USDA

United States Department of Agriculture

Food Safety and Inspection Service

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JUL 3 1 2014

Dear Ms. Klein and Ms. DeWaal:

The Food Safety and Inspection Service (FSIS) has completed its review of the May 25, 2011, petition submitted by you on behalf of the Center for Science in the Public Interest (CSPI) asking that the Agency issue an interpretive rule declaring antibiotic-resistant (ABR) strains of *Salmonella* Hadar, *Salmonella* Heidelberg, *Salmonella* Newport, and *Salmonella* Typhimurium to be adulterants when found in raw ground meat and raw ground poultry. The petition asserts that if FSIS declares these strains of ABR *Salmonella* to be adulterants in raw ground meat or raw ground poultry, the Agency must also take steps to ensure adequate sampling and testing for these pathogens and to remove contaminated ground meat and ground poultry products from the human food supply. To support the requested action, the petition references studies and includes information on recalls and outbreaks associated with ABR *Salmonella.* The petition also references data that show that certain strains of ABR *Salmonella* have been found in the retail setting.

After thoroughly reviewing the available data, FSIS has concluded that the data do not support giving the four strains of ABR *Salmonella* identified in the petition a different status as an adulterant in raw ground meat and raw ground poultry than *Salmonella* strains that are susceptible to antibiotics. Additional data on the characteristics of ABR *Salmonella* are needed to determine whether certain strains of ABR *Salmonella* could qualify as adulterants under the Federal Meat Inspection Act (FMIA) (21 U.S.C. 601 *et seq.*) and the Poultry Products Inspection Act (PPIA) (21 U.S.C. 453 *et seq.*). Therefore, FSIS is denying your petition without prejudice.

Adulteration under 21 U.S.C. 601(m)(1) and 453(g)(1)

Shiga toxin-producing E. coli (STEC)

Most foodborne pathogens, including *Salmonella*, are not considered adulterants of raw meat or poultry products because ordinary cooking and preparation of

these products is generally sufficient to destroy the pathogens.[1] However, as noted in your petition, in 1994, FSIS declared *E. coli* O157:H7 to be an adulterant of raw ground beef,[2] and on January 19, 1999, FSIS issued a policy statement on the status of other non-intact beef products contaminated with *E. coli* O157:H7.[3]

In September 2011, FSIS determined that six other STEC serogroups (O26, O45, O103, O111, O121, and O145) are also adulterants of raw non-intact beef products and product components used to manufacture these products.[4] Available data show that, like *E. coli* O157:H7, these six STECs have been associated with serious illnesses and that they have a relatively low infectious dose.[5] Like *E. coli* O157:H7, all of these strains can cause hemorrhagic colitis, and all except O45 have been shown to cause hemolytic uremic syndrome (HUS), a condition that can result in kidney failure and other serious, life-threatening complications. There is also evidence that these strains have very similar characteristics to *E. coli* O157:H7 strains so that they too can survive in raw, non-intact beef products that many consumers consider to be properly cooked.[6]

FSIS temperature recommendation for consumers to cook ground beef to achieve a safe product is 160 degrees Fahrenheit.[7] FSIS is well aware that some consumers ordinarily or typically do not cook ground beef to 160 degrees Fahrenheit,[8] and that some consumers consider ground beef to be properly cooked rare, medium- rare, or medium.[9] When cooked in such a manner, ground beef contaminated with the STECs identified above may cause serious physical problems, including death.[10] Thus, raw, non-intact

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[1] See proposed rule "Pathogen Reduction; Hazard Analysis and Critical Control Point (HACCP) Systems," February 3, 1995 (60 FR 6774, 6798-6799) and final rule "Pathogen Reduction; Hazard Analysis and Critical Control Point (HACCP) Systems," July 25, 1996 (61 FR 38806, 38835.). See also *Amer. Public Health Ass'n v. Butz*, 511 F.2d 331 (U.S. App. D.C., 1974).

[2] Michael R. Taylor, FSIS Administrator. September 29, 1994. "Change and Opportunity to Improve the Safety of the Food Supply." Speech to American Meat Institute Annual Convention, San Francisco.

[3] "Beef Products Contaminated with Escherichia Coli O157:H7," January 19, 1999 (64 FR 2803).

