Sterility Assurance & Quality Risk Management Conference

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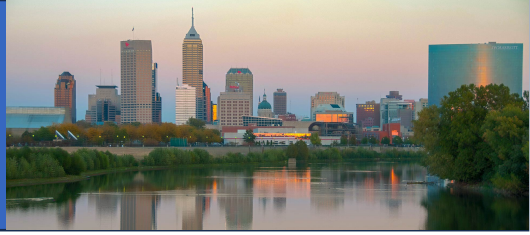
Sterility Assurance & Quality Risk Management Conference

October 25th & 26th



What's Objectionable?

A Risk-Based Approach to Determine Objectionability of Microorganisms in Non-sterile Dosage Forms

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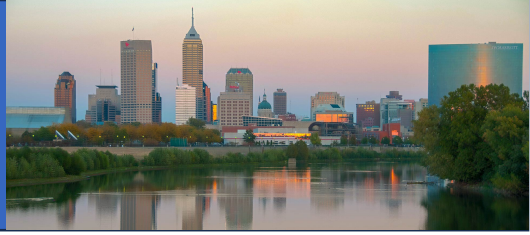
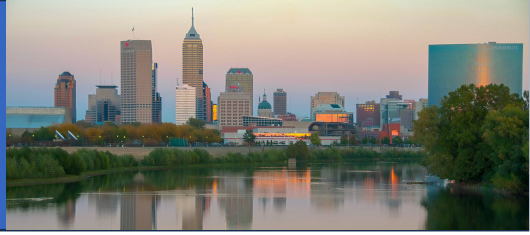


Agenda

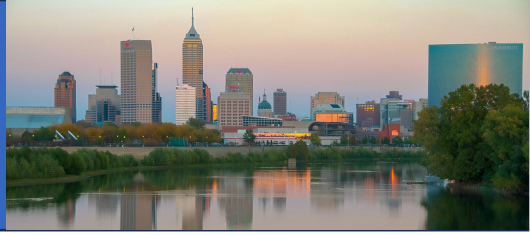
- Disclaimers and Acknowledgements
- Background
- Important Terms
- QRM Basics
- Risk Assessment Tool and Methodology
- Examples



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.



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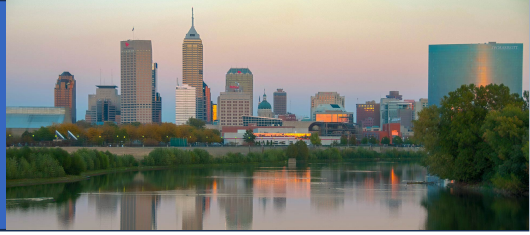
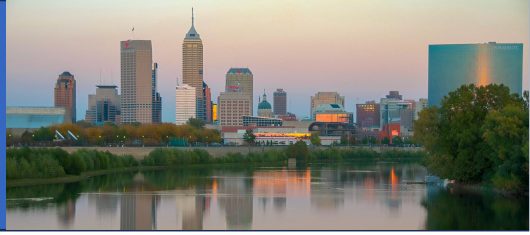


