

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



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Acting Quality Assessment Lead

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

“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

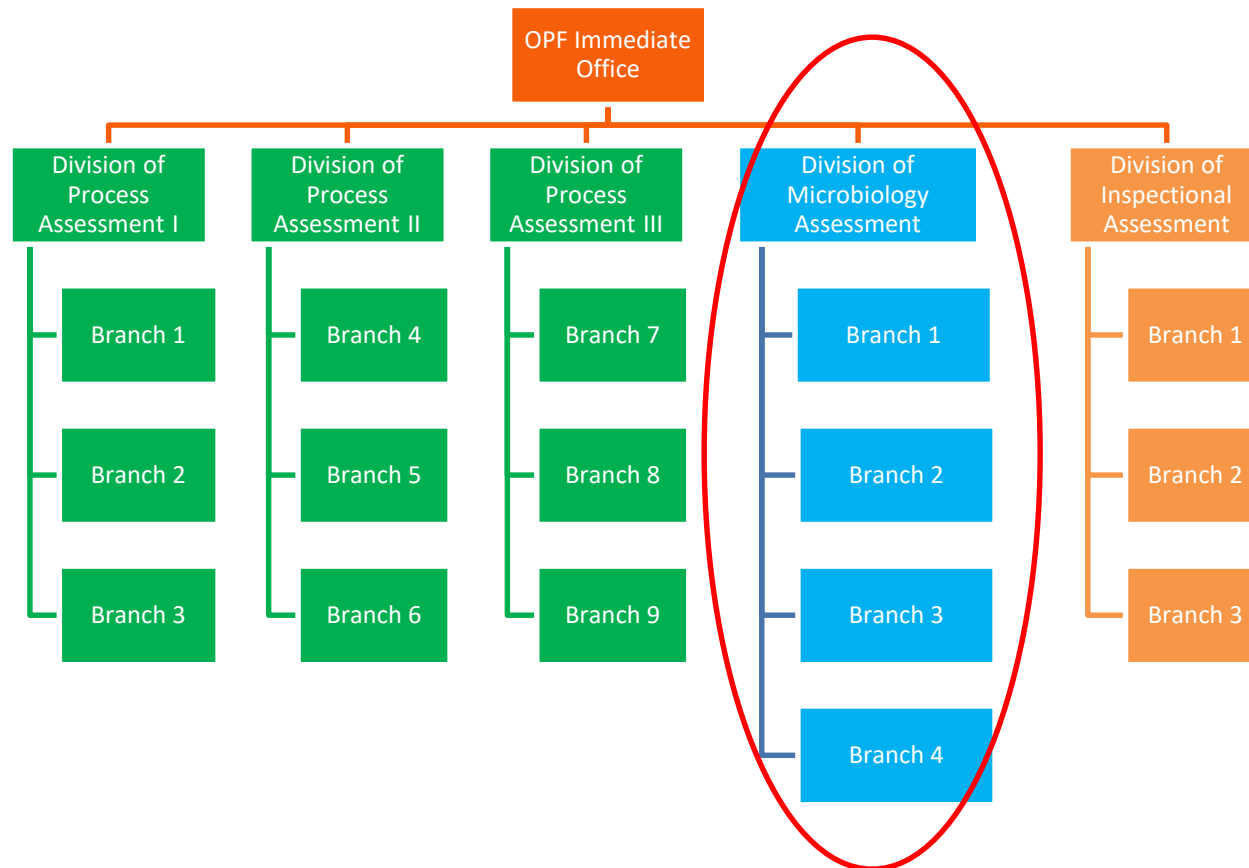
Office of
Process
and
Facilities

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”

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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





Recommendations for Nonsterile Products

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.

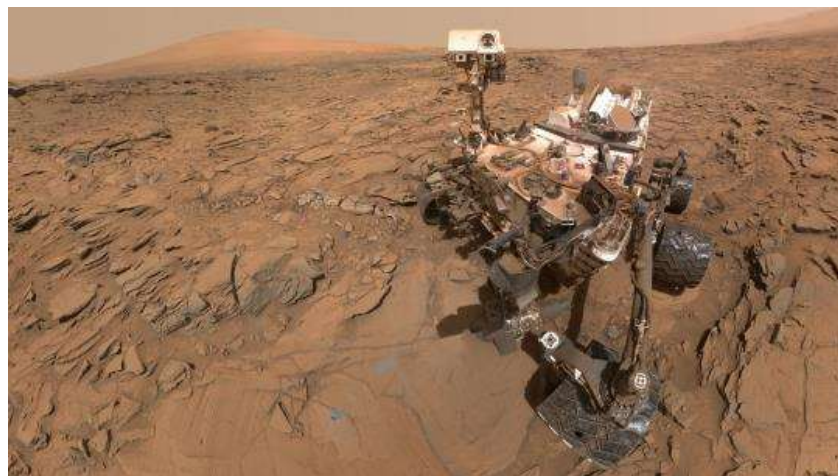
Considerations for Non-sterile Product Quality Attributes – Patient Risk

- 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 activity of more than 0.6 (see *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* <1112>).

Poll

MB1-1: How familiar are you with the concept of water activity? ☰

How familiar are you with the concept of water activity?

