United States Department of Agriculture
Food Safety and Inspection Service
Washington, D.C. 20250

APR 11 2008

Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

Re: [Docket No. FDA-2008-D-0058] Draft Compliance Policy Guide, Sec. 555.320 – *Listeria monocytogenes*; Availability and [Docket No. 2007D-0494] Draft Guidance for Industry: Control of *Listeria monocytogenes* in Refrigerated or Frozen Ready-to-Eat Foods; Availability; 73 FR 7293, Feb. 7, 2008.

Dear Sir or Madam:

In his March 27, 2008, letter to Dr. Stephen Sundlof, Director, Center for Food Safety and Applied Nutrition, FDA, Dr. Richard A. Raymond, Under Secretary, Office of Food Safety, USDA, expressed significant concerns about the subject compliance policy guide and accompanying draft guidance to industry on control of *Listeria monocytogenes* in ready-to-eat (RTE) foods. He noted that FSIS would be submitting extensive and technical comments on the draft documents.

Enclosed are comments focusing mainly on FDA's draft policy respecting a limit of 100 colony-forming units per gram of *L. monocytogenes* in RTE foods that do not support growth of the pathogen. The comments were prepared by scientific and technical staffs in the FSIS Office of Public Health Science and the FSIS Office of Policy and Program Development. Please enter these comments in the record of public comments on the subject documents.

Sincerely,

Charles E. Williams

Charles E. Williams
Program Analyst
Policy Issuances Division
Office of Policy and Program Development

Enclosure

Food Safety and Inspection Service comments on Food and Drug Administration Draft Compliance Policy and Guidance to Industry on *Listeria monocytogenes* in Ready-to-Eat Foods

I. Introduction

Our (FSIS's) comments on the FDA draft enforcement policy focus on the limit FDA would apply to foods that do not support growth of *Listeria monocytogenes*. In its February 7, 2008, Federal Register (FR) notice (at 73 FR 7303), FDA states its belief that "an enforcement policy aimed at maintaining *L. monocytogenes* below 100 cfu/g for such foods is protective of the most vulnerable populations" and that "it would be rare to find *L. monocytogenes* at greater than 100 cfu/g in RTE foods that do not support its growth." FDA therefore expects that maintaining contamination below 100 cfu/g is achievable in these foods (73 FR 7303) and would be safe for all consumers. In the draft Compliance Policy Guide for FDA Staff -- Sec. 555.320 *Listeria monocytogenes* [http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0058-GDL.pdf Accessed March 2008], FDA states that it may regard a RTE food that does not support the growth of *L. monocytogenes* to be adulterated within the meaning of section 402(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 342(a)(1)) when *L. monocytogenes* is present at or above 100 colony-forming units per gram (cfu/g) of food. The draft "Guidance for Industry: Control of *Listeria monocytogenes* in Refrigerated or Frozen Ready-to-Eat Foods" [http://www.cfsan.fda.gov/~dms/lmrtegui.html Accessed March 2008] provides information on what a food processor should do, including corrective actions to take in case of *Listeria* contamination, to prevent a "no-growth" product with greater than 100 cfu/g of *L. monocytogenes* from entering commerce.

As FDA should know, on September 13, 2005, FSIS responded to a May 31, 2005, petition from a coalition of 14 trade associations, known as the Alliance for Listeriosis Prevention, for a regulatory limit of 100 cfu/g of *L. monocytogenes* in foods that do not support growth of *L. monocytogenes*. (The same coalition had submitted a similar petition to FDA in 2004). FSIS rejected the petition, without prejudice to its revision and resubmission, expecting that the petitioners would provide us further information. We stated in our response that, while the concept of a quantitative pathogen limit for certain products under carefully defined circumstances may have merit, we were concerned about the limitations of available sampling and testing methods and the gaps in knowledge about the survival and growth of *L. monocytogenes* on products and its infectious dose for humans. We also expressed our concern about the implications of the proposed limit for the efficient and effective administration of our inspection program.

FDA's notice on its draft compliance policy and industry guidance does little to allay our concerns about having a limit for *L. monocytogenes* in the "no-growth" RTE products. Our comments below express in detail our reservations concerning FDA's draft policy and guidance and their potential implications for food safety.

II. Preliminary discussion

One concern we have with FDA's draft documents relates to the direct consequences of a 100-cfu/g limit for *L. monocytogenes* and to the question of how safe the threshold really is. In addition, FDA has not spelled out the compliance and enforcement procedures it would use to ensure that products entered in commerce do not contain levels of *L. monocytogenes* above the 100-cfu/g limit. FDA does not explain how it would, if it could, develop effective compliance procedures and is ambiguous on the subject of how the limit would be enforced.

In explaining the rationale for its enforcement policy, FDA emphasizes one of the circumstances in which a food may be considered to be adulterated – its containing a poisonous or deleterious substance which may render it injurious to health (21 U.S.C. 341(a)(1)). Although FDA notes that, "the criteria in the guidance do not establish an acceptable level of *L. monocytogenes* in food," and that it could still take legal action against food adulterated with the pathogen, FDA does not provide the basis for such action with respect to RTE foods contaminated with *L. monocytogenes*.

