Requirements of validation of packaging systems and sterility assurance

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Topics

1. Risk of infection when using sterilized products contaminated with a low count of environmental microbes

2. Validation of visual inspection of sterile barrier systems as one of the methods to detect compromised sterility; relevance of punctures, wet bursting strength, bursting strength and tearing resistance

3. Validation of maintenance of sterility: compatibility of airborne microbial filtration efficiency of sterile barrier systems with airborne microbial challenge

4. Responsibility for the handling of terminally sterilized products
Risk of infection when using sterilized products contaminated with a low count of environmental microbes
<table>
<thead>
<tr>
<th>Infection/outbreak</th>
<th>Cause</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus meningitis outbreak in 2 hospitals in Sri Lanka after spinal anaesthesia for caesarean section&lt;sup&gt;1&lt;/sup&gt;</td>
<td>“sub-optimal storage of sterile devices for over 6 months after tsunami was most plausible reason”</td>
<td>No infections when syringes are used for other injections. Unopened syringes showed growth.</td>
</tr>
<tr>
<td>Outbreak with 80 cases of BSI in 6 US states after use of heparinized saline flush syringes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Syringes were prepared as compounded medical products.</td>
<td>P. fluorescens was identified in unopened syringes; The specific source of contamination could not be identified.</td>
</tr>
<tr>
<td>Exposure to propofol in 7 hospitals was associated with postoperative infections&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Risks: “use syringes of propofol that had been prepared up to 24 h beforehand”, “prepare multiple syringes …at one time for use throughout the day.”</td>
<td></td>
</tr>
</tbody>
</table>

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Recommendations to reduce the risk of microbial growth by shortening the in-use application time

• From a microbiological point of view, the product should be used immediately\(^1\)

• Replace tubing used to administer blood, blood products, or fat emulsions (...) within 24 hours of initiating the infusion\(^2\)

• Propofol: use strict aseptic technique … discard within 12 hours of opening\(^3\)

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\(^1\) CPMP (Committee for proprietary medicinal products), 1998
\(^2\) CDC, 2011: Guidelines for the prevention of intravascular catheter-related infections, 2011
\(^3\) Labeling text of the manufacturer
Validation of visual inspection as one of methods to detect compromised sterility; relevance of punctures, wet bursting strength, bursting strength and tearing resistance
# Defect detection rates of visual inspection of compromised packagings*

<table>
<thead>
<tr>
<th>Defect size (mm)</th>
<th>Defect detection rate of visual inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>6.7 %</td>
</tr>
<tr>
<td>3.7</td>
<td>64.4 %</td>
</tr>
</tbody>
</table>

*Data from Waked et al.: Sterilization wrap inspections do not adequately evaluate instrument sterility. Clin Orthop Relat Res 2007;462:207-11*
Mechanical pressure caused bursting during steam sterilization:
Limit values of bursting strength, wet bursting strength, and internal tearing resistance according to EN 868 part 2-10

<table>
<thead>
<tr>
<th>Performance parameter</th>
<th>Material</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paper (for pouches, reels)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coated nonwoven m. of polyolefins (for pouches, lids)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncoated nonwoven m. of polyolefines (for pouches, lids)</td>
<td></td>
</tr>
<tr>
<td>Bursting strength</td>
<td>230</td>
<td>kPa</td>
</tr>
<tr>
<td>Wet bursting strength</td>
<td>35</td>
<td>kPa</td>
</tr>
<tr>
<td>Internal tearing resistance</td>
<td>550</td>
<td>mN</td>
</tr>
</tbody>
</table>
Sporadic device-associated infections caused by compromised packaging integrity are difficult to identify because:

- the microbiological status of the unopened device can no longer be examined,
- exposures and patients are scattered or isolated in time and location.
Validation of maintenance of sterility: compatibility of airborne microbial filtration efficiency of sterile barrier systems with airborne microbial challenge
ISO 11607-1

“Porous materials shall provide an adequate microbial barrier to microorganisms in order to provide integrity of the sterile barrier system and product safety.” *)

*ISO 11607-1, 2006, clause 5.2.2


ISO 11607-1

“the conditions under which the … preformed sterile barrier system are handled shall be established, controlled and recorded…to ensure that the conditions are compatible with the use for which the material and/or sterile barrier system is designed … .”: *)

• Temperature range

• Pressure range, …

• Maximum rate of change of the above. …

• Bioburden.

