Preservative Efficacy – The What:

- Spoilage and contamination with pathogens are a concern with cosmetic products.
- Water based products with a pH between 5 and 7 are the most susceptible.
- As manufacturers, we must ensure preservation of products is adequate.
- Tested via microbial inoculation of product and monitoring of microorganism die-off.
- This is the basic idea behind a preservative efficacy test (PET/AET/PCT).
Preservative Efficacy – The When:

- Official Journal of the EU, L 342/79, Guidelines on Annex 1 Regulation EC 1223, November 25, 2013:
  - Low microbiological risk products require no testing (but do require a rationale):
    - Alcohol content > 20 %,
    - Products based on organic solvents
    - High/low-pH products
  - Single-use products, and products not exposed to air require only microbial content testing (plus rationale).
  - “All other products, for which both a preservation challenge test and microbiological quality tests on the finished product are necessary.”

Preservative Efficacy – The How:

- PET methods for drug products are largely harmonized between official compendia, i.e. USP, EP, BP and JP.
- Other organizations that have efficacy tests: ASTM, PCPC, AOAC, ASEAN, ISO.
- Companies frequently have an in-house test based on one or several of the above.
- Procedurally, small differences exist that do not change the fundamental nature of the test.
- Key difference: acceptance criteria.

Regulatory Expectations

- No defined requirement for cosmetic products—a 28 day test is not mandated (unless self committed by product specification).
- However, we must show that a product is adequately preserved.
- OTCs do have the requirement for their relevant market—defer to applicable compendium.
- Thorough understanding of your product is key!
A Word on Cosmetics vs. OTCs

• US definition is by intended use as per the FD&C Act, section 201.
• Unlike cosmetics, OTCs must comply with 21 CFR 210/211 and the 28 day PET, if applicable.
• Products are either one or the other, and some products are both.
• Some examples of “cosmeceuticals”:
  • Sunscreens
  • Deodorants with antiperspirant
  • Antidandruff shampoos
  • Acne creams
• If a product has, or should have a “Drug Facts” box, it’s an OTC.

### Key Parameters of AETs

#### Topical Product Category

<table>
<thead>
<tr>
<th>Organization</th>
<th>Product Inoculum Level (cfu/ml)</th>
<th>Test Intervals with criteria (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Yeast/Mold</td>
<td></td>
</tr>
<tr>
<td>USP</td>
<td>$1 \times 10^{-10}$</td>
<td>14, 28</td>
</tr>
<tr>
<td>JP</td>
<td>$1 \times 10^{-10}$</td>
<td>14, 28</td>
</tr>
<tr>
<td>Ph. Eur</td>
<td>$1 \times 10^{-10}$</td>
<td>2, 7, 14, 28</td>
</tr>
<tr>
<td>BP</td>
<td>$1 \times 10^{-10}$</td>
<td>2, 7, 14, 28</td>
</tr>
</tbody>
</table>

USP = United States Pharmacopoeia
JP = Japanese Pharmacopoeia
Ph. Eur = European Pharmacopoeia
BP = British Pharmacopoeia

#### Water-Miscible Topical Product Category

<table>
<thead>
<tr>
<th>Organization</th>
<th>Product Inoculum Level (cfu/ml)</th>
<th>Test Intervals with criteria (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Yeast/Mold</td>
<td></td>
</tr>
<tr>
<td>PCPC</td>
<td>$1 \times 10^{6}$</td>
<td>7, 14, 21, 28</td>
</tr>
<tr>
<td>ASEAN</td>
<td>$1 \times 10^{6}$</td>
<td>7, 14, 21, 28</td>
</tr>
<tr>
<td>ASTM</td>
<td>$1 \times 10^{6}$</td>
<td>7, 14, 28</td>
</tr>
<tr>
<td>ISO</td>
<td>$1 \times 10^{-10}$</td>
<td>7, 14, 28</td>
</tr>
<tr>
<td>AOAC*</td>
<td>$1-9.9 \times 10^{7}$</td>
<td>7, 14, 28</td>
</tr>
</tbody>
</table>

PCPC = Personal Care Product Council
ASEAN = Association of Southeast Asian Nations
ASTM = American Society for Testing and Materials
ISO = International Organization for Standardization
AOAC = Association of Analytical Communities

* Method was withdrawn due to lack of comments
Acceptance Criteria of AETs
Official Compendia – Topical Products

<table>
<thead>
<tr>
<th>Organization</th>
<th>Acceptance Criteria (Log_{10} reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 2</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>USP</td>
<td>-</td>
</tr>
<tr>
<td>JP</td>
<td>-</td>
</tr>
<tr>
<td>Ph. Eur./BP (Criteria A)</td>
<td>2</td>
</tr>
<tr>
<td>Ph. Eur./BP (Criteria B)</td>
<td>-</td>
</tr>
</tbody>
</table>