FDA also states that criteria in the guidance do not excuse violations of the requirement in 21 U.S.C. 342(a)(4) that food may not be prepared, packed, or held under insanitary conditions or the requirements in FDA's current good manufacturing practices regulation (21 CFR 110). The latter regulation requires food manufacturers to take "all reasonable precautions . . . to ensure that production procedures do not contribute contamination from any source" (21 CFR 110.80). Yet in its draft documents on *L. monocytogenes* in RTE foods, FDA appears to overlook the potential for RTE product-to-product direct and indirect cross-contamination. In our view, FDA should not only show that its policy would ensure that product sold in commerce is not directly injurious to health, but also that potential cross-contamination from the product would not directly or indirectly render other products injurious to health.

Regarding the sanitation provision referred to, FDA should show that, under its draft policy and associated compliance procedures, products would be produced under sanitary conditions. We wonder about the impact of FDA's policy on maintaining sanitary conditions during production when permitting the presence of *L. monocytogenes* in the environment and on product entering commerce. FDA would, in effect, be permitting the sale in commerce of product contaminated with the pathogen. This product contamination, in our view, indicates a loss of sanitation controls in the processing environment. We think it would be difficult to show that a product contaminated with up to 100 cfu/g of *L. monocytogenes* was produced under sanitary conditions.

FDA partly justifies its draft policy in this regard by arguing that the policy would induce processing establishments to change their product mix to a greater proportion of products that do not permit the growth of *L. monocytogenes*. However, such a hopeful prognosis overlooks the sanitation issues and their possible ramifications over the long term. Further, even if FDA were correct about changes in production favoring more "no-growth" products, its policy could raise the risk of listeriosis for some consumers to the

detriment of others more vulnerable. We think FDA should consider other options that would induce establishments to provide safer product while not increasing risks to any subset of consumers, at least without warning them, and to maintain sanitary conditions during processing.

The remainder of this document addresses our concerns in some detail. Section III addresses the safety of the 100-cfu/g limit and associated issues with modeling dose-response. Section IV addresses compliance-procedure issues. Section V discusses cross-contamination. Section VI covers issues of economic analysis relating to FDA's draft policy. The final section summarizes our conclusions.

III. Is 100 cfu/g a safe threshold? Between-strain virulence variability.

FDA does not actually demonstrate that low doses are safe in all circumstances. Rather, FDA concludes, or seems to draw a conclusion, from results of derived estimates of the annual number of illnesses, on the basis of risk assessments. For example, FDA's notice presents estimates of the annual number of illnesses that indicate that, if all servings of RTE foods were at or below $10^{3.5}$cfu/g (the maximum dose, corresponding to 10^2 cfu/g for a 31.6-g serving, if there were 100-percent compliance with the limit), there would be approximately 2 cases of listeriosis per year.[1] This does not mean that a particular dose is safe in all circumstances, because these estimates, and others similar to them, are based on an averaging and depend on the distribution of *L. monocytogenes* types and levels or doses that would be consumed. That is, the estimated dose-response curve used in deriving the illness estimate depends on the particular mix and amounts of foods consumed and the estimated doses of strains of *L. monocytogenes.*[2] As these change from time to time, so would the estimated dose-response curves change.

To justify its policy decision, FDA uses estimates of annual illnesses that depend on statistical variables whose magnitudes would likely vary over time. These estimates of annual illnesses thus account for neither the uncertainty nor the temporal variability of the pertinent statistical values (e.g., the number of cases estimated by CDC) at a given time, and thus the estimated illnesses do not reflect possible occurrences.[3] In other

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[1] World Health Organization (WHO), Food and Agriculture Organization (FAO). 2004. Risk assessment of *Listeria monocytogenes* in ready-to-eat foods [the FAO/WHO risk assessment]. Rome, Italy. Part 2, Table 2.19.

[2] In the FAO/WHO risk assessment, Part 2, Hazard Characterization, page 51-52, "The general approach was to estimate the single parameter *r* in the exponential model, i.e. the probability that a single cell will cause invasive listeriosis, by pairing population consumption patterns (exposure) with epidemiological data on the number of invasive listeriosis cases in the population." "Mathematically, the *r*-value is considered to be a constant parameter for a specified population." However, this value of *r* can change over time for many reasons, including the virulence of individual strains of *L. monocytogenes* that are consumed.

[3] FDA stated that the estimate was based on the most conservative model using the nominal assigned values for certain variables considered in the FAO/WHO risk assessment, based on an assumed maximum dose per serving (of 31.6 g). The FDA estimate, taken from Table 2.19 in the aforementioned document, does not account for the uncertainty of the assigned values for various variables. Moreover, it is somewhat questionable the assigned uncertainty given in the risk assessment. For example ,it was assumed the percentage of the population with increased susceptibility to *L. monocytogenes* varied between 15% and 20%, and the estimates of the total number of cases (2518) has a degree of uncertainty of 25%. Since most

words, FDA's information does not preclude the possibility that, instead of 2 illnesses per year, there could be 20 illnesses per year, or 200 illnesses, or more. FDA does not provide grounds for using the statistic (annual illnesses) in concluding that 100 cfu/g would be an appropriate limit that will ensure safe products in all circumstances. Instead, FDA somewhat vaguely implies that its policy is justified because the figure for estimated yearly illnesses is low.