<input type="radio"/> I'm an expert!	<div style="width: 0%;"></div>	0%	(0)
<input type="radio"/> I regularly use it in my work, and am comfortable with the concept.	<div style="width: 0%;"></div>	0%	(0)
<input type="radio"/> I've heard of it, but would like to learn more.	<div style="width: 0%;"></div>	0%	(0)
<input type="radio"/> Water activity? Never heard of it...	<div style="width: 0%;"></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

Broadcast Results

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 <i>S. aureus</i> and <i>P. aeruginosa</i>
Hair shampoo	0.99	Gram-negative bacteria	TAMC, TCYMC, absence of <i>S. aureus</i> and <i>P. aeruginosa</i>
Antacid	0.99	Gram-negative bacteria	TAMC, TCYMC, absence of <i>E. coli</i> and <i>Salmonella</i> spp.
Topical cream	0.97	Gram-positive bacteria	TAMC, TCYMC, absence of <i>S. aureus</i> and <i>P. aeruginosa</i>

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 ¹	10 ²	Absence of <i>Escherichia coli</i> (1 g or 1 mL)
Aqueous preparations for oral use	10 ²	10 ¹	Absence of <i>Escherichia coli</i> (1 g or 1 mL)
Rectal use	10 ¹	10 ²	—
Oromucosal use	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1 g or 1 mL) Absence of <i>Pseudomonas aeruginosa</i> (1 g or 1 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 <i>Staphylococcus aureus</i> (1 g or 1 mL)
			Absence of <i>Pseudomonas aeruginosa</i> (1 g or 1 mL)
Cutaneous use	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1 g or 1 mL) Absence of <i>Pseudomonas aeruginosa</i> (1 g or 1 mL)
Nasal use	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1 g or 1 mL)
			Absence of <i>Pseudomonas aeruginosa</i> (1 g or 1 mL)
Auricular use	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1 g or 1 mL)
			Absence of <i>Pseudomonas aeruginosa</i> (1 g or 1 mL)
Vaginal use	10 ²	10 ¹	Absence of <i>Pseudomonas aeruginosa</i> (1 g or 1 mL)
			Absence of <i>Staphylococcus aureus</i> (1 g or 1 mL)
			Absence of <i>Candida albicans</i> (1 g or 1 mL)
Transdermal patches (limits for one patch including adhesive layer and backing)	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1 patch)
			Absence of <i>Pseudomonas aeruginosa</i> (1 patch)
Inhalation use (special requirements apply to liquid preparations for nebulization)	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1 g or 1 mL)
			Absence of <i>Pseudomonas aeruginosa</i> (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

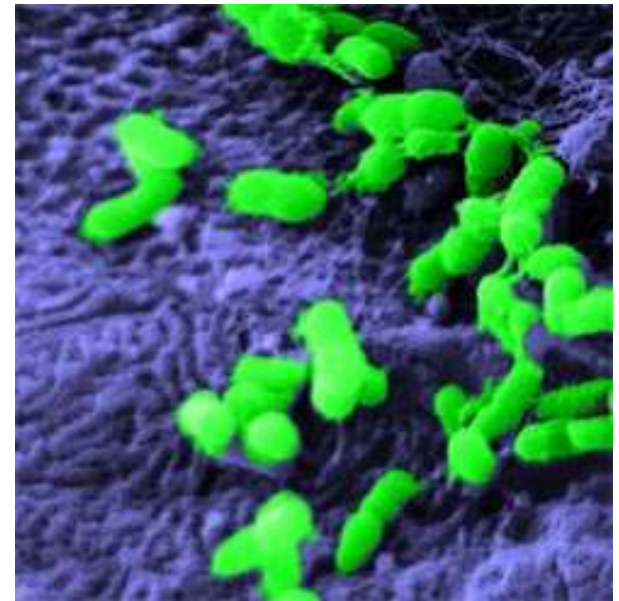
Control of Non-sterile DRUG PRODUCTS

- 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

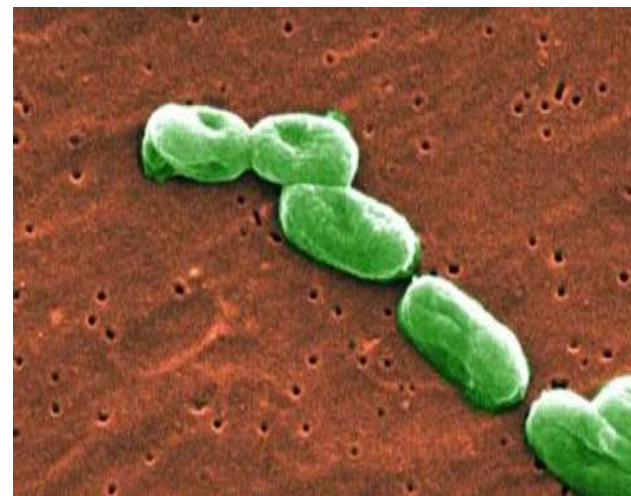
- **Concern for aqueous products**
- **Resistance/persistence**
 - organic solvents, antiseptics, disinfectants, low nutrients
- **Multi-drug resistance**
 - Efflux pumps
- **Commonly cultured on BC agar**



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??



Poll

MB1-2: If your company manufactures nonsterile products... ☰

If your company manufactures nonsterile products, has a risk assessment for BCC contamination been performed?