Background

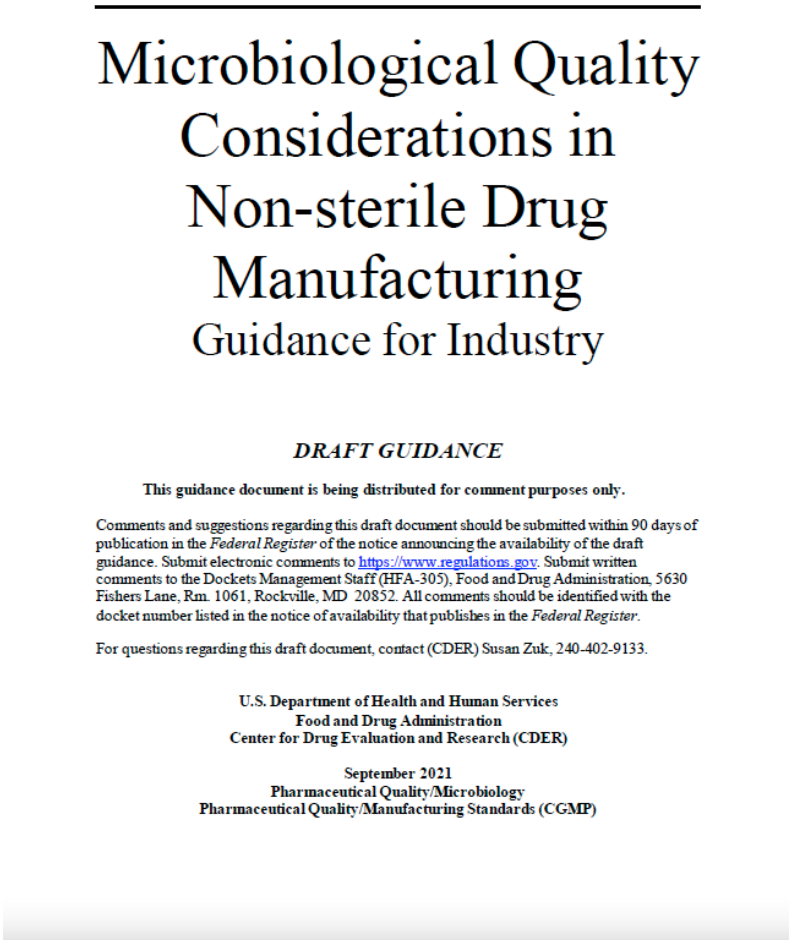
Objectionable Organism Regulations

- 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!



Microbiological Quality Considerations in Non-sterile Drug Manufacturing

Guidance for Industry

DRAFT GUIDANCE

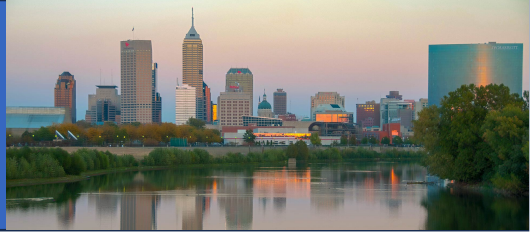
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Susan Zuk, 240-402-9133.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2021
Pharmaceutical Quality/Microbiology
Pharmaceutical Quality/Manufacturing Standards (CGMP)

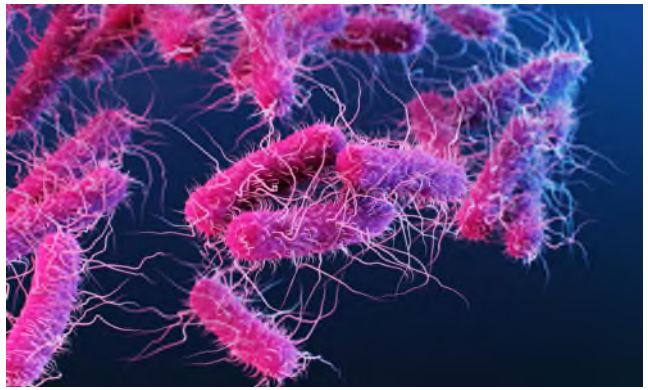


Background

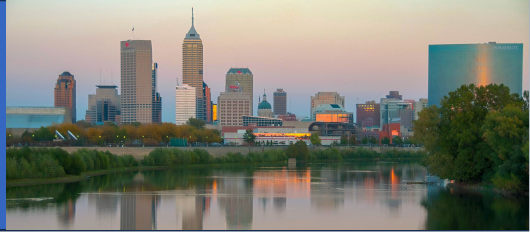
What is an Objectionable Organism?

- 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

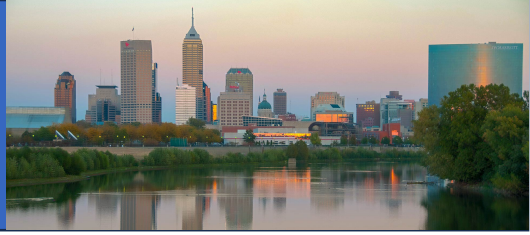


Background

What is an Objectionable Organism?

