Exclusion of Objectionable Microorganisms from Non-Sterile Pharmaceuticals, Medical Devices and Cosmetics

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Disclaimer

• The opinions expressed in this presentation are my entirely my own and not that of the USP Microbiology Expert Committee or my consulting clients.
PDA Technical Report

• As the result of the work of a broad-based industry task force, PDA TR No. 67 *Exclusion of Objectionable Microorganisms from Non-Sterile Pharmaceuticals, Medical Devices and Cosmetics* published October, 2014 in conjunction with the PDA Global Pharmaceutical Microbiology Conference.
The objective of the technical report was to define best practices on how to mitigate the risk of microbial contamination in non-sterile products

• Emphasis on:
  – Risk-based decision criteria
  – Assessing whether microorganisms if found in a non-sterile product were objectionable
Task Force Members

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- John Stone, Ph.D. Kao, USA
- Scott Sutton, Ph.D. Consultant
- Edward Tisdale, Ph.D. Baxter
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Scope of the Task Force

• The contamination of marketed products with potential objectionable microorganisms continues to be an infrequent but chronic problem. i.e. around 20 US recalls annually.

• The U.S., Japanese and European pharmacopeias have harmonized the microbial test methods for enumeration and the detection of specified microorganisms.

• Mycotoxins, viruses and sterile dosage forms were out of scope of the Technical Report.
US Recalls of Non-sterile Products

• A recent U.S. survey of 144 reported recalls of non-sterile pharmaceutical drug products (5%), over-the-counter drug products (42%), cosmetics (31%), medical devices (14%) and dietary supplements (8% of the total recalls) for microbiologically-related issues for the 7-year period from 2004 through 2011.

• Publication highlighted that the majority of these recalls (72%) were associated with objectionable microorganisms and not for exceeding microbial enumeration limits (Sutton and Jimenez, 2012).
Industry Challenge

• An absence of objectionable microorganisms requirement for a non-sterile product is a critical quality attribute without a defined test method and acceptance criteria making it a unique product specification.

• There is no consensus amongst manufacturers and regulators how to approach this issue.
Regulatory Requirements

• FDA GMPs: The FDA CGMP regulations 21 CFR 211.113 *Control of microbiological contamination* states: a) Appropriate written procedures, designed to prevent objectionable organisms in drug products not required to be sterile, shall be established and followed.

• Furthermore, 21 CFR 211.165 *Testing and release for distribution* (b) states: There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.
What are Objectionable Microorganisms?

CGMP regulations, i.e. CFR 211.113 do not define the term objectionable microorganisms, but they can be broadly defined as:

1) Microorganisms that can proliferate in a product adversely affecting the chemical, physical, functional and therapeutic attributes of that pharmaceutical product.

2) Microorganisms that due to their numbers in the product and their pathogenicity can cause infection in the patient in the route of administration when treated with that pharmaceutical product.
Microbiological Testing

Product-release and shelf-life testing

• Three levels of testing are required:
  1) microbial enumeration,
  2) testing for the absence of specified microorganisms, and
  3) screening for objectionable microorganisms.
Regulatory Requirements

• The inclusion of the phrase "as necessary" in many regulations implies a risk-based approach to product testing and decisions about which products will or will not be routinely tested.

• Drug manufacturers cannot rely solely on finished product testing to comply with regulation but must ensure the quality of their products from the receipt of production materials to the end of the manufacturing process by following current GMPs.
Regulatory Requirements

Bioburden control is achieved by:

• Procuring pharmaceutical ingredients of high microbiological quality.
• Formulating robust products low water activities and effective preservative systems that resist microbial contamination.
• Good bioburden control through sound equipment cleaning, disinfectant programs, utility management and personnel hygiene.
• Emphasis on cGMP compliance.
• Risk-based microbial testing programs.
Recommended Microbiological Quality Requirements

• The recommended microbiological quality requirements by pharmaceutical dosage form can be found in the harmonized general informational chapter USP <1111> Microbiological attributes of non-sterile pharmaceutical products.

