What’s Objectionable?
A Risk-Based Approach to Determine Objectionability of Microorganisms in Non-sterile Dosage Forms

Tiffany Baker, MBA
Senior Consultant
ValSource, Inc.

Jessica Chiaruttini, PhD
Microbiology Consultant
ValSource, Inc.
Agenda

• Disclaimers and Acknowledgements
• Background
• Important Terms
• QRM Basics
• Risk Assessment Tool and Methodology
• Examples
Disclaimer

This risk tool is not intended to replace required QRM activities and assessments to assess process or facility controls.

This is an example of a risk-based approach, your organization may alter the approach based on risk tolerance and business need.
Acknowledgements

• Stephen Langille, PhD. Senior Consultant, Valsource
• Jessica Chiaruttini, PhD. Microbiology Consultant, Valsource
• Amanda Bishop McFarland, MS. Senior Consultant, Valsource
• Kelly Waldron, PhD. Senior Consultant / Business Unit Lead Valsource
Background
Objectionable Organism Regulations

• 21 CFR 211.84(d)(6) “Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.”

• 21 CFR 211.113(a) “Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.”

• 21 CFR 211.165(b) “There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.”
2021 Guidance

• FDA Released Guidance
  • Risk tool is consistent with guidance
  • Analyzes same parameters as this tool

• Recognizes important of risk-based thinking and assessment for non-sterile drug issues

• Also speaks to risk assessments to support contamination control strategy
  • Do proactive assessments!
Background
What is an Objectionable Organism?

• A microorganism that can adversely affect the appearance, physicochemical attributes or therapeutic effect of a nonsterile product

• A microorganism that, due to its numbers and pathogenicity, can cause infection, allergic response or toxemia in patients receiving the product.

- Parenteral Drug Association TR67
Background
What is an Objectionable Organism?

“Microorganisms could be objectionable by virtue of their total numbers or their detrimental effect on the product or by their potential for causing illness in the persons ingesting them...the objectionable nature of a microorganism may develop only in relation to the unique circumstances of a particular formulation, a particular ingredient, a particular method of manufacture, or the conditions found at a particular firm.”

– US-FDA’s 1978 preamble to the CGMPs
Important Term

• **Microorganism of Concern** – a bacterium, yeast, or mold that, due to its prominence in product recalls, infection outbreaks, nosocomial infections, and the clinical literature, results in a **multifactor risk assessment** to determine whether the microorganism is objectionable in a specific non-sterile product.
Common Places we would want to assess organisms of concern if found

- In the environment / critical utilities in our facilities
- In the product stream / raw materials used in our product stream
EM / Critical Utility Excursions?

Risk-Based Microbial Assessment Tool (R-MAT): A Novel Approach to Assessing Environmental and Critical Utilities Excursions

Friday, February 16, 2018

Amanda Bishop McFarland

Abstract

When it comes to environmental and critical utilities monitoring, industry agrees that robust investigation and corrective actions are needed following recovery of objectionable organisms. However, objectionable organisms make up only a small portion of the flora that are commonly recovered in a controlled facility and the required actions may not be economically feasible or necessary. The Risk-Based Microbial Assessment Tool (R-MAT) is a novel approach to assessing environmental and critical utilities excursions.

QRM 101
Basics for Risk-Based Approaches
What is Risk?

ICH Q9R1

- The combination of likelihood of occurrence of harm and the severity of that harm.
What is a risk-based approach, and why are we using it here?

• Traditional risk tools may be less helpful for reactive risk assessment
  • Likelihood rating = 100%, it already happened!

• Risk-Based Approach
  • Mechanism to make decisions or evaluate information using a defined tool derived from the principles of quality risk management.
    • Scientific knowledge
    • Design tool approach to protect patients
The risk-based approach to determine Objectionable Organisms mirrors the ICH Q9 QRM lifecycle.

**Note:** the investigation and CAPA process are out of scope for this tool, but likely occurring at the same time.
Risk-Based Approach to Determine Objectionable Organisms in Non-Sterile Dosage Forms
Participation in the Assessment

- Assessment should be a cross functional effort
- At minimum, the following SMEs should participate:
  - Microbiology
  - Quality
  - Manufacturing
- Other SMEs may be considered helpful:
  - Medical
  - Pharmacovigilance
  - Regulatory Affairs
Where do we start?

