Lm Regulatory Update

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1. New FSMA Requirements
2. FDA Draft Guidance for Industry: Hazard Analysis & Risk-Based Preventive Controls for Human Food
3. FDA Draft Guidance for Industry: Control of Lm in RTE Foods
   - Produce is a RTE food
   - Foods that support growth of Lm?
   - Environmental Monitoring Program (EMP)
   - Ingredient Testing
   - Finished Product Testing
   - Plant Design, Construction and Operation (Misc.)
4. Inspections
   - What to do when FDA shows up?
   - For cause vs routine inspection
   - Split samples
New FSMA Requirements

PCHF requirements expressly directed to Lm & to RTE foods.

❖ The definition of “environmental pathogen” identifies Lm as an environmental pathogen (21 CFR 117.3)

❖ Hazard evaluation required by 21 CFR 117.130 must include an evaluation of environmental pathogens whenever an RTE food is exposed to the environment prior to packaging and the packaged food does not receive a treatment or otherwise include a control measure (such as a formulation lethal to the pathogen) that would significantly minimize the pathogen (21 CFR 117.130(c)(1)(ii)).
Wet processing areas be dried out as much as possible.

- **Wet floors** due to constant wet cleaning will facilitate the transfer of L. spp., including Lm, from an environmental source to food contact surfaces.
- **Wet floors** can create harborage sites if they are not well maintained.
- **Condensation** on overhead structures creates a means of transfer of L. spp., including Lm, from non-food-contact surfaces to exposed product and equipment food-contact surfaces.
- **Frost formation** (moisture accumulation) and a constant source of water for *Listeria spp.* to multiply.
- **Inadequate sanitation** practices on floor freezer and cooler units may provide the moisture to support *Listeria spp.*, including Lm, if water sources are not properly plumbed to hygienically designed drains.
Sanitation: The nature of a bacterial pathogen (e.g., whether it is a transient or a resident strain of an environmental pathogen) also impacts the selection of the appropriate CGMP sanitation procedures, practices, and processes, or the appropriate sanitation control.

Zoning: The objective of hygienic zoning is to reduce the potential for transient pathogens to enter sensitive areas in the facility, such as packing areas where an RTE product is exposed to the processing environment. Typically, this type of sanitation control is applied in facilities that make RTE products.
Monitoring: When sanitation controls are required for environmental pathogens, little or no monitoring may be needed when cleaning and sanitation are conducted in accordance with established written protocols. Occasional verification that procedures are being followed may suffice. See 21 CFR 117.140.

Monitoring programs answer four questions:
- What will be monitored?
- How will monitoring be done?
- How often will monitoring be done (frequency)? and
- Who will do the monitoring?
Corrective Action procedures that must be taken if you:

❖ detect the presence of a pathogen or appropriate indicator organism in a ready-to-eat product as a result of product testing or

❖ if you detect the presence of an environmental pathogen or appropriate indicator organism through your environmental monitoring activities. See 21 CFR 117.150(a) and (a)(1).
Appendix 3: Bacterial Pathogen Growth & Inactivation

❖ **Table 3-A** Limiting Conditions for Pathogen Growth

❖ **Table 3-B** Time and Temperature Guidance for Controlling Pathogen Growth and Toxin Formation in Food Products