• Specific requirement may be found in individual USP product monographs.
## Microbiological Quality Requirements

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>TAMC</th>
<th>TCYMC</th>
<th>Absence of Specified Microorganisms (in 1 g or 1 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-aqueous preparations for oral use (e.g., tablets and capsules)</td>
<td>$10^3$</td>
<td>$10^2$</td>
<td>E. coli Salmonella spp. (unrefined plant or animal material only)</td>
</tr>
<tr>
<td>Aqueous preparations for oral use (e.g., oral liquids, syrups and suspensions)</td>
<td>$10^2$</td>
<td>$10^1$</td>
<td>E. coli</td>
</tr>
<tr>
<td>Rectal products</td>
<td>$10^3$</td>
<td>$10^2$</td>
<td>-</td>
</tr>
<tr>
<td>Preparations for oromucosal, gingival and auricular use</td>
<td>$10^2$</td>
<td>$10^1$</td>
<td>S. aureus and P. aeruginosa</td>
</tr>
<tr>
<td>Preparations for cutaneous use (e.g., topical liquids, ointments, gels and creams)</td>
<td>$10^2$</td>
<td>$10^1$</td>
<td>S. aureus and P. aeruginosa</td>
</tr>
<tr>
<td>Nasal products (e.g. drops and sprays)</td>
<td>$10^2$</td>
<td>$10^1$</td>
<td>S. aureus and P. aeruginosa</td>
</tr>
<tr>
<td>Preparations for vaginal use (e.g., suppositories, ointments and creams)</td>
<td>$10^2$</td>
<td>$10^1$</td>
<td>S. aureus, P. aeruginosa and C. albicans</td>
</tr>
<tr>
<td>Inhalants (e.g., dry powder inhalants and aerosol inhalants)</td>
<td>$10^2$</td>
<td>$10^1$</td>
<td>S. aureus, P. aeruginosa and bile-tolerant, Gram-negative bacteria</td>
</tr>
</tbody>
</table>

* TAMC/ TCYMC counts in cfu/g or cfu/mL
Specified Microorganisms

• *Tests for the Absence of Specified Microorganisms* that are applied to different dosage forms are found in USP <62> while USP <1111> contains the acceptance criteria.

• The screening tests are absence and quantitative of bile salt-tolerant gram-negative bacteria, absence of *E. coli*, *P. aeruginosa*, *S. aureus*, *C. albicans*, and *Clostridium spp* (in 1g) and absence of *Salmonella spp* (in 10g).
Specified Microorganisms

These USP <62> tests generally consist of three steps:

• General enrichment in soybean – casein digest or Sabouraud dextrose broth to increase the number of microorganisms.

• Selective enrichment using specialized broth and incubation conditions to select for the target specified microorganisms.

• Growth on solid diagnostic media for isolation and presumptive identification of the specified microorganisms.

• Confirmatory identification to species.

• Note: These tests are too selective to screen for objectionable microorganisms
Test for Absence of *P. aeruginosa*

- After a general enrichment in TSB incubated at 30-35 °C to 24-48 hours streak out on Cetrimide Agar
- *P. aeruginosa ATCC 9027* is a growth-promotion organism & *E. coli ATCC 8739* inhibitory organism for Cetrimide Agar used for the indicative medium of *P. aeruginosa*
- Note: Related pseudomonads like *B. cepacia* or *P. fluorescens* would not be isolated
Test for Absence of *P. aeruginosa*

- Cetrimide (quaternary ammonium compound) is highly selective for *P. aeruginosa*. The water soluble blue pigment pyocyanin is stimulated by magnesium chloride and potassium sulfate in the medium. Colonies with pyocyanin production that fluoresces under ultra violet light is indicative of *P. aeruginosa*.

- The objectionable organism isolation rating is poor as CET agar is highly selective for *P. aeruginosa* inhibiting other pseudomonads, enterics, and gram-positive bacteria especially at higher incubation temperatures.
## Risk-based Microbial Testing

<table>
<thead>
<tr>
<th>Target Population for Product</th>
<th>Immune suppressed/Immune compromised/Invasive medical procedures</th>
<th>Geriatric/Pediatric</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk from Dosage Type</strong></td>
<td>• Streak on selective USP &lt;62&gt; and non-selective (TSA) media and identify atypical colonies from selective media and colonies above internal threshold on TSA</td>
<td>• Streak on selective USP &lt;62&gt; and non-selective (TSA, blood agar and LMA) media and identify all recovered colonies</td>
<td>• Streak only on selective media as specified in USP &lt;62&gt; and identify atypical colonies only</td>
</tr>
<tr>
<td></td>
<td>• Oral tablets &amp; powder-filled capsules</td>
<td>• Vaginal suppositories, ointments, and creams</td>
<td>• Aerosol and dry powder inhalants</td>
</tr>
<tr>
<td></td>
<td>• Liquid-filled capsules</td>
<td>• Topical lotions, gels, ointments, and creams</td>
<td>• Nasal sprays</td>
</tr>
<tr>
<td></td>
<td>• Oral liquids (non-aqueous)</td>
<td>• Oral liquids (aqueous)</td>
<td>• Otics</td>
</tr>
<tr>
<td></td>
<td>• Rectal suppositories, ointments and creams</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