[4] "Shiga-Toxin-Producing Escherichia coli in Certain Raw Beef Products." September 20, 2011 (76 FR 58157).

[5] 76 FR 58157, 58158-58159.

[6] Ibid.

[7] FSIS Fact Sheet "Ground Beef and Food Safety" (http://www.fsis.usda.gov/wps/portal/fsis/topics/food-safety-education/get-answers/food-safety-fact-sheets/meat-preparation/ground-beef-and-food-safety/ct_index).

[8] "Shiga Toxin-Producing Escherichia coli in Certain Raw Beef Products," May 31, 2012 (77 FR 31975, 31979).

[9] Food and Drug Administration 2010 Food Safety Survey: Key Findings and Topline Frequency Report, September 2011(http://www.fda.gov/Food/FoodScienceResearch/ConsumerBehaviorResearch/ucm259074.htm). See also *Texas Food Industry Ass'n v. Espy*, 870 F. Supp. 143 (W.D. Tex 1994).

[10] "Shiga-Toxin-Producing Escherichia coli in Certain Raw Beef Products." September 20, 2011 (76 FR 58157, 58158).

beef products and product components that are contaminated with *E. coli* O157:H7 and pathogenic STEC O26, O45, O103, O111, O121, and O145 contain a poisonous or deleterious substance and are adulterated within the meaning of 21 U.S.C. 601(m)(1).[11]

Salmonella

As noted in your petition, in the absence of a clear association with human illnesses, FSIS does not consider raw meat and poultry products, including ground meat and ground poultry, to be adulterated when they contain *Salmonella* because ordinary methods of cooking and preparing food kill *Salmonella*.[12] Your petition asserts that ABR *Salmonella* has distinguishing characteristics that support its classification as an adulterant in raw ground meat and raw ground poultry even in the absence of associated illness. We have considered information in the petition and published scientific literature through May 2014 regarding:

- Antimicrobial resistant and antimicrobial susceptible nontyphoidal salmonellosis;
- Phenotypic and genotypic attributes and the ecology of nontyphoidal salmonellae; and
- Effectiveness of thermal inactivation of antimicrobial resistant and antimicrobial susceptible strains of nontyphoidal salmonellae.

We have concluded that more data are needed to determine whether ABR *Salmonella* should have a different status as an adulterant under the FMIA and PPIA than *Salmonella* strains that are susceptible to antibiotics.

1. Legal Distinction --Added Substance

The petition asserts that the crucial legal difference between ABR *Salmonella* and susceptible *Salmonella* strains is that ABR *Salmonella* occurs as the result of human intervention, i.e., the administration of antibiotics to live animals used in the production of meat and poultry. Therefore, according to the petition, to declare ABR *Salmonella* an adulterant, FSIS must only show that it "may render" a ground meat or poultry product injurious to health (21 U.S.C. 601 (m)(1) and 453 (g)(1)). The petition notes that if a substance is not an added substance, FSIS must show that the quantity of such substance would "ordinarily render" a product injurious to health (21 U.S.C 601(m)(1)) and 453 (g)(1)).

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[11] "Shiga-Toxin-Producing Escherichia coli in Certain Raw Beef Products." September 20, 2011 (76 FR 58157, 58158).

[12] "HACCP Plan Reassessment for Not-Ready-To-Eat Comminuted Poultry Products and Related Agency Verification Procedures," December 6, 2012 (77 FR 72686, 72689-72690) See also *Amer. Public Health Ass'n v. Butz*,511 F.2d 331 (U.S. App. D.C., 1974).

At the outset, we note that the petition does not define "antibiotic resistance" or specify the number or types of antibiotics that the *Salmonella* strains identified in the petition would need to be resistant to in order to qualify as adulterants. For example, would a *Salmonella* strain be considered an adulterant if it were resistant to any antibiotic or only those antibiotics used to treat human illnesses? This information is important to our evaluation of your request because the petition asserts that only certain strains of ABR *Salmonella* should be treated differently from other strains of *Salmonella*. Therefore, understanding the characteristics of the strains that significantly increase the risk to human health is essential for developing the appropriate risk management strategies.