<input type="radio"/> We have performed a risk assessment, and conduct routine monitoring activities.	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> We have performed a risk assessment, but have not implemented any monitoring activities.	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> We have not performed any BCC risk assessment.	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> My company does not manufacture nonsterile products.	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> I'm not sure...	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

Broadcast Results

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



Thanks!



CDER Case Study: A Microbial Investigation of Contamination by *Burkholderia multivorans*

John W. Metcalfe, Ph.D.

Master Review Microbiologist

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

March 15, 2017



Disclaimer

- The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA

Presentation Themes

- *Burkholderia Cepacia Complex* (BCC) and Pharmaceutical Water Systems
- BCC and Biofilm Formation
- BCC and Resistance to Antimicrobial Preservative Systems
- BCC and Aqueous, Non-sterile Drugs

Code of Federal Regulations

- Sec. 211.113 Control of microbiological contamination
 - a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

Code of Federal Regulations

- Sec. 211.165 Testing and release for distribution.

b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

Poll

MB2-1: For Pharmaceutical Microbiologists... ☰

For Pharmaceutical Microbiologists: Do you agree with the statement, "My work on non-sterile drugs is MORE challenging than my work on sterile drugs."

<input type="radio"/> Strongly Agree	<div style="width: 0%;"></div>	0%	(0)
<input type="radio"/> Agree	<div style="width: 0%;"></div>	0%	(0)
<input type="radio"/> Neutral	<div style="width: 0%;"></div>	0%	(0)
<input type="radio"/> Disagree	<div style="width: 0%;"></div>	0%	(0)
<input type="radio"/> Strongly Disagree	<div style="width: 0%;"></div>	0%	(0)
<input type="radio"/> (Not a Microbiologist)	<div style="width: 0%;"></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

Broadcast Results

CFR: Field Alert Reports

- Sec. 314.81

(1) *NDA-- field alert report* . The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written follow up. The report and its mailing cover should be plainly marked: "**NDA-- field alert report.**"

CFR: Field Alert Reports

- Sec. 314.81(1)(ii)

Information concerning any **bacteriological contamination**, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

CFR: Field Alert Reports

- FAR Form 3331 is available at:

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/HumanDrugForms/default.htm>

- A blank FAR Form 3331 is on next slide

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION NDA-FIELD ALERT REPORT		TO: (NAME AND ADDRESS OF DISTRICT)
TYPE OF REPORT <input type="checkbox"/> Initial <input type="checkbox"/> Follow-Up <input type="checkbox"/> Final		
In accordance with Section 314.81(b)(1)(i) and (ii) of the New Drug Application Regulations (21 CFR 314) promulgated under the Federal Food, Drug and Cosmetic Act, as amended, the following information is herewith submitted:		
1. NDA/ANDA 		2. NDC No.
3. GENERIC NAME OF DRUG PRODUCT 	4. TRADE/BRAND NAME (if any) OF DRUG PRODUCT 	
5. FIRM NAME AND ADDRESS WHERE PROBLEM OCCURRED 		6. FEI/CFN
7. DOSAGE FORM, STRENGTH AND PACKAGE SIZE(S) 		
8. LOT NUMBER(S) 		
9. EXPIRATION DATE(S) OF DRUG PRODUCTS 		
10. DATE WHEN NOTIFIED ABOUT PROBLEM(S) OR WHEN PROBLEM(S) FIRST BECAME KNOWN TO APPLICATION HOLDER 		
11. HOW WAS PROBLEM DISCOVERED 		
12. STATE PROBLEM(S) 		
13. ROOT CAUSE(S) OF PROBLEM(S) 		
14. CORRECTIVE ACTION(S) TAKEN (if any) TO PREVENT RECURRENCE OF PROBLEM(S) 		
15. REMARKS 		
NOTE: SEPARATE NARRATIVE REPORTS MAY BE ATTACHED IF DESIRED		
REPORTING ESTABLISHMENT		
NAME AND MAILING ADDRESS (Include ZIP Code) 		
NAME AND TITLE OF AUTHORIZED REPRESENTATIVE 		TELEPHONE (Include Area Code)
SIGNATURE OF AUTHORIZED REPRESENTATIVE 		DATE SUBMITTED



CDER/OPQ/Office of Surveillance

- FAR is attached
- FDA is meeting with firm to discuss their investigation/plan relative to the FAR
- Request OPQ/DMA SME to provide questions for discussion with firm

CDER/OPQ/Office of Surveillance

- Contacted Clinical Review Division
 - Q: Does the presence of *B. multivorans* in the subject drug product present a risk to patients?

- Clinical Review Division
 - A: Yes, this constitutes a patient risk.

Field Alert Report

- Nasal Spray approved in late 1990s
- Aqueous formulation preserved with BAC
- Two batches positive for *B. multivorans*
- Batches still in firm's control
- Additional “expanded” testing of 10 batches
 - 5 previously negative were now positive

OPQ/DMA Q's for Firm: 1st TCON

- How were the initial batches (XX and YY) of the drug product determined to contain *Burkholderia multivorans*? Was this demonstrated following testing of the drug product according to USP<61>for total aerobic bacteria, or using a *Burkholderia* specific test? What is the concentration of *Burkholderia multivorans* per mL of the drug product in these batches?
- Regarding the additional 10 product batches that underwent expanded testing, how is the “expanded test” different from the test performed at release?

