Ethylene Oxide: Annual Requalification Review
Agenda

• ANSI/AAMI/ISO 11135
  o Requirements
  o Guidance

• Annual Revalidation Review
  o Equipment
  o Product
  o Process
  o Process history
  o Regulatory change

• Output of Requalification Review

• Summary
Section 12 – Maintaining Process Effectiveness

12.3 Requalification

12.3.1 **IQ, OQ, PQ and subsequent requalification(s) shall be reviewed annually** to determine the extent of requalification that is necessary. This shall include an assessment of the need to reconfirm the product SAL through microbiological studies. The outcome of this review, including the rationale for decisions reached, shall be documented.

12.3.2 Requalification of a sterilization process carried out with specified equipment shall be performed at defined intervals against specified acceptance criteria and in accordance with documented procedures. These intervals shall be justified.

The simplest route to compliance

- Have a documented procedure that requires an annual review of validation (IQ, OQ, PQ)
- Use the Requalification Decision Tree detailed in D.12.3.2
D.12.3.2 Requalification

Requalification Decision Tree

- Annual Review
  - Equipment
    - Changes
    - Calibration
    - Maintenance
  - Product
    - Design
    - Packaging
    - Materials
    - Manufacturing process
    - Bioburden
    - Load Configuration
  - Processing History
    - Deviations
    - Process failures

- Change(s)
  - Yes → Significant Change(s)
  - Yes → Full Qualification
  - No → Re-qualified within last 2 years
  - No → Reduced Requalification

- Re-qualified within last 2 years
  - Yes → Document Rationale
  - No → Feedback for next Annual Review

Note - Where more than one configuration is validated, this should be reflected in any requalification activity
## Requalification – Equipment Review

<table>
<thead>
<tr>
<th>Changes to Equipment</th>
<th>Calibration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Have there been any changes?</td>
<td>• Review of IQ status</td>
</tr>
<tr>
<td>• Have changes been requalified and documented correctly?</td>
<td>• Control and monitoring equipment calibrated?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Review of OQ Status</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Has periodic requalification of equipment been performed?</td>
<td>• Preventative maintenance complete?</td>
</tr>
<tr>
<td></td>
<td>• Equipment appropriately requalified after maintenance interventions?</td>
</tr>
<tr>
<td></td>
<td>• Maintenance activities properly documented?</td>
</tr>
</tbody>
</table>
## Requalification – Product Review

### Design
- Have there been significant changes and are they documented?
- Have new products been adopted into validation?

### Packaging
- Have there been significant changes and are they documented?
  - Instructions for use, Breathable area, Packaging materials

### Materials
- Have there been significant changes and are they documented?

### Maintenance
- Have there been significant changes in the manufacturing process that could impact product characteristics?
  - i.e. Bioburden, EO residues, SAL

### Bioburden
- Have bioburden tests been performed in accordance with ISO 11737-1?
- Is bioburden data consistent with original validation?

### Load Configuration
- Have there been significant changes in the load configuration?

*Has rationale been recorded for adopted changes?
Requalification – Processing History

**Process Design Changes**
Have there been any significant changes in the sterilization process design?

**Process Deviations**
- Biological Indicator failures

**Process Failures**
- Non-Conformance failures

**Parametric Release**
- Capability assessment key parameters

**Other Process History**
- Number of processes
- Capability assessment
- Ethylene Oxide residues
<table>
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<th>Process Design Changes</th>
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<tr>
<th>Process Failures</th>
<th>Parametric Release</th>
<th>Other Process History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Conformance failures</td>
<td>Capability assessment key parameters</td>
<td>• Number of processes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Capability assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ethylene Oxide residues</td>
</tr>
</tbody>
</table>
Have there been any significant changes in the sterilization process design?

- Any change to parameters / specifications for:
  - Preconditioning?
    - Time, temperature, RH, other..
  - Sterilizer phase? – (Check value change)
    - Evacuation /injection set points or rates
    - Temperature
    - Steam additions
    - Dwell phase times and set points
    - Other..
  - Aeration phase?
    - Time, temperature, other

Any changes should be detailed, assessed for their impact on Product safety/SAL and documented.
Requalification – Processing History

**Process Design Changes**

Have there been any significant changes in the sterilization process design?

