U.S. FOOD & DRUG ADMINISTRATION

Welcome!

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Division of Drug Information

Office of Communications | CDER | FDA

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Division of Microbiology Assessment: Organizational Overview and Recommendations for Nonsterile Products

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Division of Microbiology Assessment
Office of Process & Facilities
Office of Pharmaceutical Quality
Center for Drug Evaluation & Research
U. S. Food & Drug Administration

SBIA Webinar
15 March 2017

“One Quality Voice”

One Quality Voice for Drugs:
OPQ will centralize quality drug review — creating one quality voice by integrating quality review, quality evaluation, and inspection across the product lifecycle.

One Quality Voice for Patients:
OPQ will assure that quality medicines are available for the American public.

One Quality Voice for Industry:
OPQ will establish consistent quality standards and clear expectations for industry.

One Quality Voice for Health Care Professionals:
OPQ will anticipate quality problems before they develop and help prevent drug shortages.

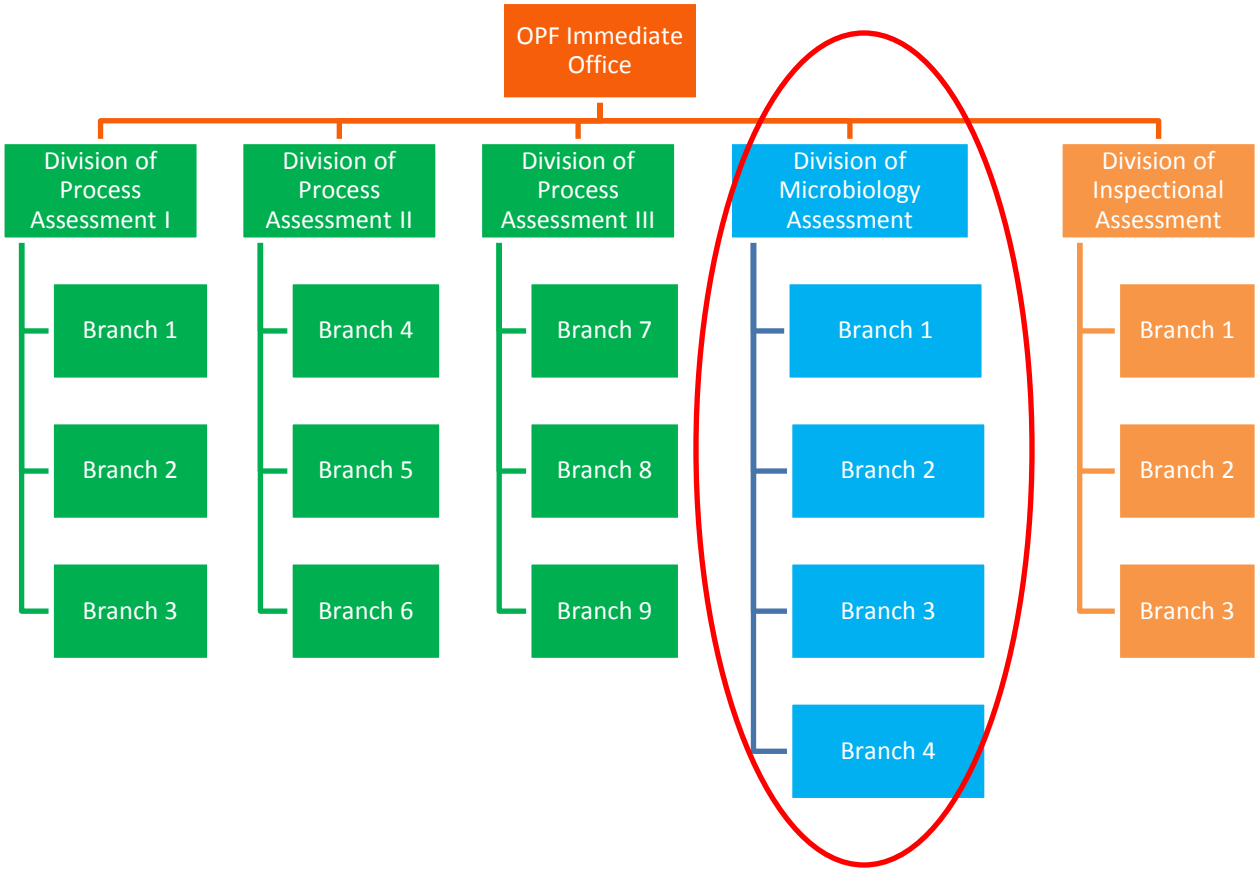
One Quality Voice for Health Care Purchasers:
OPQ will emphasize quality metrics.