We grant that consumers are routinely exposed to low levels of *L. monocytogenes* without becoming ill. We are reluctant, however, to conclude from this fact, as does FDA, that there is a known sufficiently low dose of *L. monocytogenes* that is safe, or that levels not larger than 100 cfu/g would result in safe doses. Global assessments of the impact of low doses on expected illnesses do not imply the safety of particular dose levels in all potential circumstances. FDA does not specifically discuss its implied conclusion that 100-cfu/g levels in food will result in safe doses.

The epidemiological data, upon close examination, do not warrant the conclusion about the safety of low doses. Deli meats, other high-risk meat and poultry products, and other products that support *L. monocytogenes* growth that had low measured counts of the pathogen have been implicated in illness outbreaks. For example:

1. During a 1998 multistate listeriosis outbreak associated with turkey franks, *L. monocytogenes* was found in very low levels (<0.3 cfu/g) in opened and unopened product samples collected from the refrigerators of case patients and an institutional kitchen.
2. During another outbreak among a hospitalized population in Finland, *L. monocytogenes* was found in the implicated vehicle (butter) at low levels (5 to 60 cfu/g) in most samples and one sample contained 11,000 cfu/g.[4] The investigators hypothesized that the cases were caused by prolonged daily exposure to low doses: 140 to 2,200 cfu/day (based on the most common levels observed in the butter samples) or from 22,000 to 310,000 cfu/day (based on the level observed in 1 butter sample).[5]
3. Finally, *L. monocytogenes* counts in most foods recovered from the refrigerators of patients with sporadic listeriosis were low. Forty-one of the 49 positive food samples enumerated by the MPN method were present at <100 MPN/g.[6] [7]

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cases of illnesses are sporadic (page 1), it would seem that the number of cases might vary by much more than 25%, since estimates of cases of these types of illnesses are notoriously inaccurate. The values used for the degree of uncertainty were not discussed or justified in the risk assessment (page 51). The estimate given by FDA thus cannot be said to be based on the "most conservative modeling assumptions".

[4] Lyytikäinen, O. et al. 2000. An Outbreak of Listeria Monocytogenes Serotype 3a Infections from Butter in Finland. Journal of Infectious Diseases. (181):1838-1841.

[5] Maijala, R. et al. 2001. Exposure of Listeria monocytogenes within an epidemic caused by butter in Finland. Int J Food Microbiol. 70(1-2):97-109.

[6] Hayes, P.S. et al. 1991. Comparison of Cold Enrichment and U.S. Department of Agriculture Methods for Isolating Listeria monocytogenes from Naturally Contaminated Foods. Applied and Environmental Microbiology. (57,8):2109-2113.

[7] 100 MPN/g is roughly equivalent to 100 CFU/g.

Most of the reported measurements are low, but there are occasional high results. It is not possible from the descriptions in the reports to determine what doses that were consumed led to illness. The results may be unrepresentative of the actual doses consumed for many reasons. Even so, the results prevent the conclusion that low doses are safe, or that FDA's implicit conclusion regarding the safety of 100-cfu/g levels.

Inter-strain variation in L. monocytogenes virulence adds considerable uncertainty to the dose-response relationship

FDA also refers to the FDA/FSIS *L. monocytogenes* risk assessment, in which a dose-response model is developed using mice data in attempt to capture strain variability. *L. monocytogenes* strains appear to differ markedly in their ability to cause human illness. For example, from the 12 *L. monocytogenes* serotypes that are known to have caused listeriosis, at least 95 percent of the strains isolated from sporadic and outbreak-associated cases are of 3 serotypes (4b, 1/2a and 1/2b)[8]. *L. monocytogenes* strains from RTE meat and poultry products contain markers associated with virulent *L. monocytogenes* subtypes at low frequency. Serogroup 4b markers were detected in 9 strains (6.4%) from a panel composed of FSIS product and environmental isolates, and epidemic clone markers associated with large foodborne outbreaks were detected in most of the serogroup 4b strains[9]. Other subtyping approaches have shown similar disproportional relationships between human and food isolates. These differences could be due to an inequitable distribution of genes influencing host-pathogen interactions. We would expect these genes to have an impact on dose response relationships.

A 2006 study by Chen and colleagues,[10] which is not cited in FDA's February 7 FR notice, represents an effort to determine subtype-specific dose response relationships. In the study, risk of listeriosis among different ribotypes[11] varied by as much as 4.2 orders of magnitude, or over 10,000 fold. Listeriosis risk for Lineage I subtype strains were 2-3 orders of magnitude higher than Lineage II strains. In that paper, risk of listeriosis (expressed as r, the virulence factor value or probability of listeriosis, given consumption of a single *L. monocytogenes* cell) was modeled as a function of subtype. The maximum value of r, on the $\log_{10}$ scale, was reported to be -5.4 (upper 97.5% confidence limit of -5.2) for the molecular subtype DUP-1042B.[12] This ribotype was associated with multiple listeriosis outbreaks.[13]

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[8] Kathariou, S. 2002. Listeria monocytogenes virulence and pathogenicity, a food safety perspective. J Food Prot. 65(11):1811-29

[9] Ducey, T.F. et al. 2007. A single-nucleotide-polymorphism-based multilocus genotyping assay for subtyping lineage I isolates of Listeria monocytogenes. Appl Environ Microbiol. 73(1):133-47.