• **Step 1 – Confirm Identity and Quantity of Isolates**
  • Assays and investigation should be performed by a qualified Microbiology expert

• **Step 2 – Compare results against specifications**
  • OOS results are objectionable, **no further assessment required**.
  • As database builds over time, if this isolate has been assessed previously (for this specific product), leverage the existing assessment. **No further assessment required**.
  • Organism of concern (but within specification) that has not previously been assessed using this approach **should be assessed** to determine if they are objectionable (for each specific product).
Step 3 – Gather information to perform assessment

Organism
• What is the species of the organism that was recovered?
• What is the pathogenicity of the organism? What are the known routes of infection?

Product
• What is the water activity of the product formulation?
• What inherent microbial growth controls exist in the product? (extreme pH, heat treatment steps during manufacture, chemical treatment).
• What data do we have to support antimicrobial effectiveness over the shelf-life?

Intended Patient / Consumer
• Who is the intended patient / consumer? (risk will be greater if product is intended for patients with underlying conditions)
Parameters Evaluated with the Risk-Based Approach

- Product Attributes
- Route of Administration
- Target Patient / Consumer
- Organism Pathogenicity
Risk Methodology

Step 4: Product Attributes × Route of Administration = Product Vulnerability Rating

Step 5: Product Vulnerability Rating × Target Patient / Consumer = Patient Vulnerability Rating

Step 6: Patient Vulnerability Rating × Organism Pathogenicity = Organism determination
### Product Attributes

<table>
<thead>
<tr>
<th>Product Attribute Criteria Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
</tr>
<tr>
<td><strong>Medium</strong></td>
</tr>
<tr>
<td><strong>Low</strong></td>
</tr>
</tbody>
</table>

*Step 4*

$A_w = $ water activity
## Route of Administration

### Route of Administration Criteria Example

<table>
<thead>
<tr>
<th>Major</th>
<th>Moderate</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerosol and dry powder inhalants</td>
<td>Topical lotions, gels, creams. Oral liquids vaginal suppositories, ointments, and creams.</td>
<td>Oral tablets and powder filled caplets Liquid filled capsules Rectal suppositories, ointments, and creams</td>
</tr>
<tr>
<td>Nasal sprays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otics (inside ear)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Step 4: Product Attributes $\times$ Route of Administration $=$ Product Vulnerability Rating
<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>P2</td>
<td>P3</td>
<td>P3</td>
</tr>
<tr>
<td>Moderate</td>
<td>P1</td>
<td>P2</td>
<td>P3</td>
</tr>
<tr>
<td>Minor</td>
<td>P1</td>
<td>P1</td>
<td>P2</td>
</tr>
</tbody>
</table>
## Target Patient / Consumer Population

<table>
<thead>
<tr>
<th>Target Patient / Consumer Population Criteria Example</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical</strong></td>
<td>Immunocompromised, Immunosuppressed, or recent medical procedure*</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Infant or geriatric</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td>General population</td>
</tr>
</tbody>
</table>

### Point of consideration
If you do not know the patient population (general topical cream for example), consider what your patient population could potentially be.

*Neonate and geriatric with underlying conditions would be considered immunocompromised*
### Target Patient / Consumer Population

<table>
<thead>
<tr>
<th>Patient Vulnerability Rating</th>
<th>General</th>
<th>Infant / Geriatric</th>
<th>Immuno-compromised / suppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3</td>
<td>S2</td>
<td>S3</td>
<td>S3</td>
</tr>
<tr>
<td>P2</td>
<td>S1</td>
<td>S2</td>
<td>S3</td>
</tr>
<tr>
<td>P1</td>
<td>S1</td>
<td>S2</td>
<td>S2</td>
</tr>
</tbody>
</table>
Organism Pathogenicity

<table>
<thead>
<tr>
<th>Product Attribute Criteria Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True Pathogen</strong></td>
</tr>
<tr>
<td><strong>Opportunistic Pathogen</strong></td>
</tr>
<tr>
<td><strong>Non-pathogenic</strong></td>
</tr>
</tbody>
</table>