Office of Pharmaceutical Quality

- Office of Program and Regulatory Operations
- Office of Policy for Pharmaceutical Quality
- Office of Testing and Research
- Office of New Drug Products
- Office of Biotechnology Products
- Office of Lifecycle Products
- **Office of Process and Facilities**
- Office of Surveillance

“OPF assures that quality pharmaceuticals are consistently manufactured over the product lifecycle”

Division of Microbiology Assessment



“To provide expertise for the assessment of Product Quality Microbiology to support FDA’s public health mission”

OPF Division of Microbiology Assessment

Program Support
Vera Viehmann
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Lynne Ensor
Director (Acting)

Administrative Support
Melody Lescalleet (III & IV)
Sheila Henson (I & II)

BRANCH I	BRANCH II	BRANCH III	BRANCH IV
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Branches I-III

(small molecules)

- Legacy OPS/IO (NDMS) & OGD Division of Microbiology
- Assessment of:
  - NDAs (originals & supplements)
  - ANDAs (originals & supplements)
  - INDs
  - DMFs
  - Meeting packages

Branch IV
(large molecule)

- Portion of legacy OC/BMAB staff
- Assessment of:
  - BLAs (originals & supplements)
  - INDs
  - DMFs
  - Consults from other centers (e.g., CBER, CDRH, CVM)
  - Meeting Packages
- Inspections
  - Typically lead PAI/PLI inspections for BLA drug substance
  - Participate as SMEs on other BLA inspections

Additional DMA Activities

- Subject matter experts for emerging issues:
  - Drug shortage & recall activities
  - Facility issues
  - Drug issues (focus on potential contamination concerns)
- Participation in policy development
  - With both internal & external organizations

    (e.g., FDA, PDA, USP, AAMI, GPhA, etc.)

Additional DMA Activities (2)

- Collaboration/Outreach with scientific organizations
- Training

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Recommendations for Nonsterile Products

SBIA Webinar
15 March 2017

Considerations for Non-sterile Product Quality Attributes – Patient Risk

- What's the risk to patients?
  - Infection from:
    - Exposure to excessive numbers of microorganisms
    - Exposure to pathogenic microorganisms
  - Degradation of product through microbiological activity

Considerations for Non-sterile Product Quality Attributes – Patient Risk

- **Route of Administration**
  - E.g., gastrointestinal, mucosal, dermal (transdermal patches w/ microneedles), inhalation, etc.
  - Normal flora
  - Environmental factors (pH, mucous membrane)
- **Patient Population**
  - Infants
  - Elderly
  - Immunocompromised
- **Dosage form/Formulation**
  - Emulsion, oil, **water activity**, etc.

Considerations for Non-sterile Product Quality Attributes – Patient Risk

- Risks come from contamination of the product and/or proliferation of microorganisms in the product.
- Product formulation and manufacturing control play a large role in mitigating risks.
  - These should be considered when determining the level of manufacturing control, product testing schedule, and microbiological specification

Nonsterile Products and Water

- Water is necessary for microbial *proliferation*
- Nonsterile products contain microorganisms – must control water (or other factors) to limit proliferation
- Products with no water present are lower risk, reflected by testing
- Aqueous ≠ Liquid

There's a reason why the search for water = the search for life!