As to the role human intervention plays in ABR *Salmonella*, we have reviewed published scientific literature and have found studies that indicate that ABR microorganisms may be present in food animals regardless of whether the animals have had exposure to antibiotics.[13] In fact, studies demonstrate that there can be an exchange of resistance characteristics between microorganisms through horizontal gene transfer of antibiotic resistance genes even when antibiotic pressure is not present in the bacterial environment.[14] We believe that more study is needed to evaluate the extent to which the administration of antibiotics in livestock and poultry production contributes to the presence of ABR *Salmonella* in raw meat and poultry. Accordingly, we have concluded that the available data do not clearly support the legal distinction between *Salmonella* and ABR *Salmonella* under the FMIA and PPIA that is suggested in the petition.

2. Proper Cooking and Lethality

The petition also asserts that ABR *Salmonella* in raw ground meat and raw ground poultry is injurious to health because "proper" cooking often fails to reach the necessary temperature for lethality, and it is difficult to measure internal temperature properly in ground products. As discussed above, FSIS is aware that some consumers consider ground beef to be properly cooked rare, medium- rare, or medium. However, we are not aware of any data to suggest that consumers consider ground poultry, ground pork, or ground lamb to be properly cooked when rare, medium rare, or medium. The petition does not include data on consumer preparation and cooking practices for ground poultry, ground pork, or ground lamb, or consumer views of what is considered to be properly cooked ground poultry, pork or lamb. Furthermore, as discussed below, the available data do not indicate that ABR *Salmonella* strains have a higher resistance to heat than susceptible strains. Thus, from the data presented in the petition, FSIS has no basis to conclude that proper cooking of ground poultry, ground pork, or ground lamb will not destroy *Salmonella,* whether the strain is resistant or susceptible to antibiotics.

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[13] Institute of Food Technologists. 2006. Antimicrobial resistance: implications for the food system. Comprehensive Rev. Food Sci. Food Safety. 5:71-137.

[14] Kruse, H., Sorum, H. 1994. Transfer of Multiple Drug Resistance Plasmids between Bacteria of Diverse Origins in Natural Microenvironments. Appl Environ Microbiol. 60 (11):4015-21.

With respect to raw, ground beef, the available data do not conclusively demonstrate that certain strains of ABR *Salmonella* should have a different status as an adulterant than susceptible *Salmonella* strains. As discussed above, in 2011, FSIS declared certain STEC strains to be adulterants in non-intact beef products because the available data show that, like *E. coli* O157:H7, these STECs have a relatively low infectious dose, have been associated with serious illness conditions such as hemorrhagic colitis and HUS, and that these strains have very similar physiology to *E. coli* O157:H7 strains so that they can survive what many consumers consider to be proper cooking of ground beef products. Based on the current data, *Salmonella* does not appear to present the same issues as STEC, regardless of whether it is resistant or susceptible to antibiotics.

Infectious Dose. Although the data are limited, there appears to be a range of minimum infectious dose required for *Salmonella*, including ABR *Salmonella*, to cause illness. Studies indicate that the infectious dose for *Salmonella* may be influenced by factors such as the circumstances under which the pathogen is ingested, host factors (such as prior history of taking antibiotics and immune system status), the food matrix, and the particular *Salmonella* strain.[15,16,17] There is some evidence from outbreak investigations that suggest a lower infectious dose is needed to cause salmonellosis than is seen in human volunteer studies.[18] However, more data, such as the actual number of *Salmonella* per serving in different known food products responsible for outbreaks, would be needed to improve our understanding of the actual infective dose of different strains of *Salmonella.*[19]

Virulence. More data are also needed to determine whether ABR *Salmonella* results in more severe illnesses than susceptible *Salmonella* strains and are thus more likely to render a product injurious to health, as suggested by the petition. We have found that, although some published articles suggest an association of increased severity of illness with ABR *Salmonella*,[20,21,22,23,24,25] these studies are limited in their ability to

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[15] Kothary, M.H., Babu, U.S. 2000. Infective dose of foodborne pathogens in volunteers: a review. J Food Safety. 21:49-73.

[16] Blaser, M. J., Newman, L.S. 1982.A review of human salmonellosis: I. infective dose. Rev. Infectious Diseases. 4:1096-1106.