[10] Chen, Y. et al. 2006. Attributing risk to *Listeria monocytogenes* subgroups: dose response in relation to genetic lineages. J Food Prot. 69(2):335-44.

[11] Ribotyping is a subtyping method applied to *L. monocytogenes* strains

[12] Ibid. Table 5, based on FoodNet multi-state data. For Maryland and California FoodNet data, the estimate was -5.2.

[13] Sauders, B.D. et al. 2006. Molecular epidemiology and cluster analysis of human listeriosis cases in three U.S. states. J Food Prot. 69(7):1680-9.

Given a value of r equal to $10^{-5.4}$, the probability of a dose of 10^4 cells or cfu causing or being associated with illness is equal to 1- exp(-$10^4 r$) = 0.039, or approximately 4%. A dose of 10^4 cfu corresponds to 100 cfu/g in 100 grams, which is the serving size that FDA claimed it was using (footnote 10 of FDA's notice). The FAO/WHO risk assessment used a serving size of 31.6 grams; a dose, with 100 cfu/g in such a serving, yields a probability of illness equal to 1.25 percent. FDA never specified what was considered an acceptable probability of illness, but it seems to us that probabilities of illness that might exceed 1 percent cannot be considered as demonstrating safety, considering the high likelihood of severe illness or even death when there is illness.[14]

The above results support a contention that more virulent strains of *L. monocytogenes* are present in lower levels than the levels of less virulent strains of *L. monocytogenes*. This relationship is, of course, fortunate, and in part it can explain the low estimates of illnesses that exist. However, in view of this, the low estimates of the numbers of illnesses do not imply that low doses are safe in all circumstances. The results in the Chen et al. (2006) article suggest that, in some circumstances, low doses, in the range that FDA is considering for its limit, would not be risk-free and thus potentially injurious to health. Because it cannot be expected that product that passes FDA compliance procedures (which, we repeat, have not been stated) would in fact only have levels below 100 cfu/g, the likelihood that FDA's performance standard will result in product that will be injurious to health is increased by some unknown, but potentially significant, quantity.

FDA also refers to the FDA/FSIS *L. monocytogenes* risk assessment, in which a dose-response model is developed using mice data in an attempt to address inter-strain variation in virulence. Specifically, the general shape of the mouse dose-response model is based on infection with one strain (*L. monocytogenes* F5817, a 4b serotype).[15] In addition, data from three studies were used to gauge the influence of inter-strain virulence variation, based on differences of estimated LD_{50} (the dose that provides a 50-percent probability of illness). Because the model (mouse dose-response curve) predicted too many illnesses when applied to humans, a scaling factor was applied to the mouse dose-response curve so that the estimated number of illnesses using this adjusted curve would match the estimated prevalence of human listeriosis derived from CDC data. This latter estimated prevalence, as discussed above, reflects a mixture of strains with a range of virulence, most of them presumed low. Thus, it is not clear that the assumed distribution of strain-specific virulence for the mouse data would be similar to that for humans, and thus there is a high degree of uncertainty that the estimated distribution of between-strain virulence form the mouse data (at LD_{50}), would provide an accurate estimate of the distribution the between-strain virulence of strains that are exposed to humans. The

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[14] FDA mentioned that the one-hit dose-response model: p(d) = 1-exp(-rd), is conservative, meaning that it overestimates the true probability of illness for a given dose, but does not mention what the magnitude of the bias might be. FDA did not present a mechanism for inducing convexity for low doses for listeriosis as there is, for example, for cancer from carcinogenic chemicals. Consequently it would seem that whatever criterion FDA was using for determining safety, it would have been based on the one-hit model, where possibly r would vary depending on the strain, general immunological health of the host, or other factors.

[15] FAO/WHO risk assessment, Part 2, Hazard Characterization, p. 40.

reported range of the inter-strain-specific virulence as measured by LD_{50} values was greater than 7 $\log_{10}$. For humans, the range might be even greater, as is evident from the results reported by Chen et al. (2006), cited above, compared with virulence values computed in the FAO/WHO risk assessment, which are in the range of 10^{-12} or 10^{-13}, or even less. Consequently, even if the typical strain-specific virulence is small, based on the above data, it cannot be concluded that there would not be strains with significantly higher virulence.

Because *L. monocytogenes* strains with demonstrably low dose-response are present in foods (including FSIS-regulated products), and because the existing risk assessment models did not adequately model the distribution of strain virulence variation, we are not able to characterize the risk associated with low doses, and thus we are unable to predict with any confidence that low doses in the range of the FDA limit would provide very low probabilities of illnesses in general. We therefore believe that "acceptable" levels of *L. monocytogenes* in no-growth RTE foods would pose an unacceptable listeriosis risk to consumers unless the particular subtype were known not to pose a risk.

