Control Microbial Contamination and Understand the Implications on Batch Certification/Release

Walid El Azab
Technical Service Manager
STERIS Life Science
Agenda

- Definition of objectionable microorganism
- Common microbiological contamination and control
- Why “contamination control” is the most FDA deficiencies in FY.14?
- Objectionable microorganism contamination - implication on non sterile batch certification and release
- Conclusion and open discussion
Objectionable microorganism and microorganism of concern: definition

Microorganism of concern:

- Microorganism listed in product recall, infection outbreak, nosocomial infection and literature
- Can be objectionable microorganism

Objectionable microorganism:

- Organism that can proliferate and adversely affect the quality attributes of the water or the product.
- Can cause infection in patients due to its numbers and its pathogenetic nature
- Can cause infection in patients through the drug administration route

Microorganism can be objectionable for products and not for others
US and EU guidance on objectionable microorganism

FDA guidance (211.113; 211.165; 211.64):
- Cannot be present in the process manufacturing or in batch release testing
- Objectionable microorganism to non-sterile product
- Investigation analysis and action plan should avoid recurrent objectionable contamination
- Do not include evolution of objectionable microorganism definition

EU guidance (Chap. 3 & 5; Annex 7 & 9, Eur. Ph. (5.1.4)):
- Specified and compendia microorganism should be absent
- It is up to the manufacturer to:
  - Identify and justify microbiological specifications
  - Identify objectionable microorganism per route of administration
  - Put in place all necessary SOP to ensure microbial prevention and control
  - Demonstrate good product process and use understanding for targeted patient

USP guidance: (<1111>; <1112>; <61>; <62>):
- Integrate the specification limit and specified microorganism testing per route administration
- Enable justification of other microorganism through risk assessment
- Integrate the evolution of objectionable microorganism definition – product use / shelf life and patient

SELF INTERPRETATION
Agenda

- Definition of objectionable microorganism

- Common microbiological contamination and control

- Why “contamination control” is the most FDA deficiencies in FY.14?

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- Conclusion and open discussion
Sources and factors of microbial contamination

Factors influencing

- $A_w > 0.6$ increase probability of microorganism proliferation
- Viscosity can influence microorganism proliferation
- Preservative efficiency * – USP<51>
- Product nature – enhance or inhibit microorganism proliferation

- Setting microbial limit $>$ product specification and process reduction of microbial level
- Multi-use, distribution and storage conditions

- Behavior and gowning procedure
- Respect of the cleaning and sanitization procedure

- Process/equipment/product flows
- Utilities systems under control and correctly maintained
- Personnel and cleaning program
- House keeping

- Equipment design and maintenance program
- Equipment cleaning program

- Poor cleaning or control of the CPP
- Inefficient cleaner or disinfectant against house isolate/contaminant

BEST WAY TO AVOID OBJECTIONABLE MICROORGANISM IS TO CONTROL THESE FACTORS
Poor control of the element affecting microbial control lead to recurrent microbial excursion

A Microbial residue: Is the cleaner agent used are efficient

B Basic GxP: ask for a cleanable equipment!

C Disinfection or Sanitization program again microorganism

Combination of cleaning approaches have shown effectiveness against microbial contamination

Combine strategy will be effective against microbial contamination:

1. **Use of alkaline cleaning chemistry:**
   - Increase the chemical action
   - Increase the mechanical action

2. **Use of the sporicidal chemistry or thermal to disinfect or sterilize the system**

*Fluorescently labeled *P. aeruginosa* exposed to 5% concentration at 60°C:*

- Before exposure
- Biocide (3min)
- Alkaline detergent (6min)

*Source: STERIS Technical tip 410-200-3088*
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FDA increase requirement on objectionable microorganism due to high recall in past years

### Objectionable microorganism cited in Recalls from 2004 -2011

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Count</th>
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<tbody>
<tr>
<td>Total</td>
<td>78</td>
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<tr>
<td>Burkholderia cepacia</td>
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<tr>
<td>Fungal</td>
<td>19</td>
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<tr>
<td>Bacillus cereus</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
<td>6</td>
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<td>Elizabethkingla meningoseptica</td>
<td>5</td>
</tr>
<tr>
<td>Pseudomonas putida</td>
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<tr>
<td>Pseudomonas spp and salmonella spp</td>
<td>2</td>
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</table>

### 144 non sterile recalls from 2004 -2011

#### Recall by product (%)
- Dietary supplement/ probiotics: 8%
- Pharmaceutical: 14%
- Medical device: 31%
- Cosmetic/soap: 42%
- OTC: 15%

#### Recall by reason (%)
- GMP: 1%
- Failed AET: 5%
- Microbial contamination: 72%
- Other: 15%

Cleaning and contamination control are on the top 10 US FDA deficiencies observed and Warning Letter

### Most deficiencies observed 2007 -2014

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<tr>
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<tr>
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<td>211.100(a)</td>
<td>211.192</td>
<td>211.110(a)</td>
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<td><strong>211.67(a)</strong></td>
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<td>211.25(a)</td>
<td>211.67(a)</td>
<td>211.165(a)</td>
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<td>211.166(a)</td>
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<tr>
<td>211.110(a)</td>
<td>211.165(a)</td>
<td>211.188</td>
<td><strong>211.67(b)</strong></td>
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</table>

### Approximate reflect of the deficiencies

#### 21CFR211.67(a): “Equipment and utensils are not [cleaned][maintained][sanitized] at appropriate intervals to prevent [malfunctions][contamination] that could alter the safety, identity, strength, quality or purity of the drug product. Specially”

#### 21CFR211.67(b): “Written procedures are not [established][followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a product. Specially”

#### 21CFR211.113(b): “Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established][written][followed]. Specially.”

Source: Regulatory Field Investigator Perspectives, 2014 PDA Aseptic Processing-Sterilization Conference Chicago, IL June 17-18, 2014, Sharon K. Thoma, PharmD
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Role of QP/QA and senior management is to ensure quality, compliance to the MAH and cGMP

- QP has the ultimate responsibility over product lifetime; safety, quality and efficacy
- Ensure batch in accordance with its MAH, with GMP and applicable law
- Has an on going assurance that his reliance on the QA system is well founded
Case study #1: recurrent microbial contamination of OSD batch despite several actions put in place!

Recurrent deviation – CAPA:
- CIP design – dead leg removal
- Increase rinsing step using PW
- Increase water system sanitization
- Increase gloves sanitization (IPA)
- Increase floor cleaning/disinfection

Cross Functional investigation team / Fish bone:
- Product cleaning: cleaner was inefficient against micro.
- Equipment design: presence of dead leg
- Hose product contact was on direct contact with the floor
- Disinfection program was incomplete—no sporicidal
- Presence of carton in clean room corridor
- Water sanitization time and temperature
- Presence of rouge in the water system
Case Study #2: Non conform microbial level of tank vessel after cleaning hold time testing

Description:
- Cleaning Revalidation: cleaning PW and rinse PW
- Recurrent contamination by gram - microorganism: Pseudomonas aeruginosa and Ralstonia picketti
- Several final product with micro-contamination under USP <1111> specifications

Remedial action – Root cause not found:
- Sanitization of the water system – Water microbial data were always conform
- Testing of all batch after cleaning
- Remove the clean hold time
- Identification of each CFU even under specification – because consider as objectionable microorganism.

Cross functional investigation team / Fish bone and microbial screening risk assessment:
Root cause:
- Equipment intra-design with curve – inducing water to stagnate
- After cleaning a 3 log reduction were achieved
- Disinfection process was absent vs the equipment design
- Human behavior inducing to increase probability of contamination
- Disassembling and assembling methods lead to increase probability of micro-contamination
Case Study #3: Non conform microbial level in final product QC testing

Recurrent deviation:
- Root cause unidentified
- Specification change

Cross Functional investigation team / Fish bone:
- Inadequate understanding of the disinfectant efficacy vs micro identified
  - Product cleaning:
    - Cleaner was inefficient against micro
    - Cleaning cycle was inadequate to ensure effective cleanign
  - Equipment design:
    - Presence of rouge (high level)
    - High rugosity of the surfaces – crevices & interstice
- Disinfection program was inadequate
- Personnel flow was inadequate

Action put in place:
- Increase the concentration:
  - Disinfectant X
  - NaOCl from 1% to 2%
- Increase the contact time:
  - From 15min to 45 min
Objectionable microorganism should be confirmed through microbial/product/patient risk assessment to avoid costly CAPA
A microbial contamination of non sterile batch – do not always mean batch rejection (1/2)

Sources and factors of microbial contamination

- Factors influencing
  - A, B, C: Increase probability of microorganism proliferation
  - R, S, T: Risky conditions for microorganism proliferation
  - Preservation efficiency: USP 61

RISK IDENTIFICATION
- Identification of microorganism in the production process

RISK CHARACTERIZATION
- Evaluation of the potential adverse effect or clinical effect on patient exposure to the identified microorganism

RISK ACCEPTANCE
- Clinical effect or estimation of the patient with product use:
  - Qualitative data
  - Quantitative limit
  - Safety factor addition

Microbial contamination

Under the microbial Specification

Yes

Non pharmacopeia specified

House isolates

REJECT

Objectionable microorganism*

Organism of concern

Can the number harm the patient or adversely affect the product**

Yes

REJECT: Objectionable organism

No

Approved

Batch stability?

Yes

REJECT

No

Manufacturing process step

Reduction level step

Pharmacopeia Specified

Approved

REJECT
A microbial contamination of non sterile batch – does not always mean batch rejection (2/2)

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Microbial contamination reflect inadequate motion work! However, the QA/QP decision should be risk based

- Develop robust cleaning and disinfection program
- Control factor that influence microbial contamination during your manufacturing process
- Trend and control your data for preventive action
- Understand microbial risk to patient by product use

=> Identify your objectionable microorganism
Thank You
For your listening
References

• Lopolito, P. and Rivera, E. (2013) An Audit Approach to Address Microbial Contamination in Process Equipment, Volume 1, DHI/PDA, Chapter 15,
• Food and Drug Administration (FDA) top deficiency. Accessed on April 05, 2015 at: http://www.fda.gov/ICECI/Inspections/ucm424098.htm
• USP chap 1111

Note: This is not a complete listing, just a guidance to literature the speaker has found to be interesting/beneficial.
Microorganism found in pharmaceutical water systems – control procedure

For the water system / equipment:
- Maintain the cell in “planktonic” state
  - Equipment design
  - Sanitization
  - Cleaning agent and disinfection/sterilization
  - Maintenance, etc...

For product contact:
- be under “SAFE patient” specification:
  - Filter the water
  - Product internal attributes
  - Control in-coming bioburden level
  - Avoid personnel contamination

<table>
<thead>
<tr>
<th>Gram -</th>
<th>Gram +</th>
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<tbody>
<tr>
<td>Ralstonia picketti</td>
<td>Micrococcus Luteus</td>
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<tr>
<td>Pseudomonas spicies (spores)</td>
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<tr>
<td>Chryseobacterium indologenes</td>
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<tr>
<td>Burkholderia cepacia</td>
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<tr>
<td>Pseudomonas fluorescens</td>
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<td>Maroxella species</td>
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<tr>
<td>Staphylococcus maltophilia</td>
<td></td>
</tr>
<tr>
<td>Flavimonas oryzihabitans</td>
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<tr>
<td>Ochrobactrum anthropi</td>
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</table>

Source: Assessment of the suitability of R3A agar for the subculture of microorganism isolated from pharmaceutical water; EJPPS 2014; 19(3):85-93
Microorganism found in clean room (grade C & D) – control procedure

For the Environment:
- Avoid contamination excursion:
  - Personnel behavior
  - Cleaning agent and disinfection procedure
  - Maintenance, ect...

For product contact:
- be under “SAFE patient” specification:
  - Reduce environment contact?
  - Reduce human contact?
  - Use closed system?
  - Ect...

<table>
<thead>
<tr>
<th>Gram -</th>
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<tr>
<td>Flavimonas (Pseudomonas) oryzihabitans</td>
<td>Micrococcus luteus</td>
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<tr>
<td>Moraxella spp.</td>
<td>Bacillus sphaericus/bacillus fusiformis</td>
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<tr>
<td></td>
<td>Micrococcus lylae</td>
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<td>Micrococcus spp.</td>
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<td>Staphylococcus spp.</td>
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<td></td>
<td>Corynebacterium spp.</td>
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<td></td>
<td>Rhodococcus</td>
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<td>Staphylococcus epidermidis</td>
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LIST NON EXHAUSTIVE