[17] Doyle, M.P. (Editor), Beuchat, L.R. (Editor). Food Microbiology: Fundamentals and Frontiers. 2007. Ch. 10: 206

[18] Blaser, M.M., Newman, L.S. A review of human salmonellosis: I Infective dose. Rev. Infectious diseases. 4:1096-1106.

[19] Ibid.

[20] Barza, M. 2002. Potential Mechanisms of Increased Disease in Humans from Antimicrobial Resistance in Food Animals. *Clin. Infect. Dis.* 34 (Suppl. 3):S123-5

[21] Travers. K.,M. Barza. 2002 . Morbidity of Infections Caused by Antimicrobial-resistant Bacteria. *Clin. Infect. Dis.*34 (Suppl. 3): S131-4.

conclusively determine whether the ABR in itself caused the increased severity. Limitations cited in one of the studies include a lack of information on (1) whether patients hospitalized with bloodstream infection were initially hospitalized for an ABR *Salmonella* infection, (2) whether there was co-morbidity, i.e., the presence of one or more diseases in addition to the ABR *Salmonella* infection, and (3) the extent of the patient's previous use of antibiotics.[26] Public health officials report increased bloodstream infections and hospitalizations for multi-drug-resistant *Salmonella* Typhimurium.[27, 28,29] However, one of these studies also reports that the length of hospitalization is not significantly greater for illnesses from multidrug-resistant *Salmonella* Typhimurium than it is for antibiotic-susceptible strains of *Salmonella* Typhimurium.[30] Another study found that symptoms, hospitalization, duration of illness, and other outcomes were not significantly different in persons affected with ABR *Salmonella* Newport and susceptible strains of *Salmonella* Newport.[31]

Further, most *Salmonella* species are pathogenic in that they can cause disease. Thus, the issue is whether ABR *Salmonella* strains are more virulent than susceptible strains. The level of virulence of a pathogen may vary, and determining whether a pathogen carries virulence attributes can be objectively determined. Genetic elements such as plasmids may carry combinations of antimicrobial resistance genes and virulence genes and move

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[22] Anderson, A.D., J.M. Nelson, S. Rossiter, and F. J. Angulo. 2003. Public Health Consequences of Use of Antimicrobial Agents in Food Animals in the U.S. *Microb. Drug Resist.* 9:373-379.

[23] Martin, L.J., M. Fyfe, et al. 2004. Increased Burden of Illness Associated with Antimicrobial-resistant *Salmonella enterica* Serotype Typhimurium infections. *J. Infect.Dis.* 189:377-385.

[24]Molbak, K. 2005. Human Health Consequences of Antimicrobial Drug-resistant *Salmonella* and Other Foodborne Pathogens. *Clin. Infect. Dis.* 41:1613-1620.

[25]Krueger, A.L., Greene, S.A., E., Barzilay, E.J., Henao,O., Vugia, D. Hanna, S., Meyer, S., Smith,,K., Pecic, G., Hoefer, D., Griffin, P.M. Clinical Outcomes of Nalidixic Acid, Ceftriaxone, and Multidrug-Resistant Nontyphoidal Salmonella Infections Compared with Pansusceptible Infections in FoodNet Sites, 2006-2008. 2014. *Foodborne Pathogens and Disease.* 11:335-341.

[26] Varma,J. K., K. Molbak, T. J. Barrett, J. L. Beebe, T. F. Jones, T. Rabatsky-Her, K. E. Smith, D. J. Bugia, H. H. Chang, and F. J. Angulo. 2005. Antimicrobial-resistant nontyphoidal *Salmonella* is associated with excess bloodstream infections and hospitalizations.

[27] Ibid.

[28] Varma J. K., K. D. Greene, J. Ovitt, T. J. Barrett, F. Medalla, and F. J. Angulo. 2005a. Hospitalization and antimicrobial resistance in *Salmonella* outbreaks, 1984-2002. 11:943-945.

[29] Solghan S.M., N.B. Dumas, et al. 2010. Multidrug-resistant Nontyphoidal *Salmonella* in New York State's Foodborne Diseases Active Surveillance Network Counties. *Foodborne Pathog.Dis.* 7:1-7.

[30] Ibid.