IV. Determining compliance with quantitative limit

It is not possible to evaluate the impact of a performance criterion or standard without evaluating the procedure for determining whether a product meets the criterion or standard. The estimate of the number of illnesses per year that FDA mentioned, associated with the maximum dose of $10^{3.5}$ cfu/g, assumes that all products would not contain more than 100 cfu/g, that is, there would be 100-percent compliance. This is too much to expect. FDA did not present a compliance procedure. A compliance procedure includes a sampling method, a detection method, and criteria for deciding whether to take enforcement action. The need for a well-described compliance procedure holds whether the standard, or tolerance, is 100 cfu/g, 10 cfu/g, 1 cfu/g, or even zero-tolerance.

In its draft compliance policy guidance to staff, FDA instructs its personnel to use ISO methods for detecting and enumerating *L. monocytogenes* in RTE foods that do not support growth of the pathogen and a Bacteriological Analytical Manual method for confirming *L. monocytogenes* isolates. But FDA does not offer a sampling plan or criteria for taking action, and what sort of action – other than, presumably, administrative detention and subsequent actions. Further, in its "Guidance for Industry" document,[16] FDA recommends sampling of product and important environmental surfaces, but does not indicate the frequency, sample size, or number of samples that wouild be needed in order to be sure that product meets the requirement and the process is in control. Nor

[16] Guidance for Industry Control of *Listeria monocytogenes* in Refrigerated or Frozen Ready-To-Eat Foods, DRAFT GUIDANCE. February 2008. On page 7, "Periodic sampling and testing of finished RF-RTE foods that you process can be an important reference for you to use in evaluating your control of *L. monocytogenes* over time. Therefore, we provide recommendations for such periodic sampling and testing." However, we were not able to find any recommendations. Only with respect to the environment was any mention of a number of samples made (a minimum of 5 sites, such that all critical sites are tested at least once a month). No further details were given, rather 4 articles were referenced. FDA did not analyze the impact of such environmental sampling plans.

does it provide guidance by recommending operating characteristics of sampling plans that should be achieved. Rather, these details are left for the individual processing establishment to determine.

While FDA does not present details of a sampling plan or operating characteristic objectives for sampling plans that would be used for determining compliance with the performance criterion, FSIS is aware of some sampling plans that specify the number and kind of samples needed for determining whether product is adulterated with *L. monocytogenes*. The numbers of samples required were generally small — not more than 10. For determining compliance with a tolerance, either direct plate counts would be performed on samples, or the sample size (amount of material actually analyzed) would be adjusted so that a positive result would be tantamount to adducing evidence sufficient for declaring the product to be adulterated. In the latter case, instead of the usual 25-gram sample being analyzed, considerably smaller amounts of material per sample (0.01 grams, as described in ISO 11290-2) would be analyzed. Regarding the degree of confidence that the true percentage of product containing levels of *L. monocytogenes* higher than the tolerance is less than some percentage with 10 samples, if all the samples were found negative, the minimum type of statistical statement that could be made would be, for example, that there is 99-percent confidence that the true percentage of portions of weight x (x depending on the actual weight of material being analyzed per sample) is not more than 37 percent; or, there is 95-percent confidence that the true percentage is not more than 26 percent, and so forth. Even 60 samples, all found negative, can at best provide 95-percent confidence that the true percentage is not more than 5 percent. Statements like these, even without knowing all the conditions of the sample collection, do not provide a high degree of confidence that there would not be high levels of *L. monocytogenes* within the product.

The inadequacy of this kind of statistical statement is compounded when we consider that the product sampling for the purpose of releasing product into commerce might be conducted only when someone had found evidence of a loss of environmental control.[17] In its draft documents, FDA does recognize importance of environmental sampling and of maintaining sanitation control, especially of food-contact surfaces. However, if sampling does not produce evidence of product contamination with levels of *L. monocytogenes* above the tolerance, then the product would be released into commerce and not declared to be adulterated, even if other evidence had shown that the food-contact surfaces were contaminated with *L. monocytogenes*. Because of potential contamination from a lack of environmental control, passing a product under a sampling plan with a statistical statement, as in the above example, involves uncertainty about whether the

[17] Food Directorate, Health Products and Food Branch, Health Canada. 2004. Policy on *Listeria monocytogenes* in Ready-to-Eat Foods. Ottawa, Canada. Within this document it is stated: "If the environmental sampling reveals that there is a probability of finished product becoming contaminated with *L. monocytogenes*, end product testing should be conducted ... . Once *L.monocytogenes* has been found in the finished product, it is up to each enforcement agency to determine which kind of testing/verification is necessary to ensure that the company has the problem under control."

product contains *L. monocytogenes* above the limit and, therefore, would not ensure distribution of safe product.

FDA has not provided assumptions, based on data, on the distribution of *L. monocytogenes* in food products, and thus has not justified sampling plans that would be used for compliance purposes. Nor has FDA presented any discussion of the distribution of the levels of *L. monocytogenes* that could result from environmental contamination.

There have been attempts to justify sampling plans like the one discussed above, by assuming a particular distribution (lognormal) with a specified standard deviation; however, we have seen no supporting data or proper statistical analysis of such data that would verify the reasonableness of the assumptions over a wide range of situations. The distribution of levels of contamination events is unknown, and FDA did not present a theory that would help formulate hypotheses concerning the distributions when there are contamination occurrences. It might be true that a large portion of the product would not be contaminated and that the contamination would be of limited, but unknown, extent. In that case, the distribution would not readily be well-described by a lognormal distribution. Without justification to the contrary, the small number of samples and the small sample size of material being analyzed preclude the possibility of having a high degree of confidence that the released product would not contain unsafe *L. monocytogenes* levels.