**Step 6**

Patient Vulnerability Rating $\times$ Organism Pathogenicity $=$ Organism determination
For determination, refer to route of infection for organism:

- Organisms with known routes of infection that match the product’s route of administration are **Objectionable**
- Organisms with no known infectivity via route of administration are **Not Objectionable**

<table>
<thead>
<tr>
<th>Patient Vulnerability Rating</th>
<th>Organism Pathogenicity</th>
<th>Non-pathogenic</th>
<th>Opportunistic Pathogen</th>
<th>True Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
<td></td>
<td>Not Objectionable</td>
<td>Objectionable</td>
<td>Objectionable</td>
</tr>
<tr>
<td>S2</td>
<td></td>
<td>Not Objectionable</td>
<td>Conditional*</td>
<td>Objectionable</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>Not Objectionable</td>
<td>Not Objectionable</td>
<td>Conditional*</td>
</tr>
</tbody>
</table>
Example 1: *Klebsiella oxtoca* has been identified in a topical cream non-sterile product intended for nursing home distribution. The product has $A_w$ greater than .6, and the organization has antimicrobial effectiveness data for the entire shelf life of the product. The test result was within specifications, is it objectionable?

<table>
<thead>
<tr>
<th>Product Attribute</th>
<th>Rating</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medium</td>
<td>$A_w &gt; .6$ with supporting antimicrobial effectiveness data over the entire product shelf life</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Moderate</th>
<th>Topical Cream</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Product Vulnerability Rating</th>
<th>P2</th>
<th>N/A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Target Patient/Consumer</th>
<th>Immunocompromised</th>
<th>Nursing home distribution</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient Vulnerability Rating</th>
<th>S3</th>
<th>N/A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Organism Pathogenicity</th>
<th>Non-pathogenic</th>
<th>Opportunistic Pathogen</th>
<th>True Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>K.oxtoca</em></td>
<td>Opportunistic Pathogen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Vulnerability Rating</th>
<th>S3</th>
<th>Objectionable</th>
<th>Objectionable</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient Vulnerability Rating</th>
<th>S2</th>
<th>Conditional*</th>
<th>Objectionable</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient Vulnerability Rating</th>
<th>S1</th>
<th>Not Objectionable</th>
<th>Not Objectionable</th>
<th>Conditional*</th>
</tr>
</thead>
</table>
Example 2: *Enterobacter cloacae* has been identified in a solid oral non-sterile product intended for the general public. The product has $A_w$ less than .6. The test result was within specifications, is it objectionable?

<table>
<thead>
<tr>
<th>Product Attribute</th>
<th>Rating</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Aw (&lt;.6), microbial growth not supported</td>
</tr>
</tbody>
</table>

| Route of Administration    | Minor  | Solid Oral Dosage                                   |

| Product Vulnerability Rating | P1     | N/A                                                 |

| Target Patient/Consumer     | General public | Solid oral intended for over-the-counter sale |

| Patient Vulnerability Rating | S1     | N/A                                                 |

| Organism Pathogenicity      | Opportunistic Pathogen | E. Cloacae is an opportunistic pathogen according to literature and Microbiology expert |

| Organism Designation        | Not Objectionable | N/A                                                 |
But this same example for a product intended to be distributed to AIDS patients....

<table>
<thead>
<tr>
<th>Rating</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Attribute</strong></td>
<td>Low</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Minor</td>
</tr>
<tr>
<td><strong>Product Vulnerability Rating</strong></td>
<td>P1</td>
</tr>
<tr>
<td><strong>Target Patient/Consumer</strong></td>
<td>Immunocompromised / Immunosuppressed</td>
</tr>
<tr>
<td><strong>Patient Vulnerability Rating</strong></td>
<td>S2</td>
</tr>
<tr>
<td><strong>Organism Pathogenicity</strong></td>
<td>Opportunistic Pathogen</td>
</tr>
<tr>
<td><strong>Organism Designation</strong></td>
<td>Conditional*</td>
</tr>
</tbody>
</table>

**Organism Pathogenicity**

- **Non-pathogenic**
  - S3: Not Objectionable
  - S2: Not Objectionable, Conditional*
  - S1: Not Objectionable

- **Opportunistic Pathogen**
  - S3: Not Objectionable
  - S2: Conditional*
  - S1: Not Objectionable

- **True Pathogen**
  - S3: Objectionable
  - S2: Objectionable
  - S1: Conditional*
**Example 3:** *Streptococcus pneumoniae* has been identified in an oral liquid non-sterile product intended for the general public. The product has $A_w$ greater than .6, and the organization has antimicrobial effectiveness data for the entire shelf life of the product. The test result was within specifications, is it objectionable?

