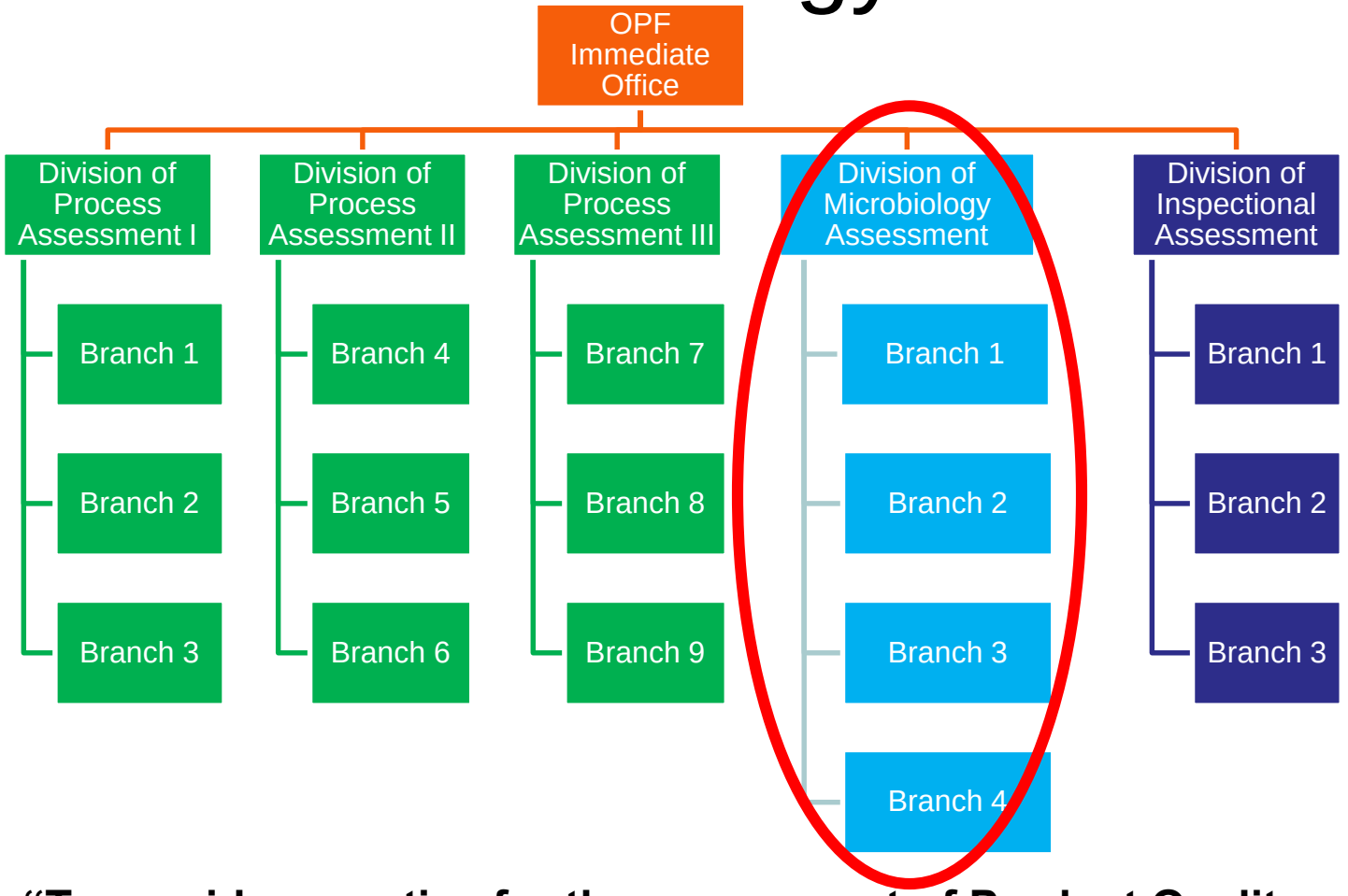
Microbiological Controls for Non-Sterile Drug Products