❖ **Table 3-D** Inactivation of Lm

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Min. pH (using salt)</th>
<th>Min. pH</th>
<th>Max. % Water Phase Salt</th>
<th>Min. Temp.</th>
<th>Max. Temp.</th>
<th>Oxygen Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacillus cereus</em></td>
<td>0.92</td>
<td>4.3</td>
<td>9.3</td>
<td>10</td>
<td>32.2°F</td>
<td>facultative anaerobe*</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>0.987</td>
<td>4.9</td>
<td>9.5</td>
<td>1.7</td>
<td>86°F</td>
<td>micro-aerophile</td>
</tr>
<tr>
<td><em>Clostridium botulinum, type A, and proteolytic types B and F</em></td>
<td>0.935</td>
<td>4.6</td>
<td>9.3</td>
<td>10</td>
<td>55°F</td>
<td>anaerobe*</td>
</tr>
<tr>
<td><em>Clostridium botulinum, type E, and non-proteolytic types B and F</em></td>
<td>0.97</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>37.9°F</td>
<td>anaerobe*</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>0.93</td>
<td>5</td>
<td>9</td>
<td>7</td>
<td>50°F</td>
<td>anaerobe*</td>
</tr>
<tr>
<td>Pathogenic strains of <em>Escherichia coli</em></td>
<td>0.95</td>
<td>4</td>
<td>10</td>
<td>6.5</td>
<td>43.7°F</td>
<td>facultative anaerobe*</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>0.92</td>
<td>4.4</td>
<td>5.4</td>
<td>10</td>
<td>31.3°F</td>
<td>facultative anaerobe*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological Hazardous Condition</th>
<th>Product Temperature</th>
<th>Maximum Cumulative Exposure Time</th>
<th>Internal Product Temperature (°F)</th>
<th>Internal Product Temperature (°C)</th>
<th>Lethal Rate</th>
<th>Time for CD Process (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth and toxin formation by <em>Bacillus cereus</em></td>
<td>35.2-41°F (2.8-6°C)</td>
<td>5 days</td>
<td>145</td>
<td>63</td>
<td>0.117</td>
<td>17.0</td>
</tr>
<tr>
<td>Growth of <em>Campylobacter jejuni</em></td>
<td>86-93°F (33.3-34°C)</td>
<td>48 hours</td>
<td>149</td>
<td>65</td>
<td>0.215</td>
<td>9.3</td>
</tr>
<tr>
<td>Germination, growth, and toxin formation by <em>Clostridium botulinum, type A, and proteolytic types B and F</em></td>
<td>50-75°F (10-21°C)</td>
<td>11 hours</td>
<td>151</td>
<td>66</td>
<td>0.253</td>
<td>6.8</td>
</tr>
<tr>
<td>Germination, growth, and toxin formation by <em>Clostridium botulinum, type E, and non-proteolytic types B and F</em></td>
<td>37.5-41°F (3.3-6°C)</td>
<td>7 days</td>
<td>153</td>
<td>67</td>
<td>0.396</td>
<td>5.0</td>
</tr>
<tr>
<td>Germination, growth, and toxin formation by <em>Clostridium perfringens</em></td>
<td>55-74°F (13-21°C)</td>
<td>21 days</td>
<td>154</td>
<td>68</td>
<td>0.541</td>
<td>3.7</td>
</tr>
<tr>
<td>Growth of pathogenic strains of <em>Escherichia coli</em></td>
<td>43.7-50°F (6.6-10°C)</td>
<td>2 days</td>
<td>155</td>
<td>69</td>
<td>0.736</td>
<td>2.7</td>
</tr>
<tr>
<td>Growth of <em>Listeria monocytogenes</em></td>
<td>31.3-34°F (0.5-1.8°C)</td>
<td>7 days</td>
<td>156</td>
<td>70</td>
<td>1.000</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Draft Guidance: Control of Lm in RTE Foods

FDA Regulatory Policy: FDA DRAFT Guidance to Industry

❖ Control of Lm in Ready-To-Eat Foods
  • Issued: January 2017
  • Comments Due: 26 July 2017

❖ Key Issues
  • Zero Tolerance for Lm
  • Produce is a RTE Food (What is covered by this guidance?)
  • Foods that support growth of Lm?
  • Environmental Monitoring
    o EMP Sampling Frequency
    o Corrective Actions
  • Ingredient Testing
  • Finished Product Testing
  • Plant Design, Construction and Operation (Misc.)
Draft Guidance: Control of Lm in RTE Foods

Fresh Produce Has Unique Challenges

❖ do not receive a listeriacidal treatment;
❖ may or may not support Lm growth;
❖ are likely to have a low persistent prevalence of Lm as they are grown in the outdoors;
❖ no known preventive controls to control, reduce or eliminate the presence of Lm in fields or on fresh produce grown outdoors.