USP <51>

cause of the addition of an antimicrobial preservative, must be demonstrated for all injections packaged in multiple-dose containers or for other products containing antimicrobial preservatives. Antimicrobial effectiveness must be demonstrated for aqueous-based, multiple-dose topical and oral dosage forms and for other dosage forms such as ophthalmic, otic, nasal, irrigation, and dialysis fluids (see *Pharmaceutical Dosage Forms* ⟨1151⟩). For the purpose of the test, aqueous is defined as a water

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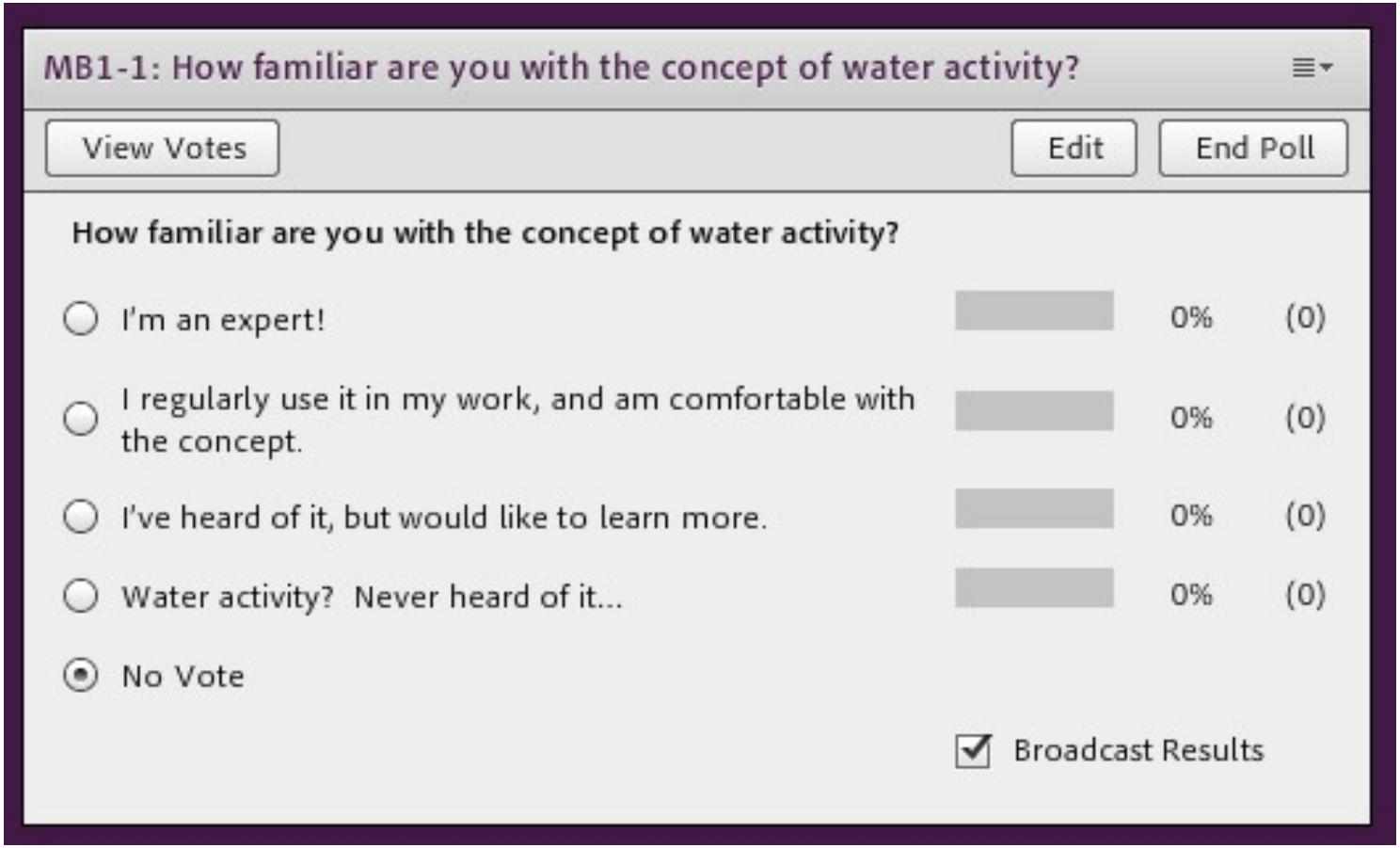


Water Activity

- $a_w = \frac{P}{P_o}$
  - P = vapor pressure of water in a substance
  - P_o = vapor pressure of pure water

- "Bound" vs. "Free" water
  - Higher a_w, more water is free or available
  - Higher a_w, more risk for microbial proliferation