Erika Pfeiler, PhD

FDA/CDER/OPQ/OPF/Division of Microbiology Assessment

July 20, 2016

Division of Microbiology Assessment



"To provide expertise for the assessment of Product Quality Microbiology to support FDA's public health mission"

Background

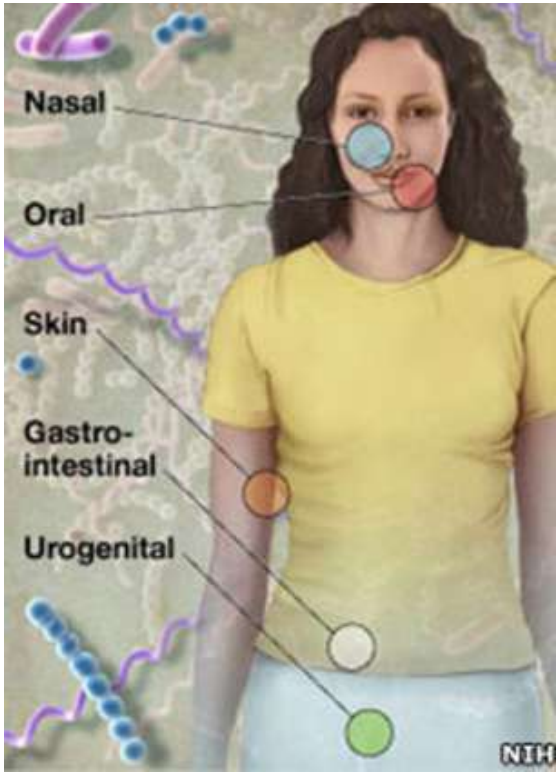
- Microbiology 101
  - Microorganisms (bacteria, yeast, mold) are ubiquitous in the environment.
    - Most are harmless to humans, but some can cause illness.
  - Manufacturers of products, such as foods and drugs, work to control the presence of microorganisms in their products.
    - Different types of products require different levels of microbial control.

Background

- Some pharmaceutical products must be sterile (completely free of viable microorganisms)
  - Injectables, ophthalmics, aqueous inhalation
- Most pharmaceutical products do not have to be sterile, but should have limits on the numbers and types of microorganisms that they may contain

Background

- The body's natural defenses are sufficient to prevent infection from normal exposure to microbes
  - Too many microbes, or the wrong kinds of microbes may cause infection
  - Depending on the indication, some products may require sterility (topical drugs for burns or wounds, products for patient skin preparation)



Agenda

- Control in pharmaceutical development
- Control in manufacturing
- Control in release/stability testing

Nonsterile Drug Products

- Solid ← Low water activity (a_w)
- Non-solid
  - Aqueous
  - Non-aqueous

Differentiated by water activity (a_w)
Generally, a water activity of < 0.6 is considered non-aqueous

Water activity (a_w) is distinct from water content – see USP <1112>

Solid, Non-aqueous

Aqueous

Lower a_w

Higher a_w

Nonsterile Drug Products

- Solid
- Non-solid
  - Aqueous
  - Non-aqueous

Risk can be increased or decreased based on whether the product is growth promoting or has antimicrobial properties (including the addition of preservatives)

Nonsterile Drug Products

- If a product is aqueous and multi-dose, it must contain an antimicrobial preservative or be self-preserving.

Table 1. Compendial Product Categories

Category	Product Description
1	Injections; other parenterals including emulsions, otic products, sterile nasal products, and ophthalmic products made with aqueous bases or vehicles
2	Topically used products made with aqueous bases or vehicles; nonsterile nasal products and emulsions, including those applied to mucous membranes

Table 1. Compendial Product Categories *(Continued)*

Category	Product Description
3	Oral products other than antacids, made with aqueous bases or vehicles
4	Antacids made with an aqueous base

  - From USP <51>
  - Test at or below the lowest specified preservative content

Agenda

- Control in pharmaceutical development
- Control in manufacturing
- Control in release/stability testing

Microbiology of Nonsteriles

- Where do microorganisms in nonsterile products come from?
  - They may be present in raw materials
  - They may be present in the manufacturing environment
  - They may proliferate in the product during manufacturing and storage
- All of these conditions can be controlled.