Issues

❖ Zero tolerance is aspirational
❖ Produce RAC’s can’t get to zero
A Brief History of FDA’s Approach to Listeria:

❖ 1985 - FDA establishes a policy that detection of Lm in a RTE food is a violation of the FD&C Act adulteration provisions 402(a)(1) & (4).
❖ 1996 - U.S. public health & regulatory agencies established a zero tolerance for Lm in cooked, ready-to-eat food.
❖ 2003 - FDA/FSIS Risk Assessment
❖ 2004 - FAO/WHO Risk Assessment
❖ 2008 - Draft Compliance Policy Guide and Notice of Public Meeting
❖ 2008 - Draft Lm Guidance for Industry
❖ 2008 - FDA/FSIS Listeria Risk Assessment for Retail Delis
❖ 2008 - Draft Lm Guidance for Industry
❖ 2008 - Draft Compliance Policy Guide and Notice of Public Meeting
❖ 2013 - FDA/FSIS Listeria Risk Assessment for Retail Delis
❖ 2015 - FDA Listeria Dose-Response Model
  • Hoelzer et al. 2013
  • Pouillot et al. 2015
❖ 2017 - FDA Draft Guidance for Industry

Hoelzer et al. 2013
Pouillot et al. 2015
Draft Guidance: Control of Lm in RTE Foods

Lm Dose Response Revisited (Pouillet et al., 2015)
Incorporating Adjustments for Variability in Strain Virulence & Host Susceptibility

Purpose:
• a novel framework
• does not provide a definitive dose-response model for policy development

Issues:
• Refinements & additional data needed for a definitive dose-response model (e.g. relative risk of listeriosis among different subgroups).
• Assumptions were preferentially chosen to be conservative and public health protective (biases the Lm dose response model results in a higher probability of infection for low doses).
  o neglects bacterial growth from retail to consumption and
  o Caps contamination max for Lm (6.1 log10 cfu/g)
• Public health policies based on this dose response model would be highly conservative, not supported by the peer-reviewed literature and therefore inappropriate.
FDA Blue Bell Ice Cream Lm Sampling

- 2,290 samples of tested
  All but 13 samples were positive (99.4% positive)
  • Range: <0.03 MPN/g to > 208 MPN/gm
- Highly consistent low contamination levels
  • 15% below 1 MPN/gm
  • 58% below 5 MPN/gm
  • 77% below 10 MPN/gm
  • 92% below 20 MPN/gm
  • 98% below 50 MPN/gm
  • 99.8% below 100 MPN/gm
- 4 samples > 100 MPN/gm (0.2%)

Chen et al, IAFP 2015
Draft Guidance: Control of Lm in RTE Foods

Ready-to-eat food (RTE food) means any food that is normally eaten in its raw state or any other food, including a processed food, for which it is reasonably foreseeable that the food will be eaten without further processing that would significantly minimize biological hazards.
(Excerpted from Preventive Controls for Human Foods Rule § 117.3 Definitions)

Issues

❖ Should FDA Lm Guidance apply to other foods, not just those covered by 21 CFR 117 (PCHF) Rule?
❖ Should FDA consider different types of RTE foods:
  • RAC
  • Fresh-cut (mild Listeriacidal treatment)
  • Blanched Frozen (Listeriacidal treatment)
Draft Guidance: Control of Lm in RTE Foods

Foods that support growth of Lm?