**Process Deviations**

Biological Indicator failures

**Process Failures**

Non-Conformance failures

**Parametric Release**

Capability assessment key parameters

**Other Process History**

- Number of processes
- Capability assessment
- Ethylene Oxide residues
Process Deviations – Biological Indicator Failures

Have their been any BI positives in routine processes since previous review/ validation?

Some considerations for review:

• Were potential causes of failure reviewed at the time?

• Are failures indicative of marginal process that could impact Product SAL?

• Are failures indicative of External Process Challenge Device that provides a too severe challenge and is unrepresentative of IPCD?

• What are laboratory ‘false positive’ levels?
## Requalification – Processing History

### Process Design Changes

Have there been any significant changes in the sterilization process design?

### Process Deviations

- Biological Indicator failures

### Process Failures

- Non-Conformance failures

### Parametric Release

- Capability assessment key parameters

### Other Process History

- Number of processes
- Capability assessment
- Ethylene Oxide residues
Some factors to be considered

• How many NC’s?
  o Were they all ‘closed out’ and documented appropriately?

• Were root causes established?

• Any associated CAPA’s?
  o Have they been closed out?
  o Effectiveness verification?

• Any trends evident?

• If equipment was the cause:
  o Was equipment repaired effectively?
  o Was equipment re-qualified (if necessary) prior to release back to production?
Requalification – Processing History

Process Design Changes
Have there been any significant changes in the sterilization process design?

Process Deviations
Biological Indicator failures

Process Failures
Non-Conformance failures

Parametric Release
Capability assessment key parameters

Other Process History
• Number of processes
• Capability assessment
• Ethylene Oxide residues
Review/Trend Capability data for key parameters (i.e.)
Minimum temperature during gas dwell over prior 12 months:

<table>
<thead>
<tr>
<th>Temperature Minimum (C)</th>
<th>Mean</th>
<th>Max</th>
<th>Min</th>
<th>STDEV</th>
<th>CSA_SP</th>
<th>CSA_Max</th>
<th>CSA_Min</th>
<th>CSA_ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Data Set</td>
<td>49.1</td>
<td>50.0</td>
<td>48.1</td>
<td>0.3</td>
<td>49.0</td>
<td>55.0</td>
<td>46.0</td>
<td>16806</td>
</tr>
</tbody>
</table>

Other parameters to consider
• Minimum product temperature prior to process, RH during Steam Dwell,
• EO concentration during Gas Dwell during gas dwell
Requalification – Processing History

Process Design Changes
Have there been any significant changes in the sterilization process design?

Process Deviations
Biological Indicator failures

Process Failures
Non-Conformance failures

Parametric Release
Capability assessment key parameters

Other Process History
- Number of processes
- Capability assessment
- Ethylene Oxide residues
Other Processing History

• Number of processes
  o How many processes ran?
  o In which chambers? (i.e. were all validated chambers used?)

• Capability assessment
  o Assess capability for key parameter?

• EO residues
  o Have residue tests been performed?
  o Any relevance in ‘spot’ test to ensure product compliance after validated aeration conditions
Requalification Review, if Not Already Done

• ISO 11135 was updated in July 2014 and contains:
  o Changes to Requirements and a
  o Significant amount of new guidance
  o As of July 2017; this is now the only applicable Standard

• During your current Requalification Review process:
  o It is appropriate to assess the existing validation vs the changes in requirements in ISO 11135:2014

• Keep records of the review and detail either:
  o Any actions to be taken or;
  o A rationale to justify no actions are needed
D.12.3.2 Requalification

Requalification Decision Tree

Annual Review
- Equipment
  - Changes
  - Calibration
  - Maintenance
- Product
  - Design
  - Packaging
  - Materials
  - Manufacturing process
  - Bioburden
  - Load Configuration
- Processing History
  - Deviations
  - Process failures