OPQ/DMA Q's for Firm: 1st TCON

- Is the water system that is used to manufacture XX[®] routinely tested for organisms belonging to the *Burkholderia cepacia complex*?
- We recognize that the investigation of this incident has not yet determined a root cause. Summarize the steps of the drug product manufacturing process that you have tested for evidence of *Burkholderia multivorans*.
- What is your plan for the drug product batches that contain *Burkholderia multivorans*?

TCON: FDA/Firm

- *B. multivorans* was picked up using Bile-Tolerant Gram Neg method in USP<62>
- Batches were TNTC
- Investigation: pipe in purified H₂O system not properly sanitized/engineered = Biofilm
- Firm states system was in control at time US batches were made



FDA Internal MTG Post TCON

- Team
 - CDER/OC
 - CDER/OPQ/OS
 - ORA/DO
 - CDER/OPQ/DMA

- Q: Do we need to recall the 58 batches in US commerce?



FDA Internal MTG Post TCON

- CDER/OPQ/DMA Comments
- Product was approved in late 90s
 - No record of an FDA micro review of the product
 - Unknown:
 - Are all batches subject to microbiological testing at release?
 - If so, what methodology is used?
 - The product is preserved: are the methods suitable for use with the subject drug product?

Additional Qs Forwarded to Firm

- Regarding the 58 lots of XX[®] that are currently in the US market, provide the test methods, acceptance criteria and data summaries from all microbiological testing performed on the drug product at release. Include data summaries demonstrating that the microbiological test methods are suitable for use with the drug product.
- Provide the stability protocol for XX[®]. Provide data summaries for any microbiological testing that has been performed to date on the XX[®] lots that are currently in the US market.

OPQ/DMA Assessment of Firm's Response: Memo for CDER

- The firm routinely performs microbiological release testing on XX[®] in excess of what is recommended in *USP<1111>Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use.*

OPQ/DMA Assessment of Firm's Response: Memo for CDER

- The microbiological release testing performed on XX[®] is performed according to methods described in *USP<61>Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and *USP<62>Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*.

OPQ/DMA Assessment of Firm's Response: Memo for CDER

- The firm has satisfactorily performed testing to demonstrate that the microbiological test methods are suitable for use with XX[®], including in the recovery of *Burkholderia multivorans*.
- The microbiological release test data on the 58 batches of XX[®] in the US market meet acceptance criteria and are acceptable.

OPQ/DMA Assessment of Firm's Response: Memo for CDER

- Microbiological testing of XX[®] samples in the stability program is routinely performed. Stability data to date meet acceptance criteria and are acceptable.



OPQ/DMA Assessment of Firm's Response-Summary to CDER

- This reviewer acknowledges that end product release testing presents limitations with regard to predicting quality of a given product batch.
- However, the information provided to the Agency by the firm regarding the microbiological release and stability testing does not suggest that a product recall of the 58 batches of XX[®] currently in the US market is warranted from the standpoint of microbiological contamination.

Additional Information: Firm's Investigation

- A study was performed to evaluate the growth potential of the contaminant in the drug product
- Of note:
 - The contaminant counts decrease over first few days
 - Day 3: start of log phase growth in the preserved drug
 - Day 7: counts $> 10^5$ CFU/mL of preserved drug

Growth Kinetic Study: BCC in XX[®]