The property of the microbial barrier of the packaging material shall be evaluated.

*) ISO 11607-1, 2006, subclauses 5.1.3 - 5.1.6
Knowing data of barrier efficiency against airborne microbes is absolutely necessary for:

• comparing and selecting the suitable and best packaging material,

• for assessing the compatibility of the packaging material with provided storage conditions.
Validation of compatibility of the sterile barrier system with events caused by airborne microbial challenge

Predetermined quality attributes
Maintenance of sterility based on quantitative risk analysis

Performance parameter
Airborne microbial retention capacity

Relevant factors to be considered
Level and relevant sizes of airborne particles bearing microorganisms
Flow rate of air through the layers of packaging material
Validation of compatibility of the sterile barrier system with events characterized by airborne microbial challenge

Volume flow based on air pressure change:
\[ p \times V = \text{const.} \]

Volume flow based on temperature change:
\[ \Delta V = V_1 \times \frac{\Delta t}{T_1} \]

Calculation of compatibility:
\[ \frac{N_0 \times 100 - \text{Filtration efficiency (\%)} \times n \leq 10^{-6}}{100} \]

Airborne bioburden (< 5 \( \mu \)m): 10 CFU/m³
Room temperature: 20 °C
Filtration efficiency: 99.6%

Microbial challenge per event:
\[ N_0 = \Delta V_{t+p} \times 10 \text{ CFU/m}^3 \]

<table>
<thead>
<tr>
<th>number of events per week</th>
<th>scenario A</th>
<th>scenario B</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta t = 1 ) °C;</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>( \Delta p = 10 \text{ hPa} )</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>bioburden sized &lt; 5 ( \mu )m</td>
<td>10 CFU/m³</td>
<td>10 CFU/m³</td>
</tr>
</tbody>
</table>
Calculation of the number of events (n) and shelf life compatible with the SAL

<table>
<thead>
<tr>
<th>exposure scenario</th>
<th>1 event per week scenario A</th>
<th>7 events per week scenario B</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of events (n)</td>
<td>shelf life</td>
<td>shelf life</td>
</tr>
<tr>
<td>single wrap</td>
<td>3.7</td>
<td>3 weeks</td>
</tr>
<tr>
<td>double wrap</td>
<td>934</td>
<td>(18 years)</td>
</tr>
</tbody>
</table>
Consequences of the proposed validation procedure

• Low variations of temperature and low rates of their changes reduce the microbial challenge;

• Transports (containership, transport plane) with relevant temperature changes and atmospheric pressure changes raise the microbial challenge;

• Outsourcing of sterilization can increase the risk of recontamination through transport routes with convulsions, temperature variations, changes in air pressure (different altitudes).
Mayworm, D:

“When products are packaged so that they remain sterile, the archaic practice of outdating is no longer necessary”. *)

Responsibilities for the handling with terminally sterilized products
Responsibility for the handling of terminally sterilized products

“In general the responsibility for the quality of the packaging material is divided accordingly, where:

1) the manufacturer of the packaging material and/or system is responsible for the quality of the packaging material as it is being supplied, and the identification of the intended use;

2) the user of the packaging material and/or system for its proper application, and by implication for the final quality of the packaging design or system.” *)

*) EN 868-1, 1997, Annex A.1.2
Summary

- The use of the best possible validation methods can help prevent hospital acquired infections.

- Event-Related Sterility Maintenance Policy is well-accepted and should be practised consistently according to International Standards.
Thank you for your attention