"Understanding USP 71 Sterility Tests and Extended BUD"

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Disclaimer

“Although I am a member of the 2010-2015 USP Compounding Expert Committee, I am speaking today in my individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>.”
A CSP’s beyond-use date identifies:

- the time by which the preparation – once mixed –
- must be used before it is at risk for chemical degradation,
- contamination, and
- permeability of the packaging.

In other words, the BUD alerts pharmacists and caregivers about the time after which a CSP cannot be administered.
Understanding BUD

- Recognizes the probability of contamination even under best conditions:
  - Optimal employee performance
    - 0.1% (1 contaminated dose out of 1,000)
  - Contamination rates published in the literature
    - 0.3% – 16%
- Patient Safety: Protect patients from dangerous or even fatal overgrowths of microorganisms that may have been accidentally introduced
- Storage time: needs to be greater than zero but less than positive infinity*
  - (> 0 and < +∞)

* Personal conversation with Dr. David W. Newton, September 30, 2009
For patient safety, BUD must be based on two factors:

- Drug’s chemical stability in conjunction with
- Microbiological limits

BUD will always be whichever is shorter

Must factor in chemical stability

Concern that microbial over-colonization of solutions would occur over time.

- pH of solution is a consideration
  - Neutral (pH 6-8) favorable for microbial colonization
# Microbiological Beyond-Use Dating

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Room Temp</th>
<th>Refrigerator</th>
<th>Freezer (≤-10°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Use</td>
<td>1 hour</td>
<td>1 hour</td>
<td>N/A</td>
</tr>
<tr>
<td>Low</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Low w/12-hr BUD</td>
<td>12 hours or less</td>
<td>12 hours or less</td>
<td>N/A</td>
</tr>
<tr>
<td>Medium</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>
Sterility Testing

- Only required when USP <797> BUD limits are exceeded
- NO testing is required for any risk-level CSP prepared if handled within the limits, terms and conditions described in USP Chapter <797>
Process Simulation Testing (PST)

- It is only a point-in-time representation of:
  - The environment
  - The equipment
  - The procedure
  - The personnel involved

- Test Media for Suitability
  - Sterility
  - Growth Promotion
    - After the incubation period is complete

- USP FAQs
  - Does not recognize PST as a means of extending BUD
Non-Visibility of Microbial Contamination

Numbers of Bacteria per mL in 1L bottles
Millipore Corp. *Hospital Pharmacy Filtration Guide* (Cat. No. MP801)
Bedford, MA; 1980:3
USP Documentary Standards for the Microbiological Control of Parenteral Products

- <71> Sterility Tests
- <85> Bacterial Endotoxins Test
- <151> Pyrogen Test
- <51> Antimicrobial Effectiveness Test
- <1211> Sterilization and Sterility Assurance of Compendial Articles
- <1222> Terminally Sterilized Pharmaceutical Products-Parametric Release
- <1207> Sterile Product Packaging- Integrity Evaluation
What is “Sterility”?

- “Free from bacteria or other microorganisms”
  - American Heritage’s Definition of Sterility
- “Within the strictest definition of sterility, a specimen would be deemed sterile only when there is complete absence of viable microorganisms from it.”
  - <1211> Sterilization and Sterility Assurance of Compendial Articles
- Is it possible to demonstrate complete absence of microorganisms from a CSP?
- Absolute sterility can’t be demonstrated without the complete destruction of every article from the lot of CSPs.
Critical Concepts of Sterilization

- Sterility Assurance Level (SAL) is the probability of a non-sterile item making it through the validated sterilization process.

- Items terminally sterilized by moist or dry heat, irradiation, or chemical sterilants have a SAL of $10^{-6}$
  - 1 nonsterile item per 1 million items sterilized

- Items prepared aseptically with a 0.22 micron filter have a SAL of $10^{-3}$
  - 1 nonsterile item per 1 thousand items sterilized
• <1> Injections
  o Parenteral articles are prepared....to ensure they meet pharmacopeial requirements for sterility, pyrogens,...
  o Sterility Tests – Preparations for injection meet the requirements under Sterility Tests <71>
Aseptic Processing from USP Chapter <1211>:

“While there is general agreement that sterilization of the final filled container as a dosage form or final packaged device is the preferred process for assuring the minimal risk of microbial contamination in a lot, there is a substantial class of products that are not terminally sterilized but are prepared by a series of aseptic steps.”
Probability

• “The sterility of a lot purported to be sterile is therefore defined in probabilistic terms, where the likelihood of a contaminated unit or article is acceptably remote.”
USP <71> Sterility Tests states:

“These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by method suitability of the sterilization process or of the aseptic processing procedure.”
Limitation of the Sterility Test with Respect to Sample Size

- It should be recognized that the USP sterility test might not detect microbial contamination if present in only a small percentage of the finished articles in the batch, because the specified number of units to be taken imposes a significant statistical limitation on the utility of the test results.