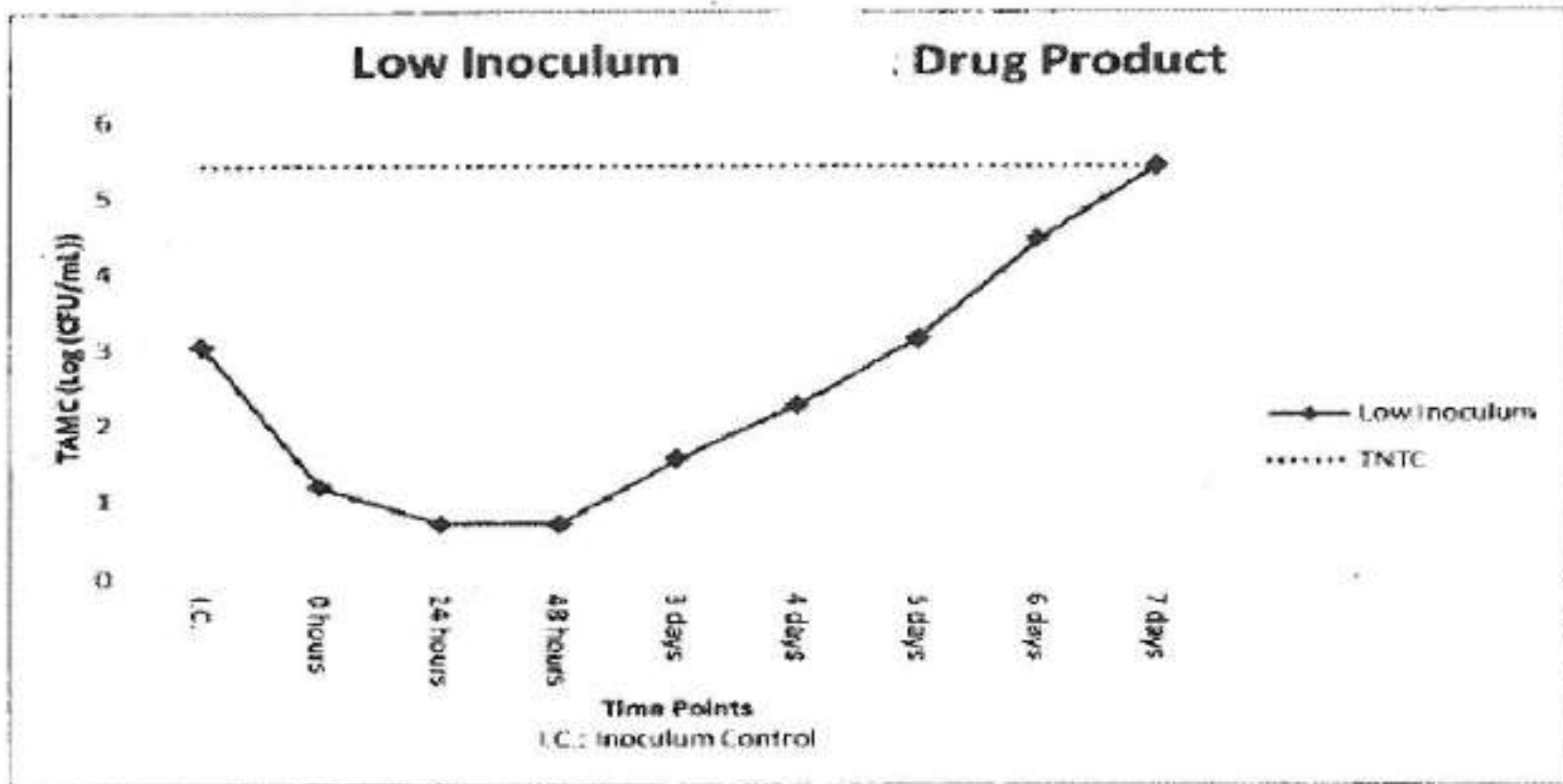


Figure 1 Low inoculum growth kinetics

Growth Kinetic Study: BCC in XX[®]

- Performing the study provided the firm with an understanding of this organism in this product
- May explain picking up the organism using the “expanded” testing
- Provided the firm with an avenue for corrective actions regarding future micro testing of this product

Additional Information: Firm's Investigation



- Testing was performed on retain samples from batches in US market
- Expanded Testing Sequence:
 - Initial: 10 batches tested with 5 batches positive
 - Next: 25 marketed batches manufactured prior to the original 10
 - None of these batches tested positive



Additional Information: Firm's Investigation

- Information from expanded testing of 35 batches
- Points to timeframe for biofilm formation
- Provided some assurance regarding patient safety and product in the market



Status of Drug Product Batches Following Expanded Testing

DOM	Marketed (Y/N)	Routine Release: Bacteria detected	Investigational Testing : Bacteria detected
2-Oct-14	Y	No	No
13-Oct-14	Y	No	No
18-Oct-14	Y	No	No
21-Oct-14	Y	No	No
3-Nov-14	Y	No	No
5-Nov-14	Y	No	No
9-Nov-14	Y	No	No
28-Oct-14	Y	No	No
12-Nov-14	Y	No	No
12-Nov-14	Y	No	No
16-Nov-14	Y	No	No
29-Nov-14	Y	No	No
14-Dec-14	Y	No	No
04-Jan-15	Y	No	No
13-Jan-15	Y	No	No
18-Jan-15	Y	No	No
01-Feb-15	Y	No	No
04-Feb-15	Y	No	No
14-Mar-15	Y	No	No
13-Apr-15	Y	No	No
20-Apr-15	Y	No	No
26-Apr-15	Y	No	No
29-Apr-15	Y	No	No
03-May-15	Y	No	No
05-May-15	Y	No	No
11-May-15	N	No	No
17-May-15	N	No	No
25-May-15	N	No	No
01-Jun-15	N	No	No
07-Jun-15	N	No	Yes
09-Jun-15	N	No	Yes
14-Jun-15	N	No	Yes
16-Jun-15	N	No	Yes
21-Jun-15	N	No	Yes
24-Jun-15	N	Yes	Yes
29-Jun-15	N	No	No
12-Jul-15	N	Yes	Yes

Summary: Case Study

- **No Recall**
- Firm implemented corrective actions following investigation
 - Re-engineered the bad plumbing
 - Improved sanitization
 - Eyes are wide open for BCC
 - Expanded micro testing for 12 months
 - Modified start time of microbiological release testing based on growth kinetics study



Summary: General Comments

- Industry wants FDA to base decision making on science and risk
 - for drugs: this means risk to patient
- CDER understands this and we agree
- In cases where scientific data are not available, then patient risk cannot be assessed by CDER, and questions arise

Summary: General Comments



- To avoid negative business outcomes such as:
 - delays in drug approvals
 - FDA enforcement action
 - product recalls
- Industry needs to be ready to provide CDER with scientific data when it is requested



Summary: Final Comments

- CDER Microbiologists understand that
“*E .coli* Happens”
- The question becomes,
“How does your firm respond when *E. coli*
hits the fan?”

Reference Material

- [21 CFR 211.113\(a\)](#) Control of microbiological contamination
- [21 CFR 211.165\(b\)](#) Testing and release for distribution
- [21 CFR 314.81\(1\)\(ii\)](#) NDA Field alert reports



THANK YOU

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Building a Better Sterility Assurance Application

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CDER/FDA

CDER SBIA Webinar
March 15, 2017

Overview

- Best practices
- Common deficiencies
- References

Two Polls

How interested are you in manufacturing a STERILE drug product? ☰

How interested are you in manufacturing a STERILE drug product?

