

Dated: February 5, 2013.

**Ron A. Otten,**

Director, Office of Scientific Integrity (OSI),  
Office of the Associate Director for Science  
(OADS), Office of the Director, Centers for  
Disease Control and Prevention.

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2012-N-1182]

#### Draft Joint Food and Drug Administration/Health Canada Quantitative Assessment of the Risk of Listeriosis From Soft-Ripened Cheese Consumption in the United States and Canada

**AGENCY:** Food and Drug Administration,  
HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or we) is announcing the availability of a draft “Joint Food and Drug Administration/Health Canada—Santé Canada Quantitative Assessment of the Risk of Listeriosis From Soft-Ripened Cheese Consumption in the United States and Canada.” This draft Quantitative Risk Assessment (the draft QRA) includes an Interpretative Summary, a Technical Report, with Appendixes, and a risk assessment model. The purpose of the draft QRA is to evaluate the effect of factors such as the microbiological status of milk, the impact of cheese manufacturing steps, and conditions during distribution and storage on the overall risk of invasive listeriosis to the consumer in the United States or Canada of soft-ripened cheese. The draft QRA makes it possible to evaluate the effectiveness of some process changes and intervention strategies in reducing the risk of listeriosis. We are making the draft QRA available for public comment.

**DATES:** Submit either electronic or written comments on the draft QRA by April 29, 2013.

**ADDRESSES:** Submit electronic comments to <http://www.regulations.gov>. Submit written comments to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Sherri Dennis, Center for Food Safety and Applied Nutrition (HFS-005), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 240-402-1914.

## SUPPLEMENTARY INFORMATION:

### I. Background

*Listeria monocytogenes* (*L. monocytogenes*) is a widely occurring pathogen that can be found in agricultural and food processing environments. Ingestion of *L. monocytogenes* can lead to the development of listeriosis, with consequences that may include septicemia, meningitis, encephalitis, spontaneous abortion, and stillbirth. Epidemiological data show that listeriosis has one of the highest hospitalization rates and one of the highest case fatality rates among foodborne diseases in the United States (Ref. 1). Serious illness may occur in people considered to be more susceptible, such as the elderly, individuals who have a preexisting illness that reduces the effectiveness of their immune system, and pregnant women (Ref. 2).

The United States and Canada have experienced sporadic illnesses and outbreaks of listeriosis associated with the consumption of soft cheese. Both FDA and Health Canada—Santé Canada continue to evaluate the safety of soft cheese, particularly soft cheese made from unpasteurized milk.

### II. Quantitative Risk Assessment

The draft QRA (Refs. 3 to 6) provides a science-based analytical approach to collate and incorporate available data into a mathematical model. It provides risk managers with a decision-support tool to evaluate the effectiveness of current and future interventions to reduce or prevent listeriosis from consumption of soft-ripened cheeses. The draft QRA also may be used to target risk communication messages, identify and prioritize research needs, and provide a framework for coordinating efforts with stakeholders. The draft QRA has undergone an independent external peer review consistent with the requirements in the Office of Management and Budget’s “Final Information Quality Bulletin for Peer Review.” FDA’s response to the peer-review is available electronically on the FDA Web site (Ref. 7).

The draft QRA focuses on the sources of *L. monocytogenes* contamination, the effects of individual manufacturing and/or processing steps, and the effectiveness of various intervention strategies on the levels of *L. monocytogenes* in the product as consumed and the associated risk of invasive listeriosis. The draft QRA’s scope is:

- Pathogen of concern: *L. monocytogenes*;

- Food(s) of concern: Camembert, as an example of soft-ripened cheese;
- Populations of interest: The general populations of the United States and Canada, and subpopulations identified as at-risk in both countries (i.e., pregnant women, immunocompromised individuals, and the elderly population);
- Endpoint of concern: Invasive listeriosis; and
- Risk metric: The probability of invasive listeriosis per soft-ripened cheese serving.

The draft QRA uses a quantitative approach, using mathematical and probabilistic modeling, to estimate the risk per serving of soft-ripened cheese (using Camembert cheese as an example) in both countries. The draft QRA tests the effects of some alternatives on those risks. The draft QRA uses data from the literature, from government nutrition surveys, from a specific survey on home storage time and temperature practices, and from specific expert elicitations. FDA invites comments that can help FDA and Health Canada—Santé Canada improve:

- The approach used;
- The assumptions made;
- The modeling techniques;
- The data used; and
- The clarity and the transparency of the draft QRA documentation.

When finalized, FDA intends to use this risk assessment (which is limited to one pathogen in one type of cheese), along with other information and scientific assessments that more comprehensively consider the different pathogens that can be present in all types of cheeses made from raw milk, in its reevaluation of the existing 60-day aging requirements for cheeses made with raw milk (e.g., 21 CFR 133.182(a)).