*Examples of RTE foods that support the growth of* L. monocytogenes *and that have been found to be contaminated with* L. monocytogenes *are unpasteurized and pasteurized milk, high fat dairy products, soft unripened cheese (Cottage Cheese, Cream Cheese, Ricotta), cooked ready-to-eat crustaceans (shrimp, crab), smoked seafood, fresh soft cheese (Queso Fresco), semi-soft cheese (Blue, Brick, Monterey), soft-ripened cheese (Brie, Camembert, Feta), deli-type salads, sandwiches, fresh-cut fruits and vegetables, and raw molluscan shellfish (Ref. 7, Ref. 26, and Ref. 27). An example of an RTE food that does not support the growth of* L. monocytogenes, *but has been found to be contaminated with* L. monocytogenes, *is ice cream (Ref. 28 and Ref. 6).*  
(Excerpted from DRAFT Lm Guidance Page 4)

**Issues**

❖ Define fresh-cut?
❖ Do all fresh-cut produce items support growth? NO
Draft Guidance: Control of Lm in RTE Foods

Environmental Monitoring Program

We concur with following FDA recommendations in the draft Lm guidance regarding environmental monitoring:

❖ It is appropriate to use *Listeria spp.* as an indicator for Lm.
❖ A finding of *Listeria spp.* does not mean that Lm is present.
❖ An initial finding of *Listeria spp.* should not trigger an automatic requirement for speciation, but should trigger corrective action.
❖ In the absence of additional data, the finding of an isolated positive for an indicator on a product contact surface does not render product adulterated.
❖ If you know that you are operating in an environment where Listeria can find a home and be a problem, you should do environmental monitoring if the product is RTE.
Draft Guidance: Control of Lm in RTE Foods

Environmental Monitoring Program

❖ Zoning for fresh produce:
  o With no listeriacidal treatment do zones apply? Maybe?
❖ Are all environmental FCS positives equal in seriousness?
❖ Frequency of environmental monitoring; Hazard Analysis Driven
❖ Sampling during a production run is problematic for produce.
❖ Corrective Action (2nd positive) = complete shut down; “not a free pass”
❖ Timing of second sampling.
Table 6.--Corrective Actions when *Listeria* species is found in an environmental sample

<table>
<thead>
<tr>
<th>Routine sampling positive #1</th>
<th>Non-FCS Food supports growth</th>
<th>Non-FCS Food does not support growth</th>
<th>FCS Food supports growth</th>
<th>FCS Food does not support growth*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Clean and sanitize area of positive</td>
<td>• Clean and sanitize area of positive</td>
<td>• Clean and sanitize area of positive</td>
<td>• Clean and sanitize area of positive</td>
</tr>
<tr>
<td></td>
<td>• Retest during next production cycle</td>
<td>• Retest during next production cycle</td>
<td>• Retest during next production cycle</td>
<td>• Retest during next production cycle</td>
</tr>
<tr>
<td>Follow up sampling positive #2</td>
<td>• Intensified cleaning and sanitizing (possibly including disassembly of equipment)</td>
<td>• Intensified cleaning and sanitizing</td>
<td>• Intensified cleaning and sanitizing (including disassembly of equipment)</td>
<td>• Intensified cleaning and sanitizing (including disassembly of equipment)</td>
</tr>
<tr>
<td></td>
<td>• Intensified sampling and testing</td>
<td>• Intensified sampling and testing</td>
<td>• Intensified sampling and testing</td>
<td>• Intensified sampling and testing</td>
</tr>
<tr>
<td></td>
<td>• Reprocess, divert or destroy product on hold if there is positive product</td>
<td>• Hold and test product</td>
<td>• Comprehensive investigation</td>
<td>• Consider hold and test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Comprehensive investigation</td>
</tr>
</tbody>
</table>

*Note: "FCS Food does not support growth" requires specific actions not listed in the table.*
## Draft Guidance: Control of Lm in RTE Foods