June 2-4, 2015

IVT Microbiology Week
Risk-based Microbial Testing

**Low Risk**
Products pass the test if the microorganisms identified in USP <1111> and in the relevant monographs were not isolated and enumeration counts are below the specified limit.

**Moderate Risk**
Products pass the test if the microorganisms identified in USP <1111> and in the relevant monographs are not isolated, other colonies observed on TSA are not objectionable (see risk decision tree in Section 9) and enumeration counts are below the specification limit.

**High Risk**
Products pass the test if the microorganisms identified in USP <1111> and the relevant monographs are not isolated, other colonies observed on TSA or blood agar or LMA are not objectionable (see risk decision tree in Section 9) and enumeration counts are below the specification limit.

June 2-4, 2015
IVT Microbiology Week
Hierarchy of Risk

- Aerosol and dry powder inhalants
- Nasal sprays
- Otics
- Vaginal suppositories, ointments and creams
- Topical lotions, gels, ointments, transdermal patches and creams
- Oral liquids (aqueous)
- Oral liquids (non-aqueous)
- Rectal suppositories, ointments and creams
- Liquid-filled capsules
- Oral tablets and powder-filled capsules
CDC Investigated Outbreaks

• 1,022 nosocomial outbreaks were reported in the clinical literature from 1966 to 2002, i.e. 28 annually.

• The most frequent species implicated in clusters of hospital patient infection were *S. aureus* (151 outbreaks, 15% of all outbreaks), *P. aeruginosa* (91 outbreaks, 9%), *K. pneumoniae* (73 outbreaks, 7%)

• It is notable that in the vast majority of outbreaks in which drug products were implicated, the products were sterile, not non-sterile products.
Microorganisms Implicated

Incidence of Infection

B. cepacia
P. aeruginosa
S. marcescens
R. mannitolilytica
B. cereus
K. pneumonia
E. cloacae
S. liquefaciens
P. lilacinus
Enterobacter spp.
Products Implicated

Incidence of Infection

- Sanitizing agents
- Mouthwash
- Preps/wipes
- Lotions/moisturizers
- Topical gels
- Medical devices
- Soaps
- Shampoos
- Nasal sprays
Most Significant Microorganisms Associated with the Ten Most Common Product Recalls, Major Outbreaks Related to Nonsterile Products and Nosocomial Infections, in Descending Order

<table>
<thead>
<tr>
<th>Product Recalls (N=144)</th>
<th>Major Infection Outbreaks (N = 23)</th>
<th>Hospital-related Infection (N = 1,022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. cepacia (34 occurrences)</td>
<td>B. cepacia complex (12)</td>
<td>S. aureus (151)</td>
</tr>
<tr>
<td>Unspecified fungi (19)</td>
<td>P. aeruginosa (3)</td>
<td>P. aeruginosa (91)</td>
</tr>
<tr>
<td>B. cereus (9)</td>
<td>S. marcescens (2)</td>
<td>K. pneumoniae (73)</td>
</tr>
<tr>
<td>P. aeruginosa (6)</td>
<td>R. mannitolilytica (2)</td>
<td>S. marcescens (67)</td>
</tr>
<tr>
<td>E. meningoseptica (5)</td>
<td>B. cereus (2)</td>
<td>E. cloacae (34)</td>
</tr>
<tr>
<td>E. gergoviae (5)</td>
<td>K. pneumonia (1)</td>
<td>E. coli (27)</td>
</tr>
<tr>
<td>P. putida (3)</td>
<td>E. cloacae (1)</td>
<td>A. baumannii (24)</td>
</tr>
<tr>
<td>Pseudomonas spp. (2)</td>
<td>S. liquefaciens (1)</td>
<td>B. cepacia (21)</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>P. lilaceous (1)</td>
<td>C. albicans (20)</td>
</tr>
<tr>
<td>N/A</td>
<td>Enterobacter spp. (1)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

June 2-4, 2015  IVT Microbiology Week
Class Exercise

Breakout Session

- 2 groups
- 1 spokesperson per group
- 1 scribe per group
- Problem review: 15 minutes
- Report back: 2-3 minutes per group
Class Exercise

Using the objectionable microorganism decision tree would the following microorganisms in the specified dosage form be objectionable and why?

