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

Tony Cundell, Ph. D.
Microbiological Consultant,
Scarsdale, New York
Presentation Overview

• Introduction to the PDA Technical Report on the exclusion of objectionable microorganisms from non-sterile drug products.
• Regulatory definition of objectionable microorganisms.
• The role of microbial testing in detecting objectionable microorganisms
• Decision trees for objectionable organisms in different dosage forms
• Review of clinical literature, product recalls and infection outbreaks
• Conclusions
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, Bethesda, Maryland.
Other Notable Publications

- USP <1115> Bioburden Control in Non-sterile Drug Substances and Drug Products that emphasizes the frequency of monitoring should reflect the potential risk associated with the dosage form was published in Second Supplement to USP 37 official on December 1, 2014.
Technical Report

The objective of the technical report was to define industry 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 or not.
  – No list of objectionable microorganisms was provided
Task Force Members

- Anil Sawant, Ph.D. J&J (Co-chair)
- Tony Cundell, Ph.D. Consultant (Co-chair)
- Donald G. Ahearn, Ph.D. Georgia State University
- Matthew Arduino, Ph.D. CDC
- Julie Barlasov, Perritt Laboratories
- Mark Dato, MD, Ph.D. P&G
- Andrew Dick, J&J
- Donald English, Avon
- Rhonda Ezell, Qualitest Pharmaceuticals
- Dennis Guilfoyle, Ph.D. FDA
- David Hussong, Ph.D, FDA
- Mark Kaiser, Lancaster Laboratories
- Michael Long, Consultant
- Patrick Murray, Ph. D. Becton Dickson
- Judith Noble-Wang, Ph.D. CDC
- Per Arne Parment, MD. Ph.D. Consultant
- Dona Reber, Pfizer
- David Roesti, Novartis
- Frank Settineri, Consultant
- Linda Skowronsksy, GlaxoSmithKline
- Donald Singer, GlaxoSmithKline
- John Stone, Ph.D. Kao, USA
- Scott Sutton, Ph.D. Consultant
- Edward Tisdale, Ph.D. Baxter
- Myriam Sosa, Novartis
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 U. S. recalls annually.

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

• Mycotoxins, viruses and sterile dosage forms were out of scope of this 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.

• Furthermore, 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.
TGA Requirements

• ICH Q4B Annex 4 A Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests (General Test Chapter); Test for Specified Microorganisms (General Test Chapter) and Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use (General Informational Chapter).

• Note: These are harmonized with USP <61>, <62> and <1111>
TGA 17.3.2 Objectionable Microorganisms

• In addition to being free from contamination with specified microorganisms, a non-sterile medicine should also be free from contamination with other microorganisms that might be objectionable in the dosage form.

• For example, pseudomonad-type bacteria are considered to be objectionable in aqueous dosage forms that are intended for inhalant, cutaneous, nasal, auricular, oromucosal, gingival or vaginal use and in transdermal patches.

• These dosage forms are expected to be free from contamination with these types of bacteria.
TGA Recommendations

Evaluation of the significance of, and risk from, other objectionable microorganisms should consider:

• the formulation of the medicine

• its route of administration

• its method of application

• the population for which the medicine is intended, including:

• the possibility of underlying illness in the user of the medicine

• the possible concurrent use of immunosuppressive agents or corticosteroids.
What are Objectionable Microorganisms?

CGMP regulations, i.e. CFR 211.113 does 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 with 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 microbial 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

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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>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>
<td></td>
</tr>
<tr>
<td>Oral tablets &amp; powder-filled capsules</td>
<td>Vaginal suppositories, ointments and creams</td>
<td>Oral liquids (aqueous)</td>
<td></td>
</tr>
<tr>
<td>Liquid-filled capsules</td>
<td>Topical lotions, gels, ointments, and creams</td>
<td>Rectal suppositories, ointments and creams</td>
<td></td>
</tr>
<tr>
<td>Oral liquids (non-aqueous)</td>
<td>Oral liquids (aqueous)</td>
<td>Aerosol and dry powder inhalants</td>
<td></td>
</tr>
<tr>
<td>Rectal suppositories, ointments and creams</td>
<td></td>
<td>Nasal sprays</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Otics</td>
<td></td>
</tr>
</tbody>
</table>

**Risk from Dosage Type**

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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.
Decision Tree

Objectionable Organism Decision Tree

Definitions

Growth in Product
1. Water Activity
2. Antimicrobial effectiveness test
3. Challenge

Organisms of Concern
1. Associated with outbreaks
2. Produced recalls
3. Clinically significant infections

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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.
Product Recalls

• The majority of these recalls (72%) were associated with objectionable microorganisms and not for exceeding microbial enumeration limits (Sutton and Jimenez, 2012).

• *B. cepacia* was the microorganism most frequently implicated in the contamination of multiple-use liquid products.
Microorganisms Implicated

Incidence of Infection

- B. cepacia
- P. aeruginosa
- S. marcescens
- R. manitolilytica
- 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><em>B. cepacia</em> (34 occurrences)</td>
<td><em>B. cepacia</em> complex (12)</td>
<td><em>S. aureus</em> (151)</td>
</tr>
<tr>
<td>Unspecified fungi (19)</td>
<td><em>P. aeruginosa</em> (3)</td>
<td><em>P. aeruginosa</em> (91)</td>
</tr>
<tr>
<td><em>B. cereus</em> (9)</td>
<td><em>S. marcescens</em> (2)</td>
<td><em>K. pneumoniae</em> (73)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> (6)</td>
<td><em>R. mannitolyltica</em> (2)</td>
<td><em>S. marcescens</em> (67)</td>
</tr>
<tr>
<td><em>E. meningoseptica</em> (5)</td>
<td><em>B. cereus</em> (2)</td>
<td><em>E. cloacae</em> (34)</td>
</tr>
<tr>
<td><em>E. gergoviae</em> (5)</td>
<td><em>K. pneumonia</em> (1)</td>
<td><em>E. coli</em> (27)</td>
</tr>
<tr>
<td><em>P. putida</em> (3)</td>
<td><em>E. cloacae</em> (1)</td>
<td><em>A. baumannii</em> (24)</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp. (2)</td>
<td><em>S. liquefaciens</em> (1)</td>
<td><em>B. cepacia</em> (21)</td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td><em>P. lilaceous</em> (1)</td>
<td><em>C. albicans</em> (20)</td>
</tr>
<tr>
<td>N/A</td>
<td><em>Enterobacter</em> spp. (1)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
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
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.