<input type="radio"/> A little; but no current plans to manufacture a sterile product	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> Interested; but not preparing any applications for sterile products	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> Very interested; actively preparing applications for sterile products	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> I'm not really sure...			
<input checked="" type="radio"/> No Vote			

MB3-2: What type of application will you be preparing? ☰

What type of application will you be preparing?

<input type="radio"/> New Drug Application	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> Abbreviated New Drug Application	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> Biologic License Application	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> Various	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input type="radio"/> None planned at this time	<div style="width: 100%; height: 10px; background-color: #ccc;"></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

Broadcast Results

Best Practices

- **Best practices benefit:**
 - Application holder: less deficiencies
 - Application reviewers: review efficiency
 - Public: necessary drug products to market

Best Practices

- **Write good narrative summaries**
 - Describe the general programs and specific processes for the drug product
 - Provide adequate details
 - Describe the “what,” “why,” “how” of studies
 - No conflicting information with reports
 - Provide rationale

Best Practices

- **Reference Drug Master Files (DMFs)**
 - Proprietary information placed in DMFs
 - Provide a reference to the DMF
 - Provide current Letter of Authorization (LOA)

Common Deficiencies

- **Conflicting information identified**
 - Between narratives in different modules
 - Between narratives in different sections
 - Between summaries of documents and the details in those documents

Common Deficiencies

- **Absence of rationale or justification**
 - Validation supports the specific commercial production process
 - Validation is not always identical to production
 - Explain how validation study supports the commercial production process

Common Deficiencies

- **Absence of information for items received as sterile or depyrogenated or both**
 - Identify who performs the process
 - Describe the process
 - Indicate the location of validation information
 - Reference DMF if necessary and provide the LOA
 - Validation in the application, if possible

Common Deficiencies

- **Failure to mention the sterilization method of the product filter**
 - Filters can be sterilized by autoclave
 - Filters can be sterilized by steam in place
 - Filters can be purchased as sterile
 - Describe the commercial sterilization process
 - Provide data to validate the sterilization process

Common Deficiencies

- **Bioburden monitoring is not described**
 - Routine performance is not described
 - Point(s) of monitoring is not described
 - Monitoring location is not adequate



Compound → hold → filter 1 → hold → filter 2 → filling

Common Deficiencies

- **No pressure or vacuum conditions for container closure integrity testing**
 - For microbial ingress and dye ingress testing
 - These conditions remove air bubbles, particulates, dried product
 - These conditions “simulate” shipping conditions

Common Deficiencies

- **Unacceptable incubation conditions for Biological Indicators**
 - *G. stearothermophilus* incubation is 7 days
 - Commercial BIs available with reduced incubation times of 24-48 hours
 - Certificate of analysis refers to FDA guidance pertaining to health care facilities
 - Concern is sub-lethally injured spores

Common Deficiencies

- **Media fills are not representative of maximum production conditions**
 - Container closure system
 - Duration
 - Interventions
 - Environmental monitoring
 - Rejected or discarded units
 - Explain. Explain. Explain.

Common Deficiencies

- **Incorrect use of pooling for endotoxins testing**
 - Pooling allowed for units of 100 mL or less
 - Pool no more than 3 units
 - Must divide the maximum valid dilution (MVD) by the maximum number of pooled units
 - Concern that that high levels in one unit will be diluted out

References

- **Guidance for Industry (1994): *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products***
- **Guidance for Industry (2004) : *Sterile Drugs Products Produced by Aseptic Processing-Current Good Manufacturing Practice***

References

- **Question-Based Review (QbR) for Sterility Assurance Evaluation of an ANDA (2011)**
 - *QbR for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions*
 - Detailed product quality microbiology information begins on page 6

References

- **Guidance for Industry (2008): *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products***
- **United States Pharmacopeia (USP) <1207> *Sterile Product Packaging***
- **Guidance for Industry (2012): *Pyrogen and Endotoxins Testing: Questions and Answers***

References

- **Guidance for Industry and FDA Staff (2007): *Biological Indicator (BI) Premarket Notification [510(k)] Submissions***
- **International Organization of Standardization (ISO) *Sterilization of health care products-biological indicators-Part 1: General Requirements 11138-1:2006/(R)2010***



Thank you

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FDA



Aseptic Processing of Biological Products: Current Regulatory Issues

“Facing the Challenges of Drug Product Manufacturing”

Candace Gomez-Broughton, Ph.D.
Senior Microbiologist
FDA/CDER/OPQ/OPF/DMA/BIV

CDER Small Business and Industry Assistance Webinar
Series

CDER Microbiology Issues: A Deeper Dive

Presentation Outline

- Quality microbiology content of BLA submissions
 - Guidance documents and regulations
- Process validation: common deficiencies
 - Sterilizing filtration
 - Post-reconstitution and post-dilution storage
 - Container Closure Integrity
- Conclusions and reference slides
 - Drug product quality micro content for CDER BLAs

Laws and Regulations

- Public Health Service Act
 - Section 351 (a)(2)(C) -- Licensure of biological establishments and products
 - The **biological product must be safe, pure and potent**
 - The **facility** in which the biological product is manufactured, processed, packed, or held **must meet standards designed to assure that the biological product continues to be safe, pure and potent**
- Federal Food, Drug, and Cosmetic (FD&C) Act (1938, 1962, 1997, 2007)
 - Interprets that “biological products” are also “drugs”
 - The FFD&C Act applies to a biological product, except no application required under section 505
 - Inspection under both the provisions of both the PHS Act and the FD&C Act
- Both the PHS and FD&C Acts require that biological products must be manufactured under CGMP as described in 21 CFR 210 and 211 and 600-680

Laws and Regulations (cont.)

- Validation of aseptic and sterilization processes:
 - 21 CFR 211.113 – **Control of microbiological contamination**
 - (b) Appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes
 - ***Addresses the validation of aseptic and sterilization processes***
- Refer to 21 CFR Part 211 for additional regulations applicable to sterile drug products

BLA Content: Guidance for Sterile Drugs

- Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994)
 - Describes sterilization process validation information that should be included in an application
- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)
 - Provides guidance on how to comply with CGMP regulations
 - Use in conjunction with other compliance programs and guidance

BLA Content: Guidance for Sterile Drugs (cont.)

- Container Closure System Integrity Testing *in lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products (2008)
- Established Conditions: Reportable CMC Changes for Approved Drug and Biologics Products (2015 draft)

Common Deficiencies

- **Sterilizing filtration**
 - Refer to PDA Technical Report 26 (Sterilizing Filtration of Liquids) for general guidance.
 - Topics:
 - Integrity testing
 - Process parameters
 - Microbial retention validation
- Post-reconstitution and post-dilution storage
- Container Closure Integrity

Sterilizing Filter Integrity Testing: Common Deficiencies

- No information or insufficient information for product bubble point determination
- Test description missing or insufficient
- Acceptance criterion listed only as “pass”
 - Wetting agent not specified
 - Numerical value for “pass” not provided
- Sterilizing filter integrity test results from process validation lots not provided

Sterilizing Filtration Parameters: Common Deficiencies

- Filtration time limit (product contact time):
 - Time limit is not included in parameters
 - Proposed time limit is significantly longer than what is required for the production process and is not appropriately validated by the microbial retention study

Sterilizing Filtration Parameters: Common Deficiencies (cont.)

- Pressure or flow rate limit:
 - Peristaltic pump speed range provided *in lieu* of pressure or flow rate limit. Pump speed should be correlated to a parameter validated by the microbial retention study (flow rate or pressure)
 - Controls should be in place to ensure that the pressure or flow rate limit validated by the microbial retention study is not exceeded during production

Microbial Retention Validation: Common Deficiencies

- Retention study report and viability data not provided in addition to the summary data, or the study report was not legible
- Scaled-down study parameters were not compared to production parameters, or the scaled-down study did not support the worst-case production parameters
 - Product contact time, flow rate or pressure, product volume per unit of membrane surface area, temperature

Microbial Retention Validation: Common Deficiencies (cont.)

- Inadequate justification for not performing the study as a single-stage direct challenge with unmodified product under worst-case conditions
 - The drug product formulation was bactericidal to the challenge organism under the conditions of the study, so water was used as a surrogate solution
 - The study design was modified to accommodate an unnecessarily long filtration time limit

Microbial Retention Validation: Case Study

- The microbial retention study was performed as a two-stage test: product conditioning followed by bacterial challenge. The challenge organism (*B. diminuta*) was suspended in water because the drug product formulation was bactericidal to *B. diminuta*
- However:
 - In general, water is not a suitable surrogate solution for BLA products
 - Studies were not performed to identify the bactericidal component of the product or process, which would allow for a more suitable study design

Microbial Retention Validation: Case Study (cont.)

- The following post-marketing commitment was agreed upon:

The microbial retention study was done with purified water as a surrogate solution for the drug product. **Perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution.** Product attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) **should model the drug product as closely as possible while preserving viability of the challenge organism.** Alternatively, a reduced exposure time approach may be appropriate.

Common Deficiencies

- Sterilizing filtration
- **Post-reconstitution and post-dilution storage**
 - Microbial challenge studies
- Container Closure Integrity

Post-Reconstitution and Post-Dilution Storage

- Lyophilized products are reconstituted prior to administration, as directed in the label
- Proposed post-reconstitution storage time should be supported by microbial challenge studies to demonstrate that the product does not support microbial growth under the proposed storage conditions
 - This requirement also applies to post-dilution storage times for liquid or reconstituted products

Post-Reconstitution and Post-Dilution Storage Studies

- Challenge studies should be conducted using a panel of microorganism provided in the USP<51> (Antimicrobial Effectiveness Testing) plus typical skin flora or species associated with hospital-borne infections.
- Challenge levels should be less than 100 CFU/mL.
- Temperature(s) described in the proposed product's labeling should be tested.

Post-Reconstitution and Post-Dilution Storage Studies (cont.)

- Test duration should be twice the recommended storage period and use the label-recommended diluent(s).
- No increase from the initial counts is defined as less than $0.5 \log_{10}$ unit higher than the initial inoculum.