- This inherent limitation, however, has to be accepted since current knowledge offers no nondestructive alternatives for ascertaining the microbiological quality of every finished article in the lot, and it is not a feasible option to increase the number of specimens significantly.
Sterility Testing

Table 1: The Relationship between the Probability of Passing the First and Repeat Sterility Tests and the Percentage of Nonsterile Units in the Lot Contamination Rate or Percentage of Nonsterile Units in a Batch

<table>
<thead>
<tr>
<th></th>
<th>0.1</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of passing the sterility test, ( n = 20 )</td>
<td>0.98</td>
<td>0.82</td>
<td>0.36</td>
<td>0.12</td>
<td>0.012</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Probability of passing the repeat sterility test, ( n = 20 )</td>
<td>0.99</td>
<td>0.99</td>
<td>0.84</td>
<td>0.58</td>
<td>0.11</td>
<td>0.002</td>
</tr>
</tbody>
</table>

End-product Evaluation

- Sterility testing required for CSPs that exceed <797> storage periods (all 3 risk levels)*
  - Comply with USP <71> standards
    - Two growth media required: TSB and FTM
    - Membrane Filtration or Direct Inoculation: this is the preferred method if the CSP is filterable
  - Or another method (not in <71>) if verification results demonstrated equivalence to USP <71>

14 days of incubation is required!
Sterility Testing (Membrane Filtration)

Millipore Equinox Steritest System
So HOW MUCH testing is enough?

- USP <71> provides recommendations in a table called:
  - “Minimum number of articles to be tested in relation to the number of articles in the batch”
  - Different CSP types have different test requirements for the quantity per container of a product as well as for the quantity per batch.
Number of Articles to be Tested in Relation to the Number of Articles in the Batch (From USP<71>)

<table>
<thead>
<tr>
<th>Number Items in Batch</th>
<th>Minimum Number Items to be Tested for Each Medium (unless otherwise justified and authorized)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral Preparations</strong></td>
<td>10% or 4 containers, whichever is the greater 10 containers</td>
</tr>
<tr>
<td>• Not more than 100 containers</td>
<td>2% or 20 containers, whichever is less 2% or 10 containers, whichever is less</td>
</tr>
<tr>
<td>• More than 100 but not more than 500</td>
<td>20 containers</td>
</tr>
<tr>
<td>• More than 500 containers</td>
<td>6 containers</td>
</tr>
<tr>
<td><strong>For large-volume parenterals</strong></td>
<td>See bulk solid products</td>
</tr>
<tr>
<td><strong>Antibiotic solids</strong></td>
<td>5% or 2 containers, whichever is the greater 10 containers</td>
</tr>
<tr>
<td>• Pharmacy bulk packages (&lt; 5g)</td>
<td>2% or 5 packages, whichever is the greater up to a maximum of 20 packages</td>
</tr>
<tr>
<td>• Pharmacy bulk packages (≥ 5g)</td>
<td>10% or 4 articles, whichever is the greater 10 articles</td>
</tr>
<tr>
<td><strong>Bulks and blends</strong></td>
<td>2% or 20 articles, whichever is less</td>
</tr>
<tr>
<td><strong>Ophtalmic and other noninjectable preparations</strong></td>
<td>Each container</td>
</tr>
<tr>
<td>• Not more than 200 containers</td>
<td>20% or 4 containers, whichever is greater 2% or 10 containers, whichever is greater</td>
</tr>
<tr>
<td>• More than 200 containers</td>
<td></td>
</tr>
<tr>
<td>If the product is presented in the form of single dose containers, apply the scheme shown above for preparations for parenteral use.</td>
<td></td>
</tr>
</tbody>
</table>

**Devices:**

Catgut and other surgical sutures for veterinary use

| • Not more than 100 articles | 2% or 5 packages, whichever is the greater up to a maximum of 20 packages |
| • More than 100, but not more than 500 articles | 10% or 4 articles, whichever is the greater 10 articles |
| • More than 500 articles | 2% or 20 articles, whichever is less |