<table>
<thead>
<tr>
<th>Rating</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Attribute</strong></td>
<td>Medium: $A_w$ (&gt; .6) with supporting antimicrobial effectiveness data over the entire product shelf life</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Moderate: Oral Liquid</td>
</tr>
<tr>
<td><strong>Product Vulnerability Rating</strong></td>
<td>P2: N/A</td>
</tr>
<tr>
<td><strong>Target Patient/Consumer</strong></td>
<td>General public: Oral liquid intended for over-the-counter sale</td>
</tr>
<tr>
<td><strong>Patient Vulnerability Rating</strong></td>
<td>S1: N/A</td>
</tr>
<tr>
<td><strong>Organism Pathogenicity</strong></td>
<td>True Pathogen: <em>S. pneumonia</em> is a respiratory pathogen, resides in the respiratory track of carriers, not always pathogenic.</td>
</tr>
<tr>
<td><strong>Organism Designation</strong></td>
<td>Conditional*: <em>S. pneumonia</em> is not pathogenic when administered to healthy general population through an oral route of administration, acceptable.</td>
</tr>
</tbody>
</table>

**Organism Pathogenicity**

- **Non-pathogenic**
  - S3: Not Objectionable
  - S2: Not Objectionable
  - S1: Not Objectionable

- **Opportunistic Pathogen**
  - S3: Objectionable
  - S2: Conditional*
  - S1: Not Objectionable

- **True Pathogen**
  - S3: Objectionable
  - S2: Objectionable
  - S1: Conditional*
### Product Attribute
- **Rating:** Medium
- **Justification:** Aw (>0.6) with supporting antimicrobial effectiveness data over the entire product shelf life

### Route of Administration
- **Rating:** Moderate
- **Justification:** Oral Liquid

### Product Vulnerability Rating
- **Rating:** P2
- **Justification:** N/A

### Target Patient/Consumer
- **Rating:** Pediatric/geriatric
- **Justification:** Oral liquid intended for over-the-counter sale

### Patient Vulnerability Rating
- **Rating:** S2
- **Justification:** N/A

### Organism Pathogenicity
- **Rating:** True Pathogen
- **Justification:** S. Pneumonia is a respiratory pathogen, resides in the respiratory track of carriers, not always pathogenic.

### Organism Designation
- **Rating:** Objectionable
- **Justification:** S. Pneumonia could be pathogenic to either the pediatric/geriatric or immunocompromised populations, objectionable.

### Organism Pathogenicity Table

<table>
<thead>
<tr>
<th>Patient Vulnerability Rating</th>
<th>Non-pathogenic</th>
<th>Opportunistic Pathogen</th>
<th>True Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
<td>Not Objectionable</td>
<td>Objectionable</td>
<td>Objectionable</td>
</tr>
<tr>
<td>S2</td>
<td>Not Objectionable</td>
<td>Conditional*</td>
<td>Objectionable</td>
</tr>
<tr>
<td>S1</td>
<td>Not Objectionable</td>
<td>Not Objectionable</td>
<td>Conditional*</td>
</tr>
</tbody>
</table>
After the assessment

• **Step 6 – Document the assessment**
  - Build a standard template for all assessments of this type at the organization.
  - This will serve as our risk communication

• **Step 7 – Update the database**
  - Each time an assessment is performed, the database grows.
  - Can be leveraged in the future if specific organism is found again.

• **Step 8 – Database As-Needed Risk Review**
  - Update the database as new information is learned.
References

- Code of Federal Regulations (CFR) Title 21
- PDA TR 67, Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics
Sterility Assurance & Quality Risk Management Conference

October 25th & 26th

Contact Info

jchiaruttini@valsourc.com  
770.235.6572  
www.valsource.com

tbaker@valsourc.com  
401.256.7242  
www.valsource.com