Bacterial Endotoxins Testing: Alternatives to Batch Testing

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Agenda

• Alternatives to Batch Testing

• Risk Assessment Framework
  – Assessment of the Severity of a Pyrogenic Response
  – Assessment of the Probability of a Pyrogenic Response
  – Overall Assessment of Risk

• Worked Examples:
  – Ceramic Hip Implant
  – Cranial Burr Hole Cover

• Endotoxin Control Measures in Lieu of Finished Product Testing
Alternatives to Batch Testing

Options include (from AAMI CDV-4 ST72, section B.11.2.4):

• Reduced number of samples
• Reduced frequency of testing
• Specified combinations of products based upon product grouping
• Testing of raw materials and monitoring of risks in the manufacturing process
• Other logical alternatives
Severity x Probability = Risk

Refer to ANSI/AAMI/ISO 14971
Assessment of the Severity of a Pyrogenic Response

- Severity is dependent on intended use of the product
- Consider:
  - Level and rate of patient endotoxin exposure
  - Type of contact (e.g. intravascular, intralymphatic, intrathecal, or intraocular) and the associated endotoxin limits
  - Type of pyrogenic response that might be expected based on type of contact (e.g. fever, meningitis, rapid fall in blood pressure, etc.)
  - Health status of patient population
  - Impact on the overall patient’s health
### Assessment of the Severity of a Pyrogenic Response: Example of Severity Classification System

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negligible</td>
<td>A pyrogenic response would result in inconvenience or temporary discomfort (e.g. low fever). Product types: no direct or indirect intravascular, intralymphatic, CSF, or intraocular contact</td>
</tr>
<tr>
<td>Minor</td>
<td>A pyrogenic response would result in temporary injury or impairment not requiring professional medical intervention (e.g. low or moderate fever). Product types: external communicating devices with indirect intravascular/intralymphatic contact, certain implants</td>
</tr>
<tr>
<td>Serious</td>
<td>A pyrogenic response would result in injury or impairment requiring professional medical attention (e.g. high fever). Product types: implants and external communicating devices with direct intravascular/intralymphatic contact, indirect intraocular contact; response could impact implant performance or require replacement of implant</td>
</tr>
<tr>
<td>Critical</td>
<td>A pyrogenic response would result in permanent impairment or life-threatening injury (e.g. high fever, rapid fall in blood pressure, organ failure). Product types: indirect CSF contact, direct intraocular contact</td>
</tr>
<tr>
<td>Catastrophic</td>
<td>A pyrogenic response would result in patient death (e.g. high fever, meningitis, rapid fall in blood pressure). Product types: direct CSF contact</td>
</tr>
</tbody>
</table>
Assessment of the Probability of a Pyrogenic Response

- Quantified based on probability of endotoxins being present
- Primarily influenced by manufacturing controls
- Consider:
  - Whether water or solutions containing water are used
  - Type of water and how frequently it is changed
  - Frequency of water system sanitization and/or cleaning/sanitization of associated equipment
  - Frequency of bioburden/endotoxin testing on water and associated limits
  - If there are any downstream processes that are effective at removing or inactivating endotoxins (e.g. cleaning, passivation, ultrafiltration, high temperatures)
  - For products that support growth of microorganisms, the controls in place to prevent/control the growth (e.g. storage conditions)
  - In-process or component testing
  - Historical data
## Assessment of the Probability of a Pyrogenic Response: Example of Probability Classification System

<table>
<thead>
<tr>
<th>Probability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td>No water used, or downstream processes are used that remove/deactivate endotoxins. Product/processes do not support growth of microorganisms. History of acceptable data.</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td>Water is used, but water is controlled for endotoxins. Product/processes could support growth of microorganisms, but controls are in place.</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>Water is used, but it is not controlled for endotoxins. Product/processes could support growth of microorganisms, and inadequate controls are in place.</td>
</tr>
</tbody>
</table>
## Overall Assessment of Risk