NI = No increase (defined as no more than a half log unit higher than the previous value measured)
- = No requirement

Acceptance Criteria of AETs
Other Methods – Topical Products

<table>
<thead>
<tr>
<th>Organization</th>
<th>Acceptance Criteria (Log_{10} reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 7</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>PCPC</td>
<td>3</td>
</tr>
<tr>
<td>ASEAN</td>
<td>3</td>
</tr>
<tr>
<td>AOAC</td>
<td>3</td>
</tr>
<tr>
<td>ASTM</td>
<td>3</td>
</tr>
<tr>
<td>ISO Criteria A</td>
<td>3</td>
</tr>
<tr>
<td>ISO Criteria B</td>
<td>-</td>
</tr>
</tbody>
</table>

NI = No increase (defined as no more than a half log unit higher than the previous value measured)
- = No requirement

Criteria as Rate of Kill
USP <51> vs. PCPC vs. a hypothetical in-house criteria (bacteria)

Log reduction

0  | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 | 4.0

0  | 24hr| 48hr| 7d  | 14d | 21d | 28d |

USP
PCPC
In-house
What is Stringent?

- Robustness can be built into in-house criteria with the following:
  - Earlier log reductions
    - 2 log reduction at 24 hours instead of 7 days
  - Higher log reductions
    - 2 log reduction for yeast/mold instead of 1 log reduction at 7 days
  - Reinoculations
    - Reinoculate product at 3 or 7 days to check for marginal preservation
  - Additional organisms
    - In-house isolates
    - Organisms of concern to intended consumer population
    - Exceptionally hard-to-kill organisms
    - More comprehensive picture of efficacy/competitive inhibition

The Path to Efficiency

Rapid Screening for Lean Testing

- For items not subject to 28 day test requirements across the board, alternate screening strategies are an option.
- Efficient qualification of products with minimal formulation changes can be accomplished with 7-day reads, via in-house methods or for example with the PCPC M-7 method:
  - Plating at 1, 2 or 3 and 7 days.
  - Provides some idea of preservative system efficacy, suitability, and any immediate effects of formulation changes.
- Not a substitute for a complete preservation efficacy assessment, but not every minor change should need one. Have a guideline for determining this!

Efficient Efficacy I

<table>
<thead>
<tr>
<th>Formula A</th>
<th>7 day test</th>
<th>Formula B</th>
<th>7 day test</th>
<th>Formula C</th>
<th>28 day test</th>
<th>Formula D</th>
<th>7 day test</th>
<th>Formula E</th>
<th>7 day test</th>
<th>(best performer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replace ingredient</td>
<td>Remove</td>
<td>Replace</td>
<td>Add</td>
<td>Replace ingredient</td>
<td>Remove</td>
<td>Replace</td>
<td>Add</td>
<td>Replace ingredient</td>
<td>Remove</td>
<td>Add</td>
</tr>
</tbody>
</table>
Efficient Efficacy II
Target: EP/BP Criteria A (2 log reduction in 48 hours)

A) AwesomeServ 1.0%
• 3 log reduction in 24 hours

B) AwesomeServ 0.8%
• 3 log reduction in 48 hours

C) AwesomeServ 0.5%
• 2 log reduction in 72 hours

D) AwesomeServ 0.3%
• 1 log reduction in 7 days

Compendia and Efficiency
Approach:
Stringent in-house test with proven equivalency that exceeds compendia criteria, ideally with market overlap.

Tools:
Reduce testing via sound risk assessment and other tools: past data, families, bracketing, packaging, analytical testing, water activity.

Focal point:
Experienced microbiologist to devise rationales and interpret requirements as well as test results.

Some Examples
Approach:
Run full testing on an unfragranced base formula. If the only changes will be adding fragrance(s) and testing multiple fragrances, consider a 7 day read and bridging.

Tools:
Single-use packets of an anhydrous oil with a water activity of 0.35 being tested for preservative efficacy. "But we've always done it this way".

Focal point:
Are these results passing?

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>1230</td>
<td>270</td>
<td>810</td>
<td>830</td>
</tr>
<tr>
<td>Yeast/mold</td>
<td>120</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Final Thoughts

- The microbiology laboratory has always worked hard, but the modern laboratory must also work smart.
- Compendia and other organizations’ methods have little variance, but acceptance criteria do vary in stringency.
- These criteria should be only a starting point.
- Understand regulatory requirements and when these criteria are mandatory for your product and target market—Regulatory Affairs are your friends!
- Efficiency should never mean cutting corners, consumer risk is never acceptable.
- Be able to back up everything that is and isn’t done.

Thank You!

Q. Who Needs Preservatives?
A. Cosmetics!