[31] Devasia, R. A., J. K. Varma, J. Whichard, S. Gettner, A. B. Cronquist, S. Hurd, S. Segler, K. Smith, S. Hoefer, B. Shiferaw, F. J. Angulo, and T. F. Jones. 2005. Antimicrobial use and outcomes in patients with multidrug-resistant and pansusceptible *Salmonella* Newport infections, 2002-2003. 4:371-377.

between strains of bacteria. The genetic composition of strains of the same serotype can vary. Some studies raise concerns about a linkage between antibiotic resistance genes and virulence genes, and there is some evidence of such a linkage or co-existence;[32,33,34] however, other studies have found no difference between antibiotic-resistant and antibiotic-susceptible *Salmonella* strains in the carriage of virulence factors.[35,36] We have not found any published scientific studies that support the proposition that antibiotic resistance and virulence genes always occur together for specific serotypes of *Salmonella*.

Heat resistance. The available data also do not suggest that ABR *Salmonella* is more heat resistant that susceptible *Salmonella* strains. While one study has suggested a potential link between antibiotic resistance and heat resistance in *S.* Typhimurium DT104,[37] in a more recent study conducted on ground beef patties, the heat resistance of antibiotic susceptible strains was higher than antibiotic resistant strains.[38]

Accordingly, because more data are needed on infectious dose, and because the available data do not definitively demonstrate that ABR *Salmonella* strains are more likely to result in serious illness or are more heat resistant than susceptible strains, or that ABR *Salmonell*a strains are otherwise more likely to render injurious to health what many consumers consider to be properly cook ground meat and ground poultry, we are unable to conclude that ABR *Salmonella* should have a different status as an adulterant in raw ground meat and raw ground poultry under 21 U.S.C. 601 (m)(1) and 453(g)(1) than antibiotic susceptible strains. As noted above, more data on the characteristics of ABR

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[32] Guerra, B., Soto, S., Helmuth, R., and M. C. Mendoza. 2002. Characterization of a Self-transferable Plasmid from *Salmonella enteric* Serotype Typhimurium Clinical Isolates Carrying Two Integron-borne Gene Cassettes Together with Virulence and Drug Resistance Genes. *Antimicrob. Agents Chemoth.* 46:2977-2981.

[33] Gebreyes, W. A., S. Thakur, P. Dorr, D. A. Tadesse, K. Post, and L. Wolf. 2009. Occurrence of spvA Virulence Gene and Clinical Significance for Multidrug-resistant *Salmonella* Strains. *J. Clin. Microbiol.* 47:777-780.

[34] Hoffmann, M. S. Zhao, J. Pettengill, Y. Luo, S.R. Monday, J. Abott, S.L. Ayers, H. N. Cinar, T. Muruvanda, C. Li, M. W. Allard, J. Whichard, J. Meng, E. W. Brown, P. F. McDermott. Comparative genomic analysis and virulence differences in closely related *Salmonella* enterica serotype Heidelberg isolates from humans, retail meats, and animals, *Genome Biol. Evol. 6(5):1046-1068).*

[35] Poppe, C., C. L. Gyles. 1987. Relation of Plasmids to Virulence and Other Properties of *Salmonellae* from Avian sources. *Avian Dis.* 31:844-854.

[36] Beutlich, J., S. Jahn, B. Malorny, E. Hauser, S. Huhn, A. Schroeter, M. R.Rodicio, B. Appel, J. Threlfall, D. Mevius, R. Helmuth, and B. Guerra. 2011. Antimicrobial Resistance and Virulence Determinants in European "*Salmonella* genomic island 1 (SGI1)" Positive *Salmonella enteric* Isolates from Different Origins. *Appl. Envrion. Microbiol.*pp. 5655-5664. Doi:10.1128/AEM.00425-11.

[37]Walsh, C., Duffy, G., Sheridan, J.J., Fanning, S., Blair, I.S. and Mcdowell, D.A. (2005). Thermal resistance of antibiotic-resistant and antibiotic-sensitive Salmonella spp. on chicken meat. Journal of Food Safety. 25: 288–302.