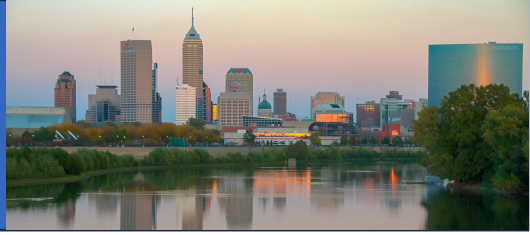
"Microorganisms could be objectionable by virtue of their total numbers or their detrimental effect on the product or by their potential for causing illness in the persons ingesting them…the objectionable nature of a microorganism may develop only in relation to the unique circumstances of a particular 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

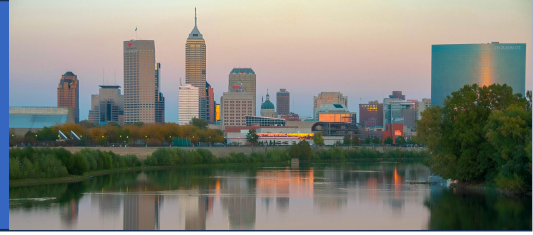
- **Microorganism of Concern** – a bacterium, yeast, or mold that, due to its prominence in product recalls, infection outbreaks, nosocomial infections, and the clinical literature, results in a **multifactor risk assessment** to determine whether the microorganism is objectionable in a specific non-sterile 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

Focus of today's approach



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

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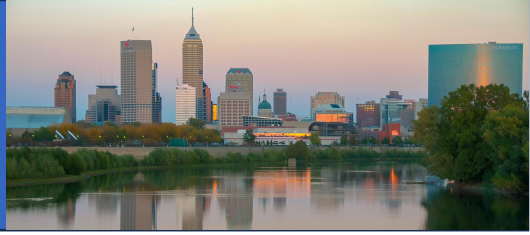
Amanda Bishop McFarland

Abstract

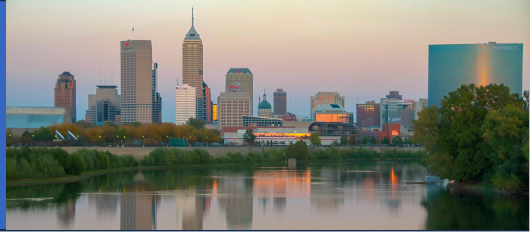
When it comes to environmental and critical utilities monitoring, industry agrees that robust investigation and corrective actions are needed following recovery of objectionable organisms.[1] However, objectionable organisms make up only a small portion of the flora that are commonly recovered in a controlled facility and the required actions

https://www.americanpharmaceuticalreview.com/Featured-Articles/347219-Risk-Based-Microbial-Assessment-Tool-R-MAT-A-Novel-Approach-to-Assessing-Environmental-and-Critical-Utilities-Excursions/



QRM 101

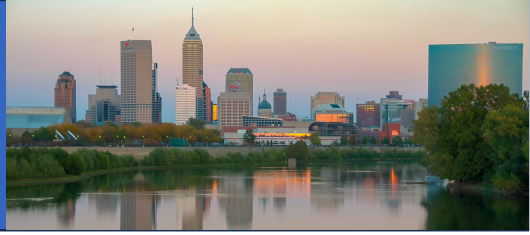
Basics for Risk-Based Approaches



What is Risk?