Microbiology of Nonsteriles

- Control of Raw materials
  - These are controlled by the drug substance/excipient manufacturer.
  - Many compendial excipients have microbial limits.
  - USP <1111> recommends limits for nonsterile substances for pharmaceutical use.
    - 10^3 colony forming units (CFU)/g total aerobic microbial count (TAMC), no more than 10^2 CFU/g total yeast and mold count (TYMC), and the absence of *Escherichia coli*

Microbiology of Nonsteriles

- Control of the manufacturing environment
  - Firms should be compliant with cGMPs
    - Cleaning, EM
  - Water systems

Microbiology of Nonsteriles

- Potential to proliferate in the product during manufacturing and storage
  - Most of what microorganisms need in order to proliferate is food, water, and time
    - If you can't control their food and water, control their time
  - Note that even if a finished product has a low water activity, extended aqueous hold steps may promote microbial proliferation.
    - Limit hold times, perform microbiological hold time studies

Agenda

- Control in pharmaceutical development
- Control in manufacturing
- Control in release/stability testing

Microbiological Product Specifications

Specification = Test + Method + Acceptance Criteria

- Preservative content
- Antimicrobial Effectiveness
  - Should be performed routinely according to ICH Q1A (R2) section 2.2.6

Microbiological Product Specifications

Specification = Test + Method + Acceptance Criteria

- Microbial Limits Specification
  - Microbial enumeration
    - Typically performed using methods described in USP <61>
  - Absence of specified microorganisms
    - Typically performed using methods described in USP <62>

But what should the acceptance criteria be?

Microbiological Product Specifications

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.

- What is an “objectionable organism”?
- Not an easy answer!
  - What patient population is your product intended for?
  - What route of administration is your product intended for?

Microbiological Product Specifications

- USP <1111> recommends microbial limits based on the product's route of administration.

Table 1. Acceptance Criteria for Microbiological Quality of Nonsterile Dosage Forms

Route of Administration	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)	Specified Microorganism(s)
Nonaqueous preparations for oral use	10^3	10^2	Absence of *Escherichia coli* (1 g or 1 mL)
Aqueous preparations for oral use	10^2	10^1	Absence of *Escherichia coli* (1 g or 1 mL)
Rectal use	10^3	10^2	—
Oromucosal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or1 mL)

Microbiological Product Specifications

- *Burkholderia cepacia* complex
  - Species in this complex are capable of surviving and proliferating in the presence of antimicrobial preservatives.
  - Should perform a risk assessment identifying areas where this microorganism may contaminate the product (e.g. water systems)

Further reading:
Burkholderia cepacia: This Decision is Overdue.
Torbeck, et. al. 2011.

Microbiological Product Specifications

- *Burkholderia cepacia* complex
  - No compendial method, so validation studies are recommended to be performed for detection tests
  - Many common detection media or tests focus on clinical isolates, which have different characteristics from those isolated from a manufacturing environment
    - Recommend that validation testing utilize multiple strains
    - Recommend that strains be ‘preconditioned’ so validation most closely mimics product testing

Stay Tuned!

- FDA Publication
  - Microbiological Quality Considerations in Non-sterile Pharmaceutical Product Manufacturing: A Concept Paper

Summary

- Control in pharmaceutical development
  - Consideration of water activity
  - Use of preservatives
- Control in manufacturing
  - Environmental controls
  - Limiting hold times for aqueous products/intermediates
- Control in release/stability testing
  - Microbial limits and preservative content/AET
  - USP <1111> describes recommended microbiological acceptance criteria

erika.pfeiler@fda.hhs.gov

Please evaluate this session:

surveymonkey.com/r/PQS-D1S3