DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Re: 02P-0321

Dear Dr. Strobos and Mr. Tsien:

This responds to the Citizen Petