What is an Objectionable Organism?

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Presentation Outline

• “Objectionable Organisms” – The Shifting Perspective:
• Bacillus cereus
  • Recovery and Identification
  • Prevalence in the Environment
  • Prevalence and Infectivity
• USP <1111> and the rationale for "other organisms"
What is an Objectionable Organism? Scott Sutton, Ph.D. Microbiology Network, Inc

Presenter’s Disclaimer

• I am an independent consultant.
• I have been involved with USP, PDA and PCPC for many years.
• I do not represent USP, PDA, PCPC or any other organization.
• Opinions expressed in this presentation are mine alone, and should not be interpreted as the policies, positions or whims of any other organization.

Objectionable Organisms - CFR

• 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.
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PCPC Perspective

“Objectionable Organism
an organism that can be harmful to the user based upon the nature of the product, its intended use and its potential hazard, or is able to compromise the physical integrity or appearance of the product.”

CTFA Microbiology Guidelines - 2007

Compendial Microbial Limits Tests

• USP <61> Enumeration, EP 2.6.12
• USP <62> Specified Organisms, EP 2.6.13
  • Test for Staphylococcus aureus
  • Test for P. aeruginosa
  • Test for Salmonella spp
  • Test for Escherichia coli
  • Test for Bile-tolerant Gram-negative Bacteria
  • Test for Clostridia
  • Test for Candida albicans
• USP <1111> Guidance on Microbial Quality, EP 5.1.4
Pharmacopeial Methods

- Provide assays to meet monograph requirements
  - Sterility
  - Preservative Efficacy
  - Antibiotic/Vitamin Potency
  - Bacterial Endotoxin
  - Bioburden
  - “Absence of...”
- Not meant to be complete release tests for finished products


PCPC Recommendations for Testing

“The presence of objectionable organisms can be determined by identification of isolates using procedures such as described in “M-2 Examination for *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*” (Section 19).”

CTFA Microbiology Guidelines – 2007 Section 11 p.141
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A Note on Publications

What can be learned from FDA recalls?

A Review of Reported Recalls Involving Microbiological Control 2004–2011 with Emphasis on FDA Considerations of “Objectionable Organisms”

Abstract
An analysis was conducted of 642 microbiologically-related recalls over the years 2004-2011. This analysis was conducted using publicly available enforcement reports as presented on the US FDA website. The microbiologically-related recall activity shows a decided increase in recent years. Most of the reported recalls involved injectable products, and of these medical devices accounted for the majority. The reasons given for sterile product recalls were varied, but the majority cited “Lack of Sterility Assurance” with sterile packaging clearly identified as the main culprit. Three major categories of infectious agents are the most frequent recall cause as well. The majority of the recalls were from CFCs and non-sealed products, with “Objectionable Organisms” as the most prevalent reason.

Introduction

**Microbiologically-related Recalls by Year**

Number of Recalls

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Recalls</th>
</tr>
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<tbody>
<tr>
<td>2004</td>
<td>100</td>
</tr>
<tr>
<td>2005</td>
<td>120</td>
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<tr>
<td>2006</td>
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<td>2008</td>
<td>90</td>
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<tr>
<td>2009</td>
<td>110</td>
</tr>
<tr>
<td>2010</td>
<td>120</td>
</tr>
<tr>
<td>2011</td>
<td>140</td>
</tr>
</tbody>
</table>

**Overall Recalls**

2004 - 2011 Recalls by Type

- **Medical Devices**: 65%
- **Pharmaceuticals**: 15%
- **Cosmetics/Soaps**: 7%
- **Dietary Supplement/Probiotics**: 2%
- **OTA**: 11%

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Recalls by Sterility

- Sterile, 498
- Non-sterile, 144

2004-2011 Recalls by Product

- Cosmetics/Soap: 31%
- Dietary Supplement/Probiotics: 8%
- Medical Devices: 14%
- OTC: 42%
- Pharmaceutical: 5%

144 Recalls during this period
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What do Recalls Teach?

- USP (<61> and <62>) and PCPC guidances are useful tools
- Don’t ignore product quality in non-steriles
- USP, PCPC are not enough

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- *Bacillus cereus*
  - Recovery and Identification
  - Prevalence in the Environment
  - Prevalence and Infectivity
- Chapter <1111> and the rationale for "other organisms"
Recovery of *B. cereus*

- Available Selective Agars
  - BACARA Agar
    (*Bacillus cereus* Rapid Agar – AES Chemunex)
  - Brilliance *Bacillus cereus* Agar from Oxoid
- FDA BAM method uses
  - BACARA
  - 11 additional phenotypic tests that “…are usually adequate for distinguishing the typical strains of *B. cereus* from other members of the *B. cereus* group.”

Prevalence in the Environment

- 14% of the healthy have identifiable levels of *B. cereus* in feces

- *Bacillus cereus* group organisms are a common contaminant in milk, even after pasteurization
  (Bartoszewicz, M et al. 2008. The members of the *Bacillus cereus* group are commonly present contaminants of fresh and heat-treated milk. *Food Microbiol.* 25:588-596).
**B. cereus as Pathogen**

- Some evidence in the literature for pathogenicity
- Need to be cautious that association with disease state is not taken as *a priori* proof of pathogenicity

<table>
<thead>
<tr>
<th>Sample Source</th>
<th>Total Count</th>
<th>Frequency of Isolation</th>
<th>Involvement in Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Ear</td>
<td>24</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Eye</td>
<td>32</td>
<td>1</td>
<td>14</td>
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<tr>
<td>Genitourinary</td>
<td>54</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>82</td>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>Respiratory</td>
<td>71</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Skin, Wound, Burn</td>
<td>35</td>
<td>5</td>
<td>48</td>
</tr>
</tbody>
</table>


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What is an Objectionable Organism?

• Objectionable in view of
  • The product’s intended use, or;
  • In terms of product stability (FDA/USP/PCPC)
  • For products not required to be sterile (FDA)

USP <1111>

“...the significance of other microorganisms recovered should be evaluated in terms of the following:

• The use of the product: hazard varies according to the route of administration (eye, nose, respiratory tract).
• The nature of the product: does the product support growth? Does it have adequate antimicrobial preservation?
• The method of application.
• The intended recipient: risk may differ for neonates, infants, the debilitated.
• The use of immunosuppressive agents, corticosteroids.
• The presence of disease, wounds, organ damage.

Where warranted, a risk-based assessment of the relevant factors is conducted by personnel with specialized training in microbiology and in the interpretation of microbiological data.”
Presentation Review

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Final Thoughts

- FDA’s proper orientation towards protection of the public above all else may lead to the conclusion that all organisms shown to cause any disease, or to be present in any disease state, will be considered objectionable in all medications.
- It is up to the manufacturer to provide evidence that the products released to market are safe.
- The manufacturer must be prepared to defend the safety of his product when challenged by FDA.
Thank you for your attention

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