FDA needs to specify a compliance procedure that would ensure a high degree of confidence that product containing high levels of *L. monocytogenes* would not be released, particularly when there is evidence of loss of control of the environment. FSIS has declared that product that has had post-processing contact with surfaces that are contaminated with *L. monocytogenes* is adulterated (9 CFR 430.4(a)); the Agency has thus emphasized control of the processing in its risk mitigation strategy. FDA, on the other hand, emphasizes the problem of determining whether the product actually contains *L. monocytogenes* in levels that exceed the tolerance. Loss of environmental control then becomes only an indication of a possible problem.

The success of FDA's risk-mitigation strategy thus depends critically on a sampling procedure for determining compliance that would provide high confidence of the safety of the released product. To gain such a high degree of confidence would require many samples and analyses. The number of samples that would be necessary depends, in turn, on knowing the distribution of *L. monocytogenes* in contaminated product. FDA would have to provide a theory of contamination that might provide insight into the distribution for many situations, along with data supporting the theory. As matters now stand, it cannot be said that FDA's draft policy of no more than 100 cfu/g in RTE product that does not support growth, together with some yet-to-be-determined compliance procedure, will provide RTE product that would be safe and not injurious to health.

The numbers of samples and analyses affect costs to manufacturers. The costs need to be considered in any risk analysis of the FDA's draft proposed policy. The policy assumes

that, by relaxing the performance criterion for products that do not support the growth of *L. monocytogenes*, establishments would have additional incentives for producing these types of product and, consequently, the net risk of listeriosis to consumers would be lower than the current risk. If the necessary sampling were too expensive, establishments would be less motivated to produce the products.

FDA listed various conditions (treatments) that render a product a no-growth product, in particular one in which the food is processed using an effective listeristatic control measure (e.g., use of an antimicrobial substance). However, FDA did not give information on how effective these antimicrobial treatments need to be (both short- and long-term). It is reasonable to suppose that their effects can vary depending on how the treatment is applied and on other conditions, such as moisture levels. The FDA guidelines have not provided criteria on how these studies should be performed or reviewed, and on how the information in them would be used to determine whether or not a product would be considered as one that does not support growth of *L. monocytogenes*. Rather, FDA stated: "A listeristatic control measure is generally considered to be effective if growth studies show less than a one-log increase in the number of L. monocytogenes during replicate trials with the food of interest,"[18] and referred to one article.[19] The article presents discussions of factors or variables that need to be considered in designing challenge studies, recommending a range of the number of strains (3-5) that should be included,[20] either individually or collectively, and two or three samples (replicates) at each sampling time. These are small numbers of strains and samples to recommend, and FDA is silent regarding the criteria for selecting strains and numbers of replicates that should be used. FDA's silence on these points gives the impression that the choice of the actual number of strains and the criteria for selecting them, and the number of replicates, will be up to the designers or sponsors of the study that is to be used for determining whether a product will qualify as a product that does not support the growth of L. monocytogenes. The article recommends that if less than 1 $\log_{10}$ growth is observed across replicates, the product can be considered as "not supporting growth." Details on a specified degree of confidence to be obtained were not given. Basically, this criterion does not ensure that there would be no growth of L. monocytogenes in the product. FDA has not actually provided an operational definition of "no growth" and has not provided operating characteristics that should be achieved in any study used for determining whether a product is to qualify as a no-growth product. FDA's criterion (given in the article referred to), implies, in effect, that levels greater than 100 cfu/g could exist on product by the time the consumer purchases and consumes it, even when the product meets the performance criterion.

It also seems to us that FDA arrived at its risk-mitigation strategy by separately considering risk factors rather than by considering all of them together in an integrated

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[18] "Guidance for Industry . . ." p. 3.

[19] Scott, et al. 2005. Guidelines for conducting Listeria monocytogenes challenge testing of foods. Food Protection Trends 25(11):818-825.

[20] An alternative approach is given, "to screen a variety of strains and determine which strain ... grows the fastest ... and conduct the challenge studies with that single strain." It is pointed out that the use of one strain is not preferred.

analysis. This partly explains how FDA considered its limit in isolation from the procedure that would be necessary to determine compliance with the limit, or from any consideration of the potential consequences of permitting low levels of *L. monocytogenes* to exist on foods and in their surrounding environment.

FDA's approach, involving a 100-cfu/g limit for "no-growth," presupposes verification evidence produced by a competent authority demonstrating that the product actually does not support the growth of *L. monocytogenes*, and that the pathogen is controlled and would not present a risk to consumers either directly on the product or through cross-contamination. However, from the lack of information given in connection with the FDA notice, we are skeptical that any country, domestic establishment, or even FDA, intends to conduct such verification or establish a viable compliance procedure that would assure a safe product.

V. Cross-Contamination

In our above comments, we contend that any analysis of risk-mitigation strategies needs to account for the potential impact of cross-contamination. FDA's proposed policy of permitting *L. monocytogenes* in no-growth products will exacerbate the potential for cross-contamination, all else being equal.