Water Activity

- Frequently confused with water content
- Very formulation dependent
- Magic number = 0.6

Table 2. Microbial Limit Testing Strategy for Representative Pharmaceutical and OTC Drug Products Based on Water Activity

Products	Water Activity (a_W)	Greatest Potential Contaminants	Testing Recommended
Nasal inhalant	0.99	Gram-negative bacteria	TAMC,* TCYMC, absence of *S. aureus* and *P. aeruginosa*
Hair shampoo	0.99	Gram-negative bacteria	TAMC, TCYMC, absence of *S. aureus* and *P. aeruginosa*
Antacid	0.99	Gram-negative bacteria	TAMC, TCYMC, absence of *E. coli* and *Salmonella* spp.
Topical cream	0.97	Gram-positive bacteria	TAMC, TCYMC, absence of *S. aureus* and *P. aeruginosa*

Non-sterile Drug Products

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

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

Sources of Microorganisms in Pharmaceutical Manufacturing

- **Contamination**
  - **Raw Materials**
    - **WATER**
  - **Manufacturing Environment**
    - **OPERATORS**
- **Proliferation**
  - **Manufacturing Process**

CONTROL IS KEY!!!

Control of Non-sterile DRUG PRODUCTS

- **Widely accepted test methods and acceptance criteria for drug products**
  - **USP <61>** *Microbial Enumeration Tests*
  - **USP <62>** *Tests for Specified Organisms*
  - **Total Aerobic Microbial Counts & Total Combined Yeast & Mold Count**
- **Acceptance criteria for specific microorganisms**
  - **USP <1111>**

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)

Table 1. Acceptance Criteria for Microbiological Quality of Nonsterile Dosage Forms *(Continued)*

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)
Gingival use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Cutaneous use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Nasal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Auricular use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Vaginal use	10^2	10^1	Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
			Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Candida albicans* (1 g or 1 mL)
Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of *Staphylococcus aureus* (1 patch)
			Absence of *Pseudomonas aeruginosa* (1 patch)
Inhalation use (special requirements apply to liquid preparations for nebulization)	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
			Absence of bile-tolerant Gram-negative bacteria (1 g or 1 mL)

Control of Non-sterile DRUG PRODUCTS

- **ICH Q6A *Test Procedures & Acceptance Criteria for New Drug Substances & New Drug Products: Chemical Substances***
  - Recommendations for conditions which may allow for 'periodic or skip testing' of microbial enumeration testing
  - Upstream controls
  - Component bioburden controls
  - Low product a_w
  - Manufacturing history
  - Typically solid oral dosage forms

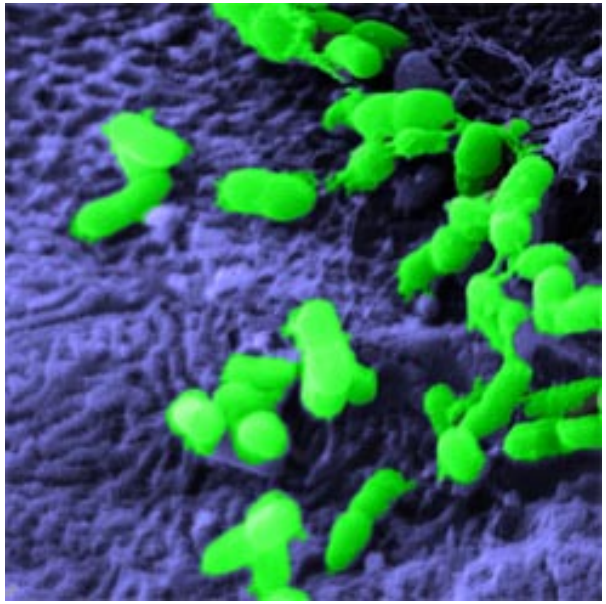
Control of Non-sterile DRUG PRODUCTS

- **If a product is aqueous and multi-dose, it must contain an antimicrobial preservative or be self-preserving (USP <51>).**
  - **Testing during development should be at or below the lowest specified preservative (or API [if self-preserving]) content**