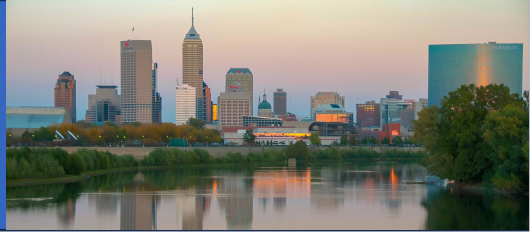
ICH Q9R1

- 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



Organism of Concern identified

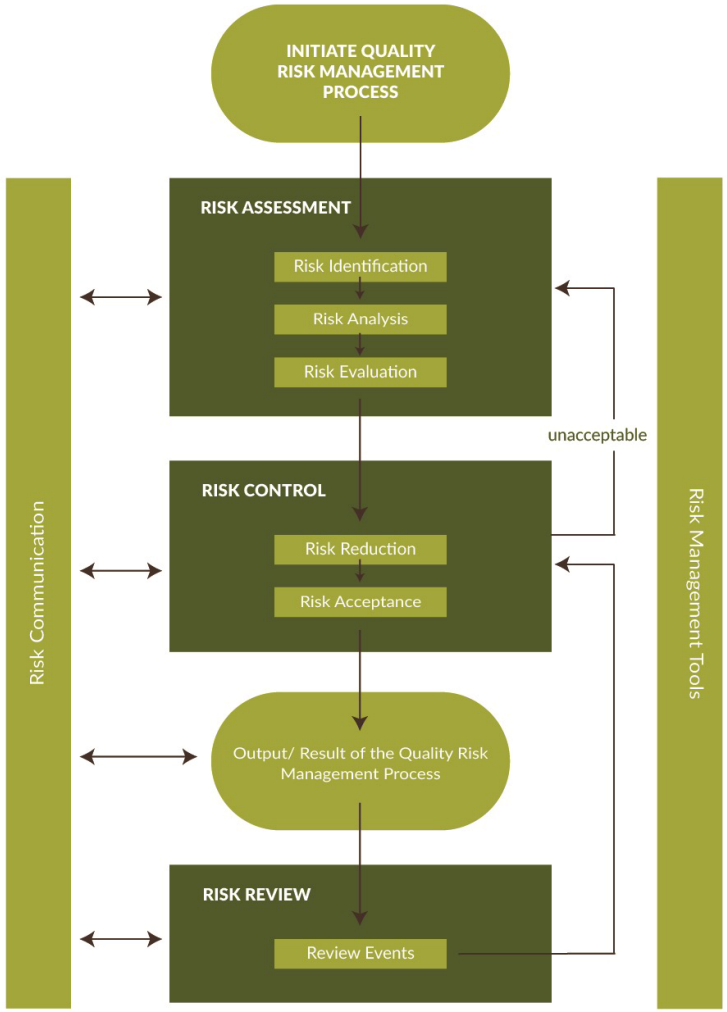
Use risk-based approach to determine if objectionable

Reject objectionable, keep acceptable lots

Risk-based approach documented

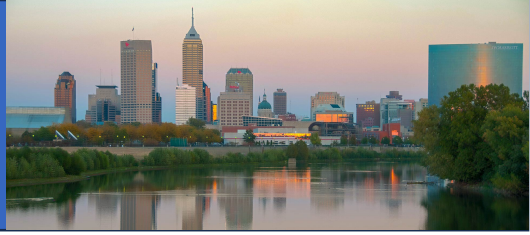
If new information is learned about an organism

Communicate to all stakeholders

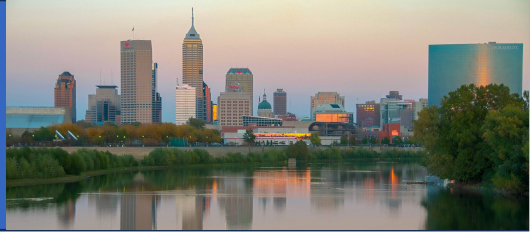


The risk-based approach to determine Objectionable Organisms mirrors the ICH Q9 QRM lifecycle

Note: the investigation and CAPA process are out of scope for this tool, but likely occurring at the same time

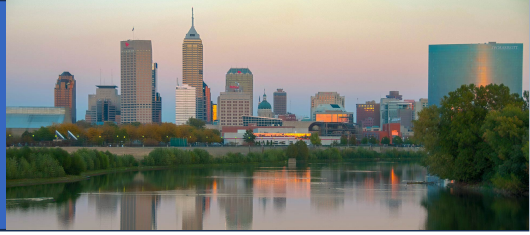


Risk-Based Approach to Determine Objectionable Organisms in Non-Sterile Dosage Forms



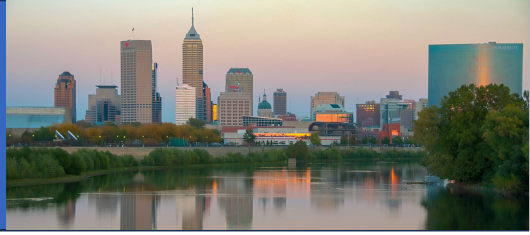
Participation in the Assessment

- 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

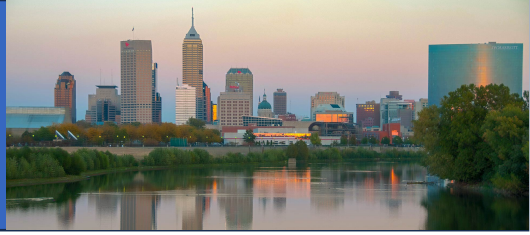
- What is the species of the organism that was recovered?
- What is the pathogenicity of the organism? What are the known routes of infection?

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?

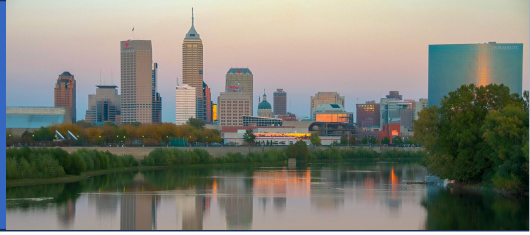
Intended Patient / Consumer

- Who is the intended patient / consumer? (risk will be greater if product is intended for patients with underlying conditions)



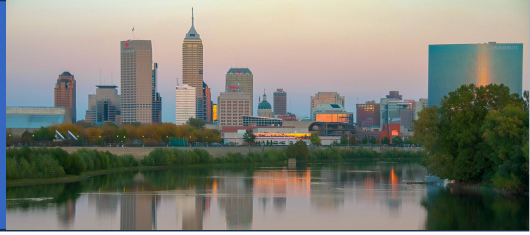
Parameters Evaluated with the Risk-Based Approach

- 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

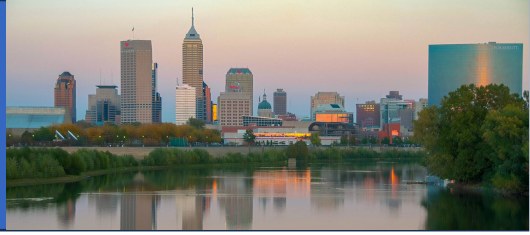


Product Attributes

Product Attribute Criteria Example	
High	A_w (> or equal to .6) with limited preservative effectiveness data or if data is in question due to organism of concern (microbe breaks down preservative effectiveness over time)
Medium	A_w (>.6) with supporting antimicrobial effectiveness data over the entire product shelf life
Low	A_w (≤.6), microbial growth not supported

Step 4 Product Attributes ✖ Route of Administration = Product Vulnerability Rating

A_w = water activity

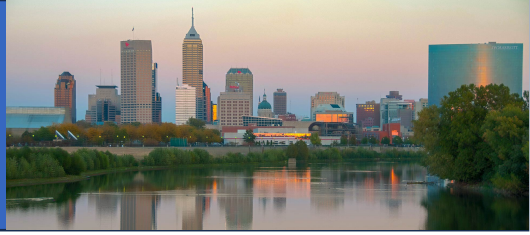


Route of Administration

Route of Administration Criteria Example	
Major	Aerosol and dry powder inhalants Nasal sprays Otics (inside ear)
Moderate	Topical lotions, gels, creams. Oral liquids vaginal suppositories, ointments, and creams.
Minor	Oral tablets and powder filled caplets Liquid filled capsules Rectal suppositories, ointments, and creams

