validation status of transfer disinfection process
  - Contact plates
  - Total immersion methods

- Resistance of organism to disinfectants

**Consequences of contamination**

**Potential of organism surviving and replicating in product**

- Does the product support growth?
  - Support growth
  - Neutral
  - Inhibits growth

- Medicine base
  - Water for injection
  - Saline
  - Dextrose
  - TPN
  - Cytotoxic

**Consequences of contamination**

**Potential of organism surviving and replicating in product**

- Immediate, 7 day or extended shelf life (aseptically up to 3 months)

- Storage conditions of Product
  - Fridge/freezer - expiry >7 days
  - Fridge/freezer - expiry >17 days
  - Room temperature - expiry <724 hours
  - Body temperature - <24 hours to 7 days

- Storage Times

**Other factors to consider 1**

- Supporting test results
  - End product testing
  - Sterility test
  - Pass, fail or no result

- End of session/batch simulation
  - Pass, fail or no result

- Other environmental results
  - Micro results from other/adjacent sample points
  - Micro results from rooms
  - Physical parameter monitoring
Other factors to consider

- Deviations during session
  - Eg leaking gloves, component problems, procedural variations
- Validation
  - Transfer disinfection – operator dependent techniques
- Recent Trends
  - Result history, trends (also discontinuous trends).
- Number of persons in the room (and or change room).
- Unusual activities in the time frame of deviation, e.g.
  - maintenance or construction?
- Results of last re-qualification.
- Batch record and log book review
- Technical issues?

Outcome of Risk Assessment

- Product
  - Released
  - Failed
- Prospective or Retrospective Release
  - Licensed units
    - Initial bias towards trending
    - More movement toward release/failure of product
- Further Trend
  - Changing profile of environmental monitoring/microflora – indicates something is wrong

Potential Outcomes/Actions

- Batch disposition
- Related batch disposition
  - Identify and review all batches that have been produced in the affected area during incubation of the samples or other defined time window around the deviation event e.g. between 2 days before and 5 days after event
- No further processing of the products
- Separation or blocking access of areas or equipment
- Maintenance and/or (re) qualification of rooms or equipment

Potential Outcomes/Actions

- Additional monitoring
- Additional cleaning, disinfection, sanitisation or sterilisation
- Counsel operators, consider re-training
- Observe operator technique - Competency Assessment
- Check work capacity, activity
- Restrict shelf life (e.g. <24 hours) of products
- Check for deviations to normal standard procedures
- Quarantine any product/batch not issued
- Check clean air device for malfunction

Deviation Costs

<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
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<tbody>
<tr>
<td>Data collection QC</td>
<td>0.25 hrs</td>
</tr>
<tr>
<td>Data collection Production</td>
<td>0.25 hrs</td>
</tr>
<tr>
<td>Review and association action</td>
<td>0.5 hrs</td>
</tr>
<tr>
<td>Competency Assessment</td>
<td>1 hr</td>
</tr>
<tr>
<td>CAPA</td>
<td>2-5 hrs</td>
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Summary

- Essential to have knowledge of pharmaceutical microbiology
- Essential to understand environmental monitoring methods
- Essential to actively assess results and perform trend analysis
  - Immediate Trending
  - Long-term Trending
- Holistic approach with many models/approaches utilised
- Robust Quality Risk Management process
- Feed into CAPA/RCA and institute change control
Conclusion

QBD  QRM

Any Questions?