<table>
<thead>
<tr>
<th></th>
<th>Non-FCS Food supports growth</th>
<th>Non-FCS Food does not support growth</th>
<th>FCS Food supports growth</th>
<th>FCS Food does not support growth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow up sampling positive #3</strong></td>
<td>Root cause analysis</td>
<td>Root cause analysis</td>
<td>• Stop production and consult experts for comprehensive investigation</td>
<td>• Intensified cleaning and sanitizing (including disassembly of equipment)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intensified cleaning and sanitizing (escalated, e.g., steam equipment)</td>
<td>• Intensified sampling and testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intensified sampling and testing</td>
<td>• Hold and test product</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resume production with product hold and test until 3 consecutive days of product and FCSs are negative</td>
<td>• Expand comprehensive investigation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Hold and test product</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Reprocess, divert or destroy positive product lots</td>
</tr>
<tr>
<td><strong>Follow up sampling positive #4</strong></td>
<td></td>
<td></td>
<td></td>
<td>Stop production and consult experts for comprehensive investigation</td>
</tr>
</tbody>
</table>

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*FCS: Food Contamination System*
Draft Guidance: Control of Lm in RTE Foods

Ingredient Testing

4. Testing when receiving raw materials and other ingredients under a COC or COA

If your controls on raw materials or other ingredients include a COC for L. monocytogenes, we recommend that you periodically test raw materials and other ingredients received under the COC to verify the efficacy of the supplier’s control programs.

Issues

❖ Produce RACs pose challenges
❖ Is L spp an alternative to testing for Lm in RAC ingredients?
Product Testing

A. Periodic Sampling and Testing of RTE Foods to Verify Adequacy of Your Controls

We recommend that you test food products for *L. monocytogenes* rather than for *Listeria* spp. because of the risk to public health from *L. monocytogenes* in food. If you choose to test food for *Listeria* spp. and find it to be positive, we recommend you determine whether the *Listeria* spp. is *L. monocytogenes* or treat the food as if it were contaminated with *L. monocytogenes*. We recommend that you hold all product that is represented by the food you test, e.g., food lots produced from cleanup to cleanup.

**Issues**

- Difficult to test and hold fresh produce.
- Product testing seems redundant to PC verification efforts.
- Recommend coordinating: EMP & product sampling.
We recommend that you separate areas where RTE foods are processed, exposed or stored from areas where raw foods are processed, exposed or …

Issues
- Separating RTE foods from other areas.
- Trench drains: new construction, may be needed.
- Employee garments.
- CVM list of animals not affected by Lm
- Testing Methods: BAM “comparable” not BAM “equivalent”
What to do when FDA knocks

FDA Inspections

Routine

Directed

❖ “For cause”
❖ Follow-up to previous inspection
❖ Recall effectiveness check
❖ Consumer complaint
❖ Criminal
What to do when FDA knocks

Pre-Inspection Do’s
❖ Have a company Inspection Manual
❖ Have a trained Inspection Team (legal counsel)
❖ Identify what FDA (or the state) may inspect
❖ Be familiar with relevant sections of FDA’s Investigations Operations Manual
❖ Include policies on:
  • Photographs
  • FDA record review
  • Complaint file review
  • Providing shipping records
  • Procedures boundaries (areas and interviews of employees)
  • Being accompanied
❖ Conduct mock inspections periodically
❖ Review prior inspection reports and check status of any promised corrective action
What to do when FDA knocks

FSMA -- broader FDA records access during inspections when “reasonable probability” of serious adverse health consequences or death from food

- Prior authority: Access records for food at issue
- Current authority: Expands access to records of related products if reasonable belief that they are likely to be affected in similar manner

FDA Forms

- 482 – notice of inspection
- 482c – request for records
- 483 – notice of observations
- 484 – samples
What to do when FDA knocks

FDA may collect samples of product or labeling
❖ Upon request, FDA to provide part of official sample to facility owner (companies usually take their own, too)
❖ Receipt to be provided for collected samples

Upon request, FDA to provide copy of analytical results of samples
What to do when FDA knocks

❖ FDA will take photographs if useful.
❖ FDA does not ask for permission.
❖ If you object FDA will:
  • Cite two court cases
  • Report objection to FDA District Office
  • Office of Chief Counsel will contact business legal counsel and/or senior management.
  • Contact State regulators.
Thank You & Questions

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