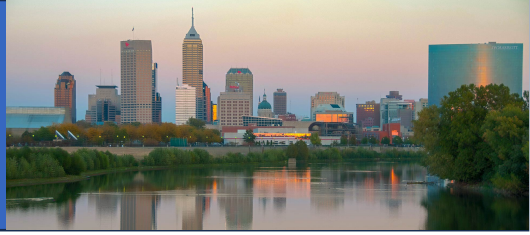
Step 4

Product Attributes ✖ Route of Administration = Product Vulnerability Rating



Product Vulnerability Rating

Route of Administration	Product Attributes: Low	Product Attributes: Medium	Product Attributes: High
Major	**P2**	**P3**	**P3**
Moderate	**P1**	**P2**	**P3**
Minor	**P1**	**P1**	**P2**



Target Patient / Consumer Population

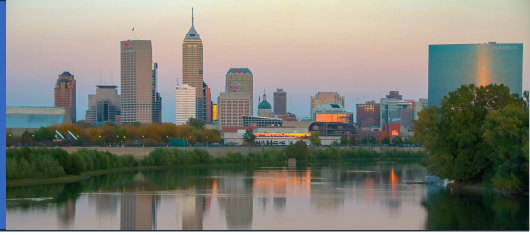
Target Patient / Consumer Population Criteria Example	
Critical	Immunocompromised, Immunosuppressed, or recent medical procedure*
Moderate	Infant or geriatric
Minor	General population

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

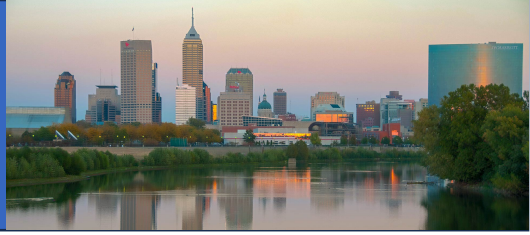
Step 5

Product Vulnerability Rating ✖ Target Patient / Consumer = Patient Vulnerability Rating



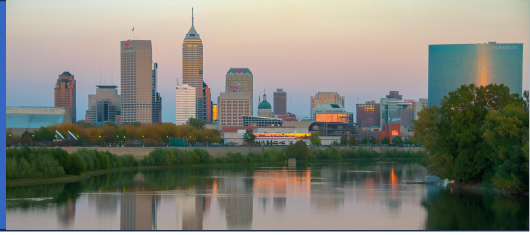
Patient Vulnerability Rating

Product Vulnerability Rating	Target Patient / Consumer Population: General	Infant / Geriatric	Immuno-compromised / suppressed
P3	S2	S3	S3
P2	S1	S2	S3
P1	S1	S2	S2



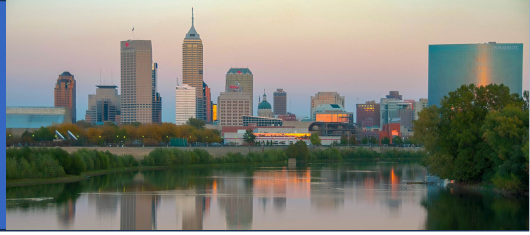
Organism Pathogenicity

Product Attribute Criteria Example	
True Pathogen	An infectious agent that causes disease in healthy patients with normal immune defenses
Opportunistic Pathogen	Potentially infectious agents that rarely cause disease in individuals with healthy immune systems
Non-pathogenic	Organisms which do not cause disease



Patient Vulnerability Rating	Organism Pathogenicity: Non-pathogenic	Organism Pathogenicity: Opportunistic Pathogen	Organism Pathogenicity: True Pathogen
S3	Not Objectionable	Objectionable	Objectionable
S2	Not Objectionable	Conditional*	Objectionable
S1	Not Objectionable	Not Objectionable	Conditional*

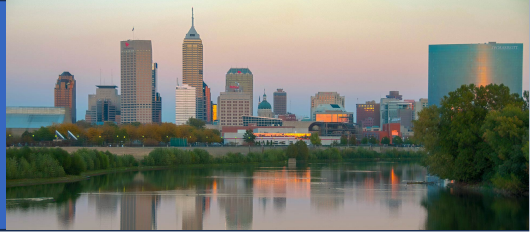
- For conditional determination, refer to route of infection for organism:
- Organisms with known routes of infection that match the product's route of administration are Objectionable
- Organisms with no known infectivity via route of administration are Not Objectionable



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?