[38] Stopforth, J.D., Suhalim, R., Kottapalli, B., Hill, E., Samadpour, M. 2008. Thermal inactivation D- and Z-values of multidrug-resistant and non-multidrug-resistant *Salmonella* serotypes and survival in ground beef exposed to consumer-style cooking. JFP. 71:509-515.

Salmonella are needed for FSIS to further evaluate whether certain strains of ABR resistant *Salmonella* could qualify as adulterants under the FMIA and PPIA.

Adulteration under 21 U.S.C. 601(m)(2)(A) and 452(g)(2)(A)

The petition also asserts that a raw ground meat or raw ground poultry product that contains certain ABR *Salmonella* strains is adulterated because "...it bears or contains (by reason of administration of any substance to the live animal or otherwise) any added poisonous or added deleterious substance...which may, in the judgment of the Secretary make such article unfit for human food" (21 U.S.C. 601(m)(2)(A) and 452(g)(2)(A)). According to the petition, ABR *Salmonella* qualifies as an adulterant under the first part of this definition because it results from the administration of antibiotics to the live animal and under the second part, i.e., that renders products "unfit for human food," because a person would be unlikely to consume a food if they knew that it had the potential to cause severe illness with a possible risk for an untreatable infection.

As discussed above, the available studies indicate that ABR microorganisms may be present in food animals, regardless of exposure of the animals to an antibiotic. We believe that further study is needed to evaluate the extent to which the administration of antibiotics contributes to the presence of ABR *Salmonella* in raw ground meat and poultry. Although some published articles suggest an association of increased severity of illness with ABR *Salmonella,* these studies are limited in their ability to conclusively establish whether the ABR in itself caused the increased severity. Therefore, we have no basis to conclude that raw ground meat and raw ground poultry products that contain certain strains of ABR *Salmonella* are unfit for human food within the meaning of 21 U.S.C. 601(m)(2)(A) or 452(g)(2)(A).

Additional Considerations

In addition to the factors addressed above, FSIS believes that the Codex Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance[39] should also be considered when evaluating specific risk management options for antimicrobial resistant microorganisms.

In July 2011, the Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance adopted international guidelines for assessing and managing risks from foodborne antibiotic resistance because determining the relative risk of antibiotic-resistant microorganisms over antibiotic-susceptible microorganisms to human health is a complex and challenging task. The Codex guidelines defined the antibiotic resistance food safety issue as the combination of: 1) the hazard (the antibiotic-resistant

[39] Codex Alimentarius. Codex Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance. 2011. CAC/GL 77- 2011Accessible at: http://www.codexalimentarius.org/committees-and-task-forces/en/?provide=committeeDetail&idList=40

microorganism and resistance determinants), 2) the antibiotic agent to which resistance is expressed, and 3) the food commodity in which the hazard is identified. Similar to microbiological risk assessments for antibiotic susceptible microorganisms, the guidelines recommend that the risk outcome for foodborne antibiotic resistant microorganisms focus on disease. However, the guidelines also recommend that in addition to disease, the risk outcome for ABR microorganisms be based on consideration of whether there is treatment failure from an antibiotic drug used to treat illness or other complications that may result from microorganisms that have acquired resistance.

This Codex guidance document is in line with the current FSIS approach used to assess the human health risks associated with specific pathogens. The Codex document clearly illustrates the types of additional information that would be necessary to declare the ABR strains of *Salmonella* Hadar, *Salmonella* Heidelberg, *Salmonella* Newport, and *Salmonella* Typhimurium as adulterants when found in raw ground meat and raw ground poultry. At this time FSIS believes that neither the petition nor our own research provide sufficient data to support such a claim.

Because more scientific data about the characteristics of ABR *Salmonella* are needed to evaluate whether certain ABR strains qualify as adulterants in raw ground meet and raw ground poultry products, FSIS does not find it necessary to address the petition's assertions regarding the creation or expansion of existing sampling and testing programs of FSIS regulated products at this time.

For the reasons discussed above, FSIS is denying your petition. Because our denial is without prejudice, CSPI is not precluded from submitting a revised petition that contains additional information to support the requested action. In accordance with our regulations, we have posted your petition on the FSIS Web site. We intend to post this response as well.

Sincerely,

Daniel L. Engeljohn, Ph.D.
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Office of Policy and Program Development