Infection Control

Low Temperature Sterilization (LTS)
Critical Aspects on Selection and Validation of LTS-Processes

Dr. Tronje von dem Hagen
tronje@vondemhagen.com
Lübeck (Germany)
Criteria to evaluate and to compare low temperature sterilizers and applied processes.

- **Safety for the patient** (microbicidal efficacy, residuals)
- **Safety for the operator** (occupational health)
- **Equipment performance and process validation in compliance to applicable standards and regulations**
- **Short cycle times** (operational capacity)
- **Low life cycle costs** (investments and operation)
- **Reliable operation** (fail safe, availability)
- **Easy to handle and to operate** (ergonomics)
- **Efficient service and maintenance** (time to repair)
Three subprocesses in Sterilization

1. **Transportation**
   - Sterilant supply from source

2. **Microbicidal interaction**

3. **Transportation**
   - Sterilant removal

Three significantly different types of subprocesses, these individually to be designed and validated!
pressure profile steam sterilization
(fractionated pre-vacuum process)

- Conditionning
- Holding time (e.g. 5 min)
- Drying

Graph:
- Pressure profile over time
- Saturation steam pressure: 2 bar at 134°C
- Holding time: ca. 40 min
- Conditionning:
  - 70 mbar abs.

WFHSS Prag, Oct 2014
T. v. dem Hagen, Lübeck/Germany
pressure profile ETO-sterilization

(STERIVIT- high/low pressure process)

<table>
<thead>
<tr>
<th>Conditionning</th>
<th>Holding time</th>
<th>Desorption phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>pressure [bar]</td>
<td></td>
<td>ca. 8 - 10 hrs</td>
</tr>
<tr>
<td>5.5 bar (ca. 1 hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7 bar</td>
<td></td>
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</tr>
</tbody>
</table>

ca. 10 - 12 hrs

T. v. dem Hagen, Lübeck/Germany

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pressure profile LTSF-process
(Matachana 130 LF)

- Conditionning
- Holding time
- Desorption & drying

Saturation steam pressure at 60°C \(\approx p = 218 \text{ mbar}\)

- 53mbar
- 200mbar
- 1013mbar

- 15x
- 30 min
- 25x

ca. 180 min.

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pressure profile NTP / HPO - process
(STERRAD 100NX)

Pressure

H2O2 injection & diffusion
plasma
H2O2 injection & diffusion
plasma

ca. 50 min.

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pressure profile NTP / HPO - process
(V-pro 1)

Time

0 10 20 30 40 50

Pressure

1000
100
10
1
0.1

Conditioning

H₂O₂ Injection & diffusion

Pulse 1

Pulse 2

Pulse 3

Pulse 4

aeration

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**Most important applicable international standards**

**ETO standards:**

- **EN 1422:2014** Sterilizers for medical purposes - Ethylene oxide sterilizers - Requirements and test methods

- **EN ISO 11135-1:2014** Sterilization of health care products - Ethylene oxide - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices
Most important applicable international standards

LTSF standards:

EN 14180:2014  Sterilizers for medical purposes – Low temperature steam and formaldehyde sterilizers – Requirements and testing

EN ISO 25424:2011  Sterilization of medical devices - Low temperature steam and formaldehyde - Requirements for development, validation and routine control of a sterilization process for medical devices
Most important applicable international standards

Biological Indicators:

EN ISO 11138-1:2006  Sterilization of health care products - Biological indicators - Part 1: General requirements


EN ISO 11138-5:2006  Sterilization of health care products - Biological indicators - Part 5: Biological indicators for low-temperature steam and formaldehyde sterilization processes
HPO: No specific standards available!

In most cases EN ISO 14937 is referenced for compliance, however, this standard does not describe any technical requirement on equipment or process performance, rather than just management requirements on how to specify, to perform development and to verify design of such equipment and processes.

Note:
Each manufacturer of H2O2 Sterilizers is creating and documenting his own individual specifications for equipment performance, for process performance, for monitoring and safety features, for test & validation procedures, test items (PCDs), and pass / fail criteria!
**Germ reduction by sterilization**

Schematic presentation, 1st order kinetics

\[ \Delta N = -k \, N \, \Delta t \quad \Rightarrow \quad N = N_0 \, e^{-t / D(T, c)} \]

(T = temperature, c = sterilant concentration, t = time)

e.g. G. Stearothermophilus ATCC 7953:

- \( D_{121^\circ C/steam} = 2,5 \) min
- \( D_{60^\circ C/3\% \text{ FA}} = 6 \) min

Holding time

12x \( D \)

Overkill buffer

\( EN 556-1: \text{SAL} < 10^{-6} \)
Germ reduction by sterilization

Schematic presentation, 1st order kinetics

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E.g. G. Stearothermophilus ATCC 7953:

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In practice not available for reliable measurement

Overkill buffer

EN 556-1: SAL < 10^{-6}
Linear extrapolation of the killing curve is the basic concept of EN ISO 14937 for development and performance verification of any kind of sterilization process.

EN ISO 14937 allows also for non-linear killing curves, however then there should be a clear evidence based rationale and mathematical relationship for the curve to allow extrapolation to the required SAL (clause 5.3).