	Rating	Justification
Product Attribute	Medium	Aw (>.6) with with supporting antimicrobial effectiveness data over the entire product shelf life
Route of Administration	Moderate	Topical Cream
Product Vulnerability Rating	P2	N/A
Target Patient/Consumer	Immunocompromised	Nursing home distribution
Patient Vulnerability Rating	S3	N/A
Organism Pathogenicity	Opportunistic Pathogen	K.oxtoca is an opportunistic pathogen according to literature and Microbiology expert
Organism Designation	Objectionable	N/A

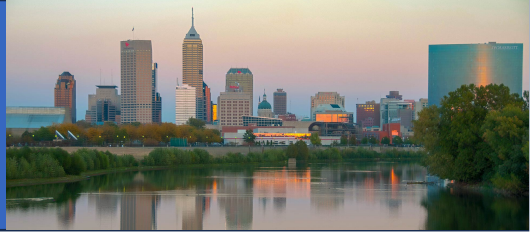
Patient Vulnerability Rating	Organism Pathogenicity: Non-pathogenic	Organism Pathogenicity: Opportunistic Pathogen	Organism Pathogenicity: True Pathogen
S3	Not Objectionable	Objectionable	Objectionable
S2	Not Objectionable	Conditional*	Objectionable
S1	Not Objectionable	Not Objectionable	Conditional*



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?

	Rating	Justification
Product Attribute	Low	Aw (<.6), microbial growth not supported
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

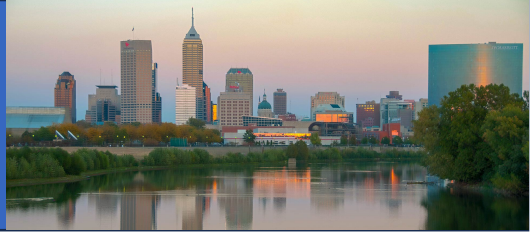
Patient Vulnerability Rating	Organism Pathogenicity: Non-pathogenic	Opportunistic Pathogen	True Pathogen
S3	Not Objectionable	Objectionable	Objectionable
S2	Not Objectionable	Conditional*	Objectionable
S1	Not Objectionable	Not Objectionable	Conditional*



But this same example for a product intended to be distributed to AIDS patients….

	Rating	Justification
Product Attribute	Low	Aw (<.6), microbial growth not supported
Route of Administration	Minor	Solid Oral Dosage
Product Vulnerability Rating	P1	N/A
Target Patient/Consumer	Immunocompromised / Immunosuppressed	Solid oral intended population is AIDS patients
Patient Vulnerability Rating	S2	N/A
Organism Pathogenicity	Opportunistic Pathogen	E.Cloacae is an opportunistic pathogen according to literature and Microbiology expert
Organism Designation	Conditional*	E.Cloacae has documented cases of infection specifically within the immunocompromised population, organism is objectionable.

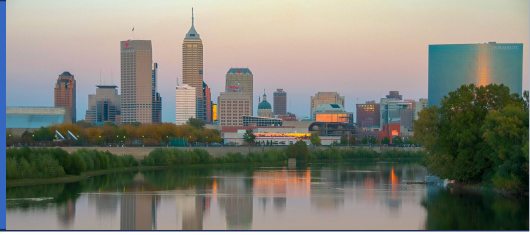
Patient Vulnerability Rating	Organism Pathogenicity: Non-pathogenic	Opportunistic Pathogen	True Pathogen
S3	Not Objectionable	Objectionable	Objectionable
S2	Not Objectionable	Conditional*	Objectionable
S1	Not Objectionable	Not Objectionable	Conditional*



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?