The draft "Compliance Policy Guide" that FDA provided with its FR notice mentions that, for many RTE foods, "contamination can be avoided – e.g., through the application of good manufacturing practice requirements that establish controls on ingredients, ..., separation of foods that have been cooked from those that have not, and sanitation. Sanitation controls include effective monitoring programs.... " The draft document acknowledges the importance of ensuring control of all possible sources of *L. monocytogenes* contamination. We would add that, before permitting product with potentially high levels of *L. monocytogenes* to leave the processing establishment, there should be assurances that the product will not cause other products to become contaminated.

Permitting the sale in commerce of RTE product with non-zero levels of *L.monocytogenes*, as opposed to no (detectable) *L. monocytogenes*, increases the likelihood that the product could or would contaminate the surrounding environment or other products in retail operations. This can very easily occur in a delicatessen, e.g., if the same slicer is used to cut a hard salami that would not support growth and uncured turkey meat that would. If the product is then mishandled by consumers, it could cause illness. Consequently, FDA needs to include in its list the potential of contaminating other products, especially after the product leaves the establishment, and guidance and a compliance procedure to provide assurance that such cross-contamination does not occur.

As it stands now, without a tolerance for *L. monocytogenes*, the rate of non-compliance in retail food establishments, as documented in the FDA Report on the Occurrence of Foodborne Illness Risk Factors in Selected Institutional Foodservice, Restaurant, and

Retail Food Store Facility Types (CFSAN, 2004), is significant.[21] The report reads, "Failure to control product holding temperatures and times was the risk factor with the highest Out of Compliance percentage. Poor personal hygiene, contaminated equipment/protection from contamination and chemical contamination also had notable Out of Compliance percentages."

In the draft documents made public with its February 7 FR notice, FDA did not explore what consumers believe when they realize a product is pasteurized or RTE. While it may well be the case that the RTE status of a product correctly implies that it is safe to eat, a vulnerable consumer might also assume that the product is completely without harmful pathogens. Also, anyone might assume that the product would not be a source of contamination. In any case, FDA should address the risk due to possible cross-contamination because of allowing a low level of *L. monocytogenes* on RTE product. FDA should also address procedures (including compliance procedures) for preventing cross-contamination.

VI. Contention that a limit would induce greater compliance and, hence, public health protection

FDA relies on statements like one in the FAO/WHO risk assessment (Pt. 6, "Key findings and conclusions," p. 150):

> ... the vast majority of cases of listeriosis are associated with the consumption of foods that do not meet current standards for *L. monocytogenes* in foods, whether the standard is zero tolerance or 100 cfu/g. Raising a zero tolerance standard to a higher value (e.g. changing the standard from 1 cfu/25 g to 100 cfu/g) would be expected to result in increased incidence of listeriosis. However, if by relaxing the standard, there was a greater level of compliance with that standard through the improved adoption of control measures that significantly decreased the incidence of RTE food servings that exceeded the standard, particularly the number of servings with elevated levels of *L. monocytogenes*, then increasing the standard would actually have a positive impact on public health.

FDA argues on the basis of statements like this that a relaxed performance standard for inherently safer products would induce processors to use control measures to decrease the level of *L. monocytogenes* and, thus, make safer types of products. Consequently, there would be a "net reduction" of risk. However, the "net reduction of risk" will be realized only if the reduction in risk from greater compliance with the limit outweighs the increase in risk from having the limit. To calculate the net reduction, at least the following information items are needed:

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[21] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. 2004. FDA Report on the Occurrence of Foodborne Illness Risk Factors in Selected Institutional Foodservice, Restaurant, and Retail Food Store Facility Types. Washington, D.C. http://www.cfsan.fda.gov/~dms/retrsk2.html Accessed April 2008. See Section III, Results and Discussion: Retail Food. The report indicates that significant percentages of retail deli operations were noncompliant with respect to holding time and temperature (64.4%), personal hygiene (23.5%), and protecting equipment from contamination (23.4%).

(1) The extent of the substitution, i.e., the quantity of the safer products that will emerge in the market and the amount of the relatively unsafe products that will be replaced as a result of relaxing the limit.
(2) Information on how consumers will react to the change in the product-mix supply in terms of the quantity consumed and the way the products are consumed
(3) The positive public health effect from the new, safer products
(4) The negative public health effect from possible increased levels of *L. monocytogenes* in product sold in commerce and potential cross-contamination that could render other foods injurious to health

FDA has not presented any empirical evidence regarding the above that would show that its policy would produce any net reduction in public health risk in any jurisdiction. Neither has FDA presented any risk assessment information that addresses how much behavior change, on the part of either the producer or the consumer, would be needed to compensate for the possible increased risk — for all the reasons we have discussed — from permitting higher levels of *L. monocytogenes*, and to yield a reduction in risk.

In summary, relaxing a limit on *L. monocytogenes* for the safer RTE products would be beneficial only if any negative effect on public health due to increased amounts of *L. monocytogenes* on the products were outweighed by the benefits from the larger quantity of safer products. Without a risk assessment incorporating compliance procedures and accounting for cross-contamination that demonstrates the contrary, FSIS has no grounds for believing that permitting up to 100 cfu/g *L. monocytogenes* in "no-growth" RTE products would be more protective of public health than the current policy.