### III. Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

### IV. Electronic Access

The draft QRA is available electronically on the FDA Web site <http://www.fda.gov/food/scienceresearch/researchareas/>

[riskassessmentsafetyassessment/](http://www.regulations.gov/riskassessmentsafetyassessment/) and at <http://www.regulations.gov>.

## V. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m. Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site addresses in this reference section, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

- Goulet, V., M. Hebert, C. Hedberg, et al., "Incidence of Listeriosis and Related Mortality Among Groups at Risk of Acquiring Listeriosis." *Clinical Infectious Diseases*, 54(5): 652–660, 2012.
- Scallan, E., R. M. Hoekstra, F. J. Angulo, et al., "Foodborne Illness Acquired in the United States—Major Pathogens," *Emerging Infectious Diseases*, 17(1): 7–12, 2011.
- U.S. Food and Drug Administration and Health Canada (2012). "Joint Food and Drug Administration/Health Canada—Santé Canada Quantitative Assessment of the Risk of Listeriosis from Soft-Ripened Cheese Consumption in the United States and Canada: Draft Interpretative Summary." Accessible at <http://www.fda.gov/Food/ScienceResearch/ResearchAreas/RiskAssessmentSafetyAssessment/default.htm>.
- U.S. Food and Drug Administration and Health Canada (2012). "Joint Food and Drug Administration/Health Canada—Santé Canada Quantitative Assessment of the Risk of Listeriosis from Soft-Ripened Cheese Consumption in the United States and Canada: Draft Technical Report." Accessible at <http://www.fda.gov/Food/ScienceResearch/ResearchAreas/RiskAssessmentSafetyAssessment/default.htm>.
- U.S. Food and Drug Administration and Health Canada (2012). "Joint Food and Drug Administration/Health Canada—Santé Canada Quantitative Assessment of the Risk of Listeriosis from Soft-Ripened Cheese Consumption in the United States and Canada: Draft Technical Report Appendices." Accessible at <http://www.fda.gov/Food/ScienceResearch/ResearchAreas/RiskAssessmentSafetyAssessment/default.htm>.
- U.S. Food and Drug Administration and Health Canada (2012). "Joint Food and Drug Administration/Health Canada—Santé Canada Quantitative Assessment of the Risk of Listeriosis from Soft-Ripened Cheese Consumption in the United States and Canada: Draft Risk Assessment Model." Analytica file. Accessible at <http://www.fda.gov/Food/ScienceResearch/ResearchAreas/RiskAssessmentSafetyAssessment/default.htm>.
- U.S. Food and Drug Administration and Health Canada (2012). "Joint Food and

Drug Administration/Health Canada—Santé Canada Quantitative Assessment of the Risk of Listeriosis from Soft-Ripened Cheese Consumption in the United States and Canada: Answer to the Peer Review." Accessible at <http://www.fda.gov/ScienceResearch/SpecialTopics/PeerReviewofScientificInformationandAssessments/ucm079120.htm>.

Dated: February 5, 2013.

**Leslie Kux,**

*Assistant Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA–2013–D–0092]

#### Draft Guidance for Industry on Immunogenicity Assessment for Therapeutic Protein Products; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Immunogenicity Assessment for Therapeutic Protein Products." Therapeutic protein products may elicit immune responses, and these responses may lead to serious or life-threatening adverse events for the patient or loss of efficacy of the product. This draft guidance is intended to assist manufacturers to develop a risk-based approach in both the preclinical and clinical phases of the development of therapeutic protein products to evaluate and mitigate immune responses that may adversely affect their safety and efficacy.

**DATES:** Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by April 12, 2013.

**ADDRESSES:** Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993–0002, or Office of Communication, Outreach and Development (HFM–40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, suite 200N,

Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

#### FOR FURTHER INFORMATION CONTACT:

Amy Rosenberg, Center for Drug Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bldg. 29A, rm. 2D–16, Bethesda, MD 20892, 301–827–1790; or Stephen Ripley, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–6210.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Immunogenicity Assessment for Therapeutic Protein Products." The purpose of this document is to assist manufacturers and clinical investigators involved in the development of therapeutic protein products for human use. The guidance outlines, and recommends adoption of, a risk-based approach to evaluating and mitigating the potential for immunogenicity that may affect the safety and efficacy of therapeutic protein products. The guidance describes various product- and patient-specific factors that can affect the immunogenicity of protein therapeutics and provides recommendations pertaining to each of these factors that may reduce the likelihood that these products will generate an immune response. In addition, the guidance offers a series of recommendations for risk mitigation in the clinical phase of development of protein therapeutics. The draft guidance also provides supplemental information on the diagnosis and management of particular adverse consequences of immune responses to protein therapeutics and contains brief discussions of the uses of animal studies and the conduct of comparative immunogenicity studies.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on immunogenicity assessment of therapeutic protein products. It does not