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

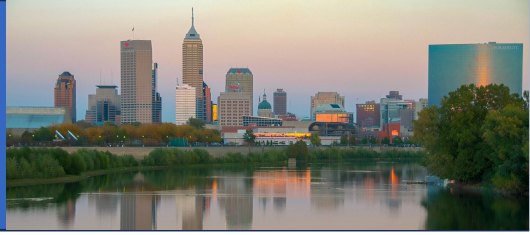
Patient Vulnerability Rating	Organism Pathogenicity: Non-pathogenic	Opportunistic Pathogen	True Pathogen
S3	Not Objectionable	Objectionable	Objectionable
S2	Not Objectionable	Conditional*	Objectionable
S1	Not Objectionable	Not Objectionable	Conditional*



Same example for ANY population other than general population

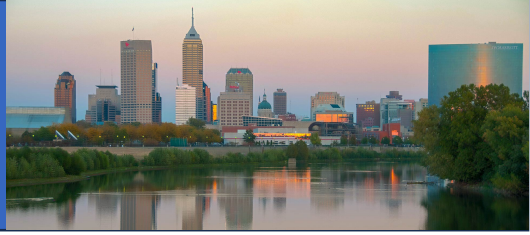
	Rating		Justification
Product Attribute	Medium		Aw (>.6) with with supporting antimicrobial effectiveness data over the entire product shelf life
Route of Administration	Moderate		Oral Liquid
Product Vulnerability Rating	P2		N/A
Target Patient/Consumer	Pediatric/ geriatric	Immunoco-mpromised	Oral liquid intended for over-the-counter sale
Patient Vulnerability Rating	S2	S3	N/A
Organism Pathogenicity	True Pathogen		S.Pneumonia is a respiratory pathogen, resides in the respiratory track of carriers, not always pathogenic.
Organism Designation	Objectionable		S.Pneumonia could be pathogenic to either the pediatric/geriatric or immunocompromised populations, objectionable.

Patient Vulnerability Rating	Organism Pathogenicity: Non-pathogenic	Opportunistic Pathogen	True Pathogen
S3	Not Objectionable	Objectionable	Objectionable
S2	Not Objectionable	Conditional*	Objectionable
S1	Not Objectionable	Not Objectionable	Conditional*



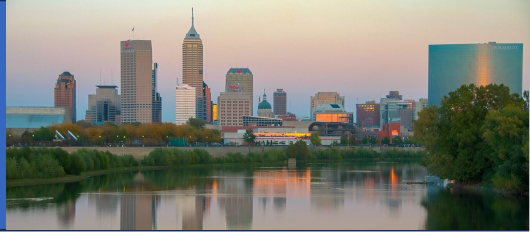
After the assessment

- **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

- Booth, C (2019). Regulatory Expectations for Objectionable Organisms in Nonsterile Pharmaceuticals. Pharmaceutical Online, April 5, 2019.
- Booth, C (2019). Risk Assessment of Objectionable Organisms in Nonsterile Pharmaceuticals. Pharmaceutical Online, April 19, 2019.
- Code of Federal Regulations (CFR) Title 21
- Cundell, T.(2019). Microbial Contamination Risk Assessment in Non-sterile Drug Product Manufacturing and Risk Mitigation. In D. Roesti (Ed.), *Pharmaceutical Microbiological Quality Assurance and Control: Practical Guide for Non-Sterile Manufacturing*. essay, John Wiley & Sons, Inc.
- Cundell, T. (2019). Exclusion of Objectionable Microorganisms from Non-sterile Pharmaceutical Drug Products. In D. Roesti (Ed.), *Pharmaceutical Microbiological Quality Assurance and Control: Practical Guide for Non-Sterile Manufacturing*. essay, John Wiley & Sons, Inc.
- McFarland, A (2018). Risk-Based Microbial Assessment Tool (R-MAT): A Novel Approach to Assessing Environmental and Critical Utilities Excursions. American Pharmaceutical Review, February 16, 2018.
- PDA TR 67, Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics
- Sutton, S. Ph.D. (2006) How to Determine if an Organism is “Objectionable”. The Microbiology Network. July, 2006.
- Sutton, S. Ph.D. (2012) What is an “Objectionable Microorganism”. American Pharmaceutical Review, October 12, 2012.



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