**Bulk Solid Products**

| • Up to 4 containers | Each container |
| • More than 4 containers, but not more than 50 containers | 20% or 4 containers, whichever is greater 2% or 10 containers, whichever is greater |
| • More than 50 containers | |

*refer to USP <71> for additional information
Minimum Quantity to be Used for Each Medium (from USP <71>)

<table>
<thead>
<tr>
<th>Quantity Per Container</th>
<th>Minimum Quantity to be Used (unless otherwise justified and authorized)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liquids (other than antibiotics)</strong></td>
<td></td>
</tr>
<tr>
<td>• Less than 1 mL</td>
<td>The whole contents of each container</td>
</tr>
<tr>
<td>• 1 – 40 mL</td>
<td>Half the contents of each container, but not less than 1 mL</td>
</tr>
<tr>
<td>• Greater than 40 mL and not greater than 100 mL</td>
<td>20 mL</td>
</tr>
<tr>
<td>• Greater than 100 mL</td>
<td>10% of the contents of the container, but not less than 20 mL</td>
</tr>
<tr>
<td><strong>Antibiotic liquids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other preparations soluble in water or in isopropyl myristate</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Insoluble preparations, creams, and ointments to be suspended or emulsified</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Solids</strong></td>
<td></td>
</tr>
<tr>
<td>• Less than 50 mg</td>
<td>The whole contents of the container to provide not less than 200 mg</td>
</tr>
<tr>
<td>• 50 mg or more, but less than 300 mg</td>
<td>Use the contents of each container to provide not less than 200 mg</td>
</tr>
<tr>
<td>• 300 mg – 5 g</td>
<td></td>
</tr>
<tr>
<td>• Greater than 5 g</td>
<td></td>
</tr>
<tr>
<td><strong>Devices</strong></td>
<td></td>
</tr>
<tr>
<td>Catgut and other surgical sutures for veterinary use</td>
<td>3 sections of a strand (each 30 cm long)</td>
</tr>
<tr>
<td>Surgical dressing/cotton/gauze (in packages)</td>
<td>100 mg per package</td>
</tr>
<tr>
<td>Sutures and other individually packaged single-use material</td>
<td>The whole device</td>
</tr>
<tr>
<td>Other medical devices</td>
<td>The whole device, but into pieces or disassembled</td>
</tr>
</tbody>
</table>

*refer to USP <71> for additional information
Flow of the Sterility Test

1. Media and Bacteriostasis/Fungistasis Testing
2. Eliminate any bacteriostatis/fungistatic properties
3. Determine number of articles, quantity from each, to test
4. Incubate the samples
5. Examine test articles for signs of growth
6. Examine suspect tubes microscopically for signs of growth
7. Subculture if necessary
8. Write the report

Reminder: All Compendial Microbiological Test Methods, including Sterility Tests, are Classical Growth Based Methods
Who Should Conduct the Tests?

- Sterility testing shall be performed in a qualified microbiology laboratory/microbiologists.
  - Pharmacies do not have the education, qualifications or the physical facilities to do the testing.
    - This testing involves the use of live bacteria and fungi to test the ability of the media to support growth of a variety of microorganisms.
- Ideally, media used to perform a sterility test should be validated by following the Growth Promotion Tests (GPT) in USP <71>.
  - Each lot of media should have a Certificate of Performance that demonstrates that the lot meets USP compendial standards.
Due to the inherent low probability that a Sterility Test can detect low levels of contamination in a batch, **sterility assurance must always be based** on process design and control.
“Absence of Evidence Does Not Equal Evidence of Absence.”

Dr. David Hussong (of FDA and the USP Microbiology and Sterility Assurance Expert Committee)
Remember the Patient

- Even though you may not see the patient, always remember that real people receive the CSPs made at your pharmacy.
- Patients who receive CSPs are mothers and fathers, brothers and sisters.
- They are loved ones who need to receive our best efforts.
References

- Revised Sterility Tests and Sterility Assurance Slides presented at the IPC-USP 8th Annual Scientific Meeting February 11-12, 2009, Hyderabad, India. Radhakrishna S. Tirumalai, Ph.D, Senior Scientist and Staff Liaison, Microbiology and Sterility Assurance Expert Committee


References