Indeed, the approach to risk management that FDA takes in its draft policy might have the unintended consequence of increasing risks to a subset of consumers. FDA may not have considered other approaches that might induce establishments to change production to ostensibly safer products while not increasing risks to any subset of consumers. An approach that focuses on risk-based strategies while not relaxing standards may be just as much of an inducement to establishments to change their production or processing while not increasing risks to any subset of consumers.

VII. Conclusion

FDA notes that the FDA/FSIS risk assessment estimates that it would be rare to find *L. monocytogenes* at greater than 100 cfu/g in RTE foods that do not support growth of the pathogen (73 FR 7303, middle column). However, this "fact" does not justify selecting a 100-cfu/g limit. Nor do the "low" hypothetical estimates of the number of illnesses per year if the levels of *L. monocytogenes* were not more than 100 cfu/g that FDA refers to in support of its draft policy. These estimates do not account for statistical and temporal uncertainties. Nor does this "fact" establish safety, in all circumstances, of doses from product that would contain 100 cfu/g. We have presented information, reported in the literature (Chen et al., 2006), that suggests that low levels or amounts of *L. monocytogenes* that are in the range that FDA is considering for its limit present an

unacceptable risk of illness. Outbreak data we have mentioned hardly warrant a contrary conclusion.

We have also discussed the potential for cross-contamination from RTE product carrying *L. monocytogenes*. And we have questioned whether FDA can effectively enforce its draft policy, inasmuch as FDA did not present compliance procedures for ensuring that product with levels above the limit would not be sold in commerce and did not provide a "no-growth" criterion that would ensure that a product designated as "not supporting growth" actually does not support the growth of *L. monocytogenes*. But even more than this, we are concerned that the FDA policy can have a deleterious effect on environmental sanitation that could affect listeriosis risk over time. Many studies demonstrate that the persistence (harborage) of *L. monocytogenes* in production facilities may lead to an enhanced ability to form biofilms[22] as well as the development of resistance to sanitizers[23] and acid.[24] It is not clear if persistence promotes virulence,[25] but this possibility cannot be ruled out. In some cases, persistent strains have been associated with human listeriosis and outbreaks. One example is the strain responsible for a multi-state listeriosis outbreak in 2000 that was associated with turkey deli product.[26] The isolates from a 1989 case patient and the outbreak of 2000 were indistinguishable from eachother by routine PulseNet protocols (indistinguishable PFGE pattern) and evaluation criteria. This example suggests that FDA should address possible long-term ramifications of the policy it is considering.

For these reasons, we believe that before FDA adopts the policy announced in its February 7, 2008, Federal Register notice, FDA should compare alternative approaches and their benefits and costs. In so doing, FDA should take into account not only the safety of low doses of *L. monocytogenes* and the variability among strains of the pathogen, but also the impact of compliance procedures, cross-contamination, and long-term possible consequences.

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[22] Jensen A et al., 2007. Sodium chloride enhances adherence and aggregation and strain variation influences invasiveness of Listeria monocytogenes strains. J Food Prot. 70(3):592-9;
Lundén JM et al., 2000. Persistent Listeria monocytogenes strains show enhanced adherence to food contact surface after short contact times. J Food Prot. 63(9):1204-7.

[23] Pan, Y. et al., 2006. Resistance of Listeria monocytogenes biofilms to sanitizing agents in a simulated food processing environment. Appl Environ Microbiol. 72(12):7711-7.
Lundén, J. et al., 2003. Adaptive and cross-adaptive responses of persistent and non-persistent Listeria monocytogenes strains to disinfectants.. Int J Food Microbiol. 82(3):265-72.
Romanova, N. 2002. Sensitivity of Listeria monocytogenes to sanitizers used in the meat processing industry Appl Environ Microbiol. 68(12):6405-9.

[24] Skandamis, P.N. et al. 2008. Heat and acid tolerance of Listeria monocytogenes after exposure to single and multiple sublethal stresses. Food Microbiol. 25(2):294-303.

[25] Jensen, A. et al. 2007. Sodium chloride enhances adherence and aggregation and strain variation influences invasiveness of Listeria monocytogenes strains. J Food Prot. 70(3):592-9

[26] Olsen S.J. et al. 2005. Multistate outbreak of Listeria monocytogenes infection linked to delicatessen turkey meat. Clin Infect Dis. 40(7):962-7.

In conclusion, we think that the FDA notice does not address adequately (if at all):

1. The several circumstances under which a food can be deemed adulterated
2. The risk due to cross-contamination of RTE products from other products (RTE or not) carrying *L. monocytogenes*
3. The economic incentives for companies to change their product mix to a greater proportion of products that do not support growth
4. Consumer perceptions of RTE or pasteurized food containing up to 100 cfu/g of *L. monocytogenes* or more
5. Alternative approaches to reducing the risk of listeriosis to all subgroups of consumers
6. Compliance procedures (sampling and definition of no-growth product) that ensure that products released into commerce will have safe, low levels of *L. monocytogenes*
7. The long-term impact of permitting potentially virulent strains of *L monocytogenes* on products and in the environment
8. The actual safety of the tolerance of 100 cfu/g.

We believe that it would be imprudent to adopt a policy that allows a level of *L monocytogenes* on certain RTE products without fully addressing these issues in an integrated way.