- **Preservative content testing may be used as a surrogate for some testing timepoints**
  - **Once validated, preservative content may be used as a surrogate, BUT *testing should be performed at the end of shelf life, per ICH Q1A.***

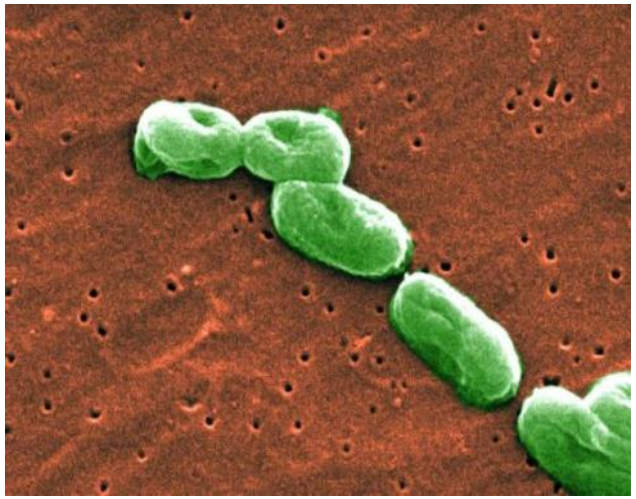
Burkholderia cepacia complex

- **Concern for aqueous products**
- **Resistance/persistence**
  - organic solvents, antiseptics, disinfectants, low nutrients
- **Multi-drug resistance**
  - Efflux pumps
- **Commonly cultured on BC agar**



BCC Recommendation: Aqueous Non-sterile Drug Products

- Provide BCC risk mitigation strategy
- Provide test method & acceptance criteria to demonstrate drug product free of BCC
- Potential validation for BCC test method
  - USP chapter??



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Recent BCC Drug Incidents

FDA Updates on Multistate Outbreak of Burkholderia cepacia Infections

UPDATE [10/12/2016]: FDA and CDC find direct link of contaminated water at PharmaTech to the multistate B. cepacia outbreak

An FDA investigation associated with a multistate outbreak has identified the bacteria, Burkholderia cepacia in more than 10 lots of oral liquid docusate sodium manufactured by PharmaTech, Davie, Florida. The investigation also detected B. cepacia in the water system used to manufacture the product. These products were manufactured by PharmaTech and distributed and labeled by six firms – Rugby, Major, Bayshore, Metron, Centurion, and Virtus.

- **Hospitalized Patients**
  - **60 cases, 8 states (CDC)**
  - **Pediatric or adult intensive care**

Recent BCC Drug Incidents

Nurse Assist Inc. Recalls Normal Saline Flush IV Syringes Due to Possible Burkholderia Cepacia Bloodstream Infections

The FDA has identified this as a Class I recall, the most serious type of recall. Use of these devices may cause serious injuries or death.

- **Hospitalized patients**
  - **162 cases, 5 states (CDC)**
  - **Long-term care or rehabilitation facilities**

Recent BCC Drug Incidents

Sage Products Issues Voluntary Nationwide Recall of Comfort Shield Barrier Cream Cloths Due to Microbial Contamination

CARY, IL, USA July 29, 2016 -- Sage Products announced today it is voluntarily initiating a nationwide recall of one lot of Comfort Shield Barrier Cream Cloths to the distributor and health care facility/user level. The recall is being initiated due to product contamination with the bacteria, *Burkholderia cepacia*.

- **No adverse events reported**

Other Recent DMA SME Activity for Non-sterile Contamination Events

- **Rx Non-sterile Nasal Spray** (*Burkholderia multivorans*)

- **2016 OTC Contaminations**
  - **Topical Cough Relief Ointment**
    (*Pseudomonas fluorescens/putida*)
  - **Shampoo, lotions, hair products**
    (*Staphylococcus aureus*)

Summary

- **Top priority = risk to patients**

- **Risk comes from microbial contamination and/or proliferation in the product**

Summary

- Risk can be mitigated by controlling the formulation and the manufacturing environment
  - There is no one-size-fits-all approach to risk mitigation
  - End-product testing demonstrates that these aspects have been suitably addressed

Summary

- **Impending publication for microbiological control of non-sterile products**

Contact Information

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THANK YOU