Change(s) Yes
Significant Change(s) Yes
Full Qualification

No

No

Reduced Requalification

No

Yes

Document Rationale

Note – Where more than one configuration is validated, this should be reflected in any requalification activity.
After reviewing all of above:

- Some changes, but not significant
- Good processing history
- Previous validation 1 year ago

Decision might be **NO NEED FOR REQUALIFICATION**

- If so, Document the decision and any rationale used to reach this decision
- Might consider residue tests to confirm compliance to ISO 10993-7
### After reviewing all of above:

<table>
<thead>
<tr>
<th>✅ Some changes, but not significant</th>
<th>✅ Good processing history</th>
<th>✅ Validation or last requalification 1 year ago</th>
</tr>
</thead>
</table>

**Or:**

<table>
<thead>
<tr>
<th>✅ No changes</th>
<th>✅ Good processing history</th>
<th>✅ Validation or last requalification 2 years ago</th>
</tr>
</thead>
</table>

**Decision might be REDUCED REQUALIFICATION**

- If so, Document the decision and any rationale used to reach this decision
- Typically, 1x Half Cycle with T/RH monitoring
After reviewing all of above:

- Some changes, and significant
- Good processing history

Or:

- No changes
- Poor processing history*
  *i.e. regular BI failure

Decision might be **FULL REQUALIFICATION**

- If so, Document the decision and any rationale used to reach this decision
- Typically, 3 or 4x Half Cycle with T/RH monitoring
- 1-3 Full Cycle processes
# Requalification – Case Study 1

## Annual Review Discovery

During the review you noticed your bioburden shifted higher as the year progressed. Further investigation revealed there was a manufacturer change in the last year that was not evaluated.

## Consider the Following

- Perform an adoption study to evaluate the change in manufacturing location.
- Perform in-depth evaluation of bioburden at new location to identify any possible problem organisms.
- Compare bioburden levels with original validation levels.
There was a product adoption performed. During the adoption study the Candidate was shown to be more resistant than the validated master PCD (internal PCD). However, because the D-values were within 20% the adoption was determined to be acceptable.

**Annual Review Discovery**

- Perform reduced requalification to confirm more resistant internal PCD does not impact SAL.
  - If requalification is unsuccessful may have to perform full requalification.
- Confirm the external PCD is still appropriate for the sterilization process.
- Has residual testing been performed on the new device?

**Consider the Following**
You have a parametric release process. During your review you noticed the average EO gas concentration during gas dwell has trended down so it is closer to the minimum specification. You also noticed there was a routine load that did not meet the minimum specification for EO concentration.

Consider the Following

- Evaluate equipment.
- Evaluate your product.
- A new analysis may be required to determine a new specification.
  - Process Definition run may be needed.
### Annual Review Discovery

- **Equipment** – The vacuum pump in the chamber was replaced. The replacement was considered like for like
- **Product** – Person performing annual review was not aware of any changes
- **Processing History** – BI failure associated with 1 routine load. Root cause was equipment failure
- **Cycle** was validated 3 years ago

### Consider the Following

- Perform a reduced requalification
- There were no significant changes noted during the Annual Review. However, the original validation or previous requalification was performed over 2 years ago so a physical requalification run is needed
# Requalification – Case Study 4

## Perform Reduced Requalification Half Cycle
- Internal PCDs – 20 positives out of 40 samples tested (20+ / 40)
- External PCDs – No growth on samples tested (0+ / 40)

## Investigation
- No deviation was found with the processing of the half cycle
- The company was using a different type of shipper box compared to the original validation

## Consider the Following
- Company can chose to return to the shipper box used during the validated
  - Repeat Reduced Requalification with correct shipper boxes
- Company can chose to move forward with the new shipper box type
  - Perform a full qualification using the new shipper boxes
Requalification – Summary

• Have procedure that defines:
  o How validated product list is maintained
  o How Product families, Master products PCD’s are established
  o How products might be adopted on to validated product list
  o Annual validation review process
  o Changes/circumstances that define need for requalification

• Perform review annually
  o Document outcome of review and rationale to make decisions

• Perform a requalification run at least every 2 years
Questions?
Thanks for Listening