Post-Dilution Storage: Case Study

- Initial labeling:
 - “Product A” is diluted in 0.9% NaCl prior to administration.
 - Proposed post-dilution storage conditions: up to 24 hours at 2-8°C or up to 12 hours at 23-27°C.
- Growth promotion study results:
 - Growth-promoting for *P. aeruginosa*:
 - By 32 hours at 2-8°C
 - By 24 hours at 23-27°C
 - Growth-promoting for *E. coli*:
 - By 16 hours at 23-27°C
 - Two-fold increase in CFU at the 12 hour time point (duplicate samples)
- Labeling revision: Storage at 23-27°C was removed

Common Deficiencies

- Sterilizing filtration
- Post-reconstitution and post-dilution storage
- **Container closure integrity**

FDA 1994 Guidance: Container Closure Integrity Tests

“.....sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container-closure system. Documentation of the sensitivity of the container-closure integrity test should be provided.”

FDA 2008 Guidance: Container Closure Integrity Tests

- Sterility tests are **not recommended** as a component of a stability program for confirming the continued sterility throughout a product's shelf-life or dating period
- Alternatives to sterility testing ...might include any **properly validated physical or chemical container and closure system integrity testor microbiological container and closure system integrity tests** (e.g., microbial challenge or immersion tests)

FDA 2008 Guidance: Container Closure Integrity Tests (cont.)

- A test method is adequately validated if it has been proven through **scientifically accepted studies** to be capable of detecting a breach in container and closure system integrity
- An appropriate container and closure system integrity test **should be conducted annually and at expiration** or as otherwise required by applicable regulations

Common Deficiencies

- Container closure integrity test (CCIT) not included in the stability program
- Inadequate qualification of the container closure system for integrity
 - Inadequate description of the CCIT methods
 - Sensitivity of method not known or described
 - Lack of appropriate controls
- Vial capping parameters not described
 - Worst case capping parameters not validated
- CCI of syringes
 - Shipping of syringes

Example: Container-closure integrity test with an inadequate positive control

- Applicant proposed to use a CCIT capable of detecting defects as small as 160 microns
 - Positive control used during method validation was a container prepared with a 160 micron defect.
- Current CCIT methods are capable of detecting leaks \leq 20 microns
- System suitability controls with a smaller defect size should be used for routine testing..

Resolution

- The following information request was sent to the applicant:

The system suitability controls for container closure integrity testing of syringes and pens are prepared with a relatively large defect size (removing the needle shield). System suitability controls with a smaller defect size should be used for routine testing. The study performed by [XXXYY contract lab] showed that the method is capable of detecting 5, 10, and 30 micron defects.

- The applicant committed to implementing a system suitability control with a smaller defect size (≤ 20 microns).

Conclusions

- Sterilizing filtration:
 - Integrity testing information and data should be provided.
 - Filtration parameters should be supported by the microbial retention study.
 - Modifications to the microbial retention study design should be made only when necessary and should be supported by viability study data.
- Post-reconstitution and post-dilution storage conditions indicated in the labeling should be supported by growth promotion study data.

Conclusions (cont.)

- CCIT should be used in lieu of sterility for drug product on stability (annually and at expiry)
- CCIT method validation studies should demonstrate adequate sensitivity using appropriate controls
- Refer to the guidance documents and pre-meeting comments for the drug product information that should be included in your BLA.
 - **FDA review timelines are based on the expectation that applications are complete at the time of submission.**

Acknowledgements

- **Lynne Ensor, Ph.D.**
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- **Patricia Hughes, Ph.D.**
 - Branch Chief (Actg), Division of Microbiology Assessment (DMA)
- **Colleen Thomas, Ph.D.**
 - Quality Assessment Lead (Actg), DMA

Reference: Drug Product Micro Content for CDER BLAs

- Provide the following information in section 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:
 - Description of the manufacturing areas and fill line, including air classifications.
 - Description of the environmental and personnel monitoring programs.
 - Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.
 - Description of the sterilizing filter (supplier, membrane material, membrane surface area, etc.), the pressure limit or flow rate limit for sterilizing filtration, and the acceptance criterion for post-use integrity testing.
 - Parameters for filling, stoppering, and capping.
 - Processing and hold time limits, including the time limit for sterilizing filtration.
 - Bioburden and endotoxin limits.

Reference: Drug Product Micro Content for CDER BLAs

- Provide protocols and reports with validation data in section 3.2.P.3.5:
 - Bacterial filter retention study for the sterilizing filter.
 - Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
 - Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program.
 - Note that this requirement includes disposable filtration/filling assemblies and storage bags which are supplied “ready to use.”
 - For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.

(continued on the next slide)

Reference: Drug Product Micro Content for CDER BLAs

- Provide protocols and reports with validation data in section 3.2.P.3.5:
(continued from the previous slide)
 - Three successful consecutive media fill runs, including summary environmental and personnel monitoring data obtained during the runs.
 - Isolator decontamination, if applicable.
 - Maintenance of container closure integrity during production (vial capping, syringe or autoinjector assembly, etc.).
 - Summary of shipping validation studies and data.
 - For pre-filled syringes, the effects of varying air pressure on plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data that demonstrate that plunger movement during air transportation does not impact product sterility.

Reference: Drug Product Micro Content for CDER BLAs

- Provide drug product testing information and data in the appropriate sections of Module 3:
 - Verification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. In addition, the test methods should be described.
 - Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).
 - Low endotoxin recovery studies. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin standard (CSE or RSE) into undiluted drug product and testing for recoverable endotoxin over time.
 - Container closure integrity testing information and data. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) and at expiry.