- 1200 cfu/g of the bacterium *Bacillus cereus* in a compressed tablet.
- Positive test for the absence of the bacterium *Staphylococcus aureus* in a liquid-filled capsule.
- The bacterium *Buckholderia cepacia* in a nasal spray.
- The bacterium *B. cepacia* in an alcohol-free mouthwash.
- The fungus *Aspergillus fumigatus* in a dry powder inhalant.
- The fungus *Rhizopus microsporus* in compressed tablet used to treat hyperuricemia or gout in cancer patients.
Class Exercise

Points to consider in your risk assessment:

• Does the drug product meet the compendial microbiological quality requirements?

• Is the microorganism a potential concern given the route of administration of the dosage form?

• Does the dosage form have a low water activity so it will not survive or growth in the product?

• Does the microorganism have a reputation of overcoming preservative systems?

• Does the target patient population susceptible to infection due to the microorganism?
Manufacturing Process

For example, the processing steps for the manufacture of a film-coated compressed tablet are:

• Procurement of pharmaceutical ingredients
• Warehousing pharmaceutical ingredients
• Batching of the pharmaceutical ingredients
• Blending
• Wet granulation and milling
• Fluid-bed drying
• Tablet compression
• Tablet coating
• Packaging
• Distribution
Manufacturing Steps
Sources of Microbial Contamination

• Based on the analysis of drug product recalls, the origin of microorganisms isolated from non-sterile drug products, in descending order, is pharmaceutical ingredients ≥ ingredient water > process equipment >> manufacturing environment >> manufacturing personnel.

• Cundell, A.M. Risk-based Approach to Pharmaceutical Microbiology In Encyclopedia of Rapid Microbiological Methods. Edited Michael J. Miller Davis Harwood/PDA 2005
Bioburden Mapping

• Bioburden-enhancing Steps
• Wet Granulation
• Tray Drying
• Film Coating
• Bioburden-reducing Steps
• Fluid-bed Drying
• Hot Melt Extrusion
• Tablets Compression
Film Coating Solutions

• Aqueous film coating solutions are susceptible to microbial contamination and the hold time should be limited to prevent microbial growth.
• Contamination may originate from the coating material, ingredient water and/or the equipment train.
• Tanks, pumps, distribution lines and spray nozzles should be of sanitary design, cleaned using validated methods and the equipment stored dry.
The mechanism of bioburden reduction in a fluid-bed drying process is: 1) thermal decay and 2) desiccation (dehydration). The resistance of microorganisms to these stresses are Gram-positive bacteria > yeast and mold >> Gram-negative bacteria.

Fu, N and X.D. Chen, 2006 Towards a maximal cell survival in convective thermal drying processes. Food Res. Intern. 44: 1127-1149
Tablet Compression

• The tablet compression process due to the temperature and pressure generated significantly reduce the number of vegetative microorganisms within a blend


Hot Melt Extrusion

- In general, the risk of microbial contamination is less with direct compression (absence of granulation fluid) and hot melt extrusions (elevated temperatures and pressure) than wet granulation.
Conclusions

• The frequency of product recalls for objectionable microorganisms is low, and the incidence of infections traced back to the use of contaminated products is extremely low and primarily associated with the recipient’s health condition.

• Non-sterile product manufacturers share customer and regulatory agency concerns about the serious health hazards that objectionable microorganisms can pose and wants to continuously improve manufacturing controls, detection and decision making to exclude objectionable microorganisms from its products.
Conclusions

• A risk-based approach must be used for determining the level and type of testing to be conducted to identify potentially objectionable microorganisms in different products.

• Standard microbiological testing procedures may be used with slight modifications to screen products for objectionable microorganisms.

• Organisms of concern must be identified based on a review of the published literature, such as the reference materials cited in this technical report.
Conclusions

• The task force developed technically sound policies, procedures and training that ensure the exclusion of objectionable microorganisms from non-sterile products.

• Policies and procedures developed by each company must result in consistent decision making that complies with the applicable regulations.
Thanks for Your Attention

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