### PROBABILITY OF PYROGENIC RESPONSE

<table>
<thead>
<tr>
<th>SEVERITY OF PYROGENIC RESPONSE</th>
<th>LOW</th>
<th>MEDIUM</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negligible</td>
<td>A</td>
<td>A</td>
<td>A/B</td>
</tr>
<tr>
<td>Minor</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Serious</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Critical</td>
<td>B</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Catastrophic</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>
Overall Assessment of Risk

A (low risk) = alternative to batch testing approach is acceptable
  • Reduce sample size (e.g. 3 samples instead of 10)
  • Reduce frequency (e.g. monthly, quarterly, or annual)
  • Testing representatives from product families (e.g. testing the largest size from a family of implants)
  • Alternatives to end-product testing (e.g. in-process or component testing)

B (medium risk) = alternative to batch testing approach is acceptable
  • Reduce sample size (e.g. 3 samples instead of 10)
  • Testing representatives from product families (e.g. testing the largest size from a family of implants)
  • Testing must still be conducted on every batch

C (high risk) = alternative to batch testing approach is NOT acceptable
  • Consider implementing additional controls
Worked Example: Ceramic Hip Implant

- Implant with tissue/bone contact
- Permanent contact duration (greater than 30 days)
- Not intended to have direct or indirect intravascular, intralymphatic, intrathecal, or intraocular contact
- Endotoxin limit: 20 EU/device
Worked Example: Ceramic Hip Implant

• Severity of pyrogenic response: SERIOUS

• Rationale:
  – Pyrogenic response could impact product performance (e.g. bone ongrowth)
  – Response could require intervention (e.g. replacement of implant)

• Probability of pyrogenic response: LOW

• Rationale:
  – Final cleaning process is performed that has been demonstrated to produce parts with very low endotoxin levels
    • Data is available for the product in question (3 lots)
    • Data is available for many other products cleaned per the same process at the same site
  – DI water system is controlled (monthly sanitization, monthly endotoxin and bioburden testing)
  – Cleaning equipment is drained/cleaned weekly and all bath temperatures are elevated to prevent microbial growth
Worked Example: Ceramic Hip Implant

- Overall risk: A (low risk)
- Alternative to batch testing plan: test 3 samples on a quarterly basis

- Reaction plan in case a failure occurs:
  - Initiate an investigation
  - Temporarily revert to batch release testing until the investigation has been completed
  - Identify lots produced in the time period since the last acceptable test result and either quarantine (pending results of the investigation) or perform batch release testing
  - Upon completion of the investigation (and any corrective/preventive actions, if applicable), determine the impact on the risk assessment and whether any adjustments should be made to the sampling plan/frequency
Worked Example: Cranial Burr Hole Cover

- Burr hole cover is used following cranial surgery to hold catheters and leads in place
- Not intended to directly contact CSF, but has potential to contact CSF via leads and catheters
- Endotoxin limit: 2.15 EU/device
Worked Example: Cranial Burr Hole Cover

• Severity of pyrogenic response: CRITICAL
  • Rationale:
    – Indirect CSF contact

• Probability of pyrogenic response: MEDIUM
  • Rationale:
    – Product is injection molded at a high temperature and for a sufficient duration that is effective at providing a 1 log reduction in endotoxins
    – Water is not used, but a byproduct of resin manufacturing process is water
    – Resin manufacturing process is not controlled for endotoxins
Worked Example: Cranial Burr Hole Cover

• Overall risk: C (high risk)

• Alternative to batch testing is NOT acceptable

• If risk can be reduced by incorporating additional endotoxin controls, alternative to batch testing might be acceptable
Endotoxin Control Measures in Lieu of Finished Product Testing

- Consider use of water (and other liquids) and associated endotoxin controls
- Sub-component testing in lieu of finished product testing
- Validated endotoxin reduction step
Figure B.3 — Example of a risk assessment flow diagram that could be used to evaluate endotoxin contamination risks from incoming components and to determine any ongoing monitoring requirements.
I'M SO CUTE

DON'T STARTLE ME CUZ MY TEMP WILL JUMP 1°C AND FAIL YOUR MMP TEST
Questions

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