Further, it requires means for control and monitoring of the relevant process variables, here temperature T and sterilant concentration c(t) within specified limits (clauses 6.2, 6.3).
Germ reduction by sterilization
Schematic presentation, higher order kinetics

\[ \Delta N = - k N \Delta t \implies N = N_0 e^{-t/D(T, c)} \]

(T = temperature, c = sterilant concentration, t = time)

H₂O₂: \( D = D(T, c^n(t)) \)

In practice not available for reliable measurement

overkill buffer??
Germ reduction by sterilization
Half cycle concept, decreasing sterilant concentration
Germ reduction by sterilization

Half cycle concept, decreasing sterilant concentration assuming deficient transportation conditions in part
Safety for the patient (microbicidal efficacy)
here: penetration performance, example

<table>
<thead>
<tr>
<th>Sterilization methods</th>
<th>EOG</th>
<th>HPO-PLASMA</th>
<th>LTSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCD No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.1</td>
<td>2mm×1,500mm</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>No.2</td>
<td>3mm×1,500mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.3</td>
<td>5mm×1,000mm</td>
<td></td>
<td></td>
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<tr>
<td>No.4</td>
<td>2mm×3,000mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.5</td>
<td>4mm×1,500mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.6</td>
<td>2mm×4,500mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.7</td>
<td>3mm×3,000mm</td>
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</tr>
<tr>
<td>No.9</td>
<td>4mm×3,000mm</td>
<td></td>
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</tr>
<tr>
<td>No.10</td>
<td>5mm×3,000mm</td>
<td></td>
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<tr>
<td>No.11</td>
<td>2mm×250mm</td>
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<tr>
<td>No.12</td>
<td>2mm×500mm</td>
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<td>No.13</td>
<td>2mm×750mm</td>
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<td>No.14</td>
<td>2mm×1,000mm</td>
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<td></td>
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<tr>
<td>No.15</td>
<td>2mm×1,500mm</td>
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</tr>
</tbody>
</table>

These positive results were gave to us when we used 2mm and 33mm diameter dead end PCDs with HPO-PLASMA sterilization.

Keiji Kanemitsu et al.; Comparitive study of current low-temperature sterilization methods; Annual WFHSS and JSMSI Conference 2012, 13th World Sterilization Congress, Session 2-03, 21.-24 Nov. 2012, Osaka, Japan
Safety for the patient (sterilant residues): HPO

for example:

R. Yoshida and H. Kobayashi\(^\ddagger\) from Tokyo University have found residue levels at sterilized plastic test items from 14 to 280 µg/L for several hours after sterilization, which are significantly above allowed limit values from public health requirements (e.g. 1.41 µg/L)

\(^\ddagger\) Rika Yoshida, Hiroyoshi Kobayashi; Problems on hydrogen peroxide sterilization - New proposal for safety and effective use:

Annual WFHSS and JSMI Conference 2012, 13th World Sterilization Congress. Session 7-2, 21.-24-Nov. 2012, Osaka, Japan
Safety for the operator (occupational health): HPO here: inhalative exposition

Recent publications, e.g. at WFHSS in 2012 have stated pollution levels to the ambient of operating HPO sterilizers reaching up to 2,3 ppm (Y. Saito et.al.), and even up to 50 ppm just after opening the chamber at the end of cycle (R. Yoshida, H. Kobayashi).

These values exceed by far generally accepted limit values from occupational health authorities, i.e. 8 hrs Time Weighted Average (TWA) = 1 ppm and proposals for Europe to reduce it to 0,5 ppm.

Yuhei Saito, Satoshi Murakoshi, Takami Komatsu, Kazuhiko Fukatsu, Yushi Uetera, Hiroshi Yasuhara; Hydrogen peroxide concentration around gas plasma sterilizers;

and further

Rika Yoshida, Hiroyoshi Kobayashi; Problems on hydrogen peroxide sterilization - New proposal for safety and effective use;

both at Annual WFHSS and JSMI Conference 2012, 13th World Sterilization Congress, Session 7-2, 21.-24. Nov. 2012, Osaka, Japan
Criteria to evaluate and to compare low temperature sterilizers and applied processes (within the responsibility of the user!)

Safety for the patient (microbicidal efficacy, residuals)

Safety for the operator (occupational health)

Equipment performance and process validation in compliance to applicable standards and regulations

Short cycle times (operational capacity)

Low life cycle costs (investments and operation)

Reliable operation (fail safe, availability)

Easy to handle and to operate (ergonomics)

Efficient service and maintenance (time to repair)

These criteria depend much on local installation and very specific operational frame conditions, → no objective criteria are available
• Reported results from practice have shown inconsistencies with respect to patients safety and operators safety when using specific HPO sterilizers.

• Limited penetration performance for narrow lumen items ask for individual verification on site for such medical devices by validation tests.

For comparison: No such alarming results have been reported for ETO or LTSF sterilization.
Concerning HPO sterilization, no specific harmonized technical standards are available for sterilizer design, for process performance, and for respective tests and validation; severe differences can be found in practice for different brands.

No standardized Biological Indicators for HPO are available, D-values for evaluation of sterilization performance are not comparable.
These findings for HPO sterilization, which persists already since many years, do not allow consistent and respectable interpretation or evidence based evaluation

- with respect to the state of the art, and
- in comparison with ETO and LTSF sterilization.
This underlines the compulsory necessity to establish practicable harmonized standards for HPO sterilizers, processes, and test requirements.

THANK YOU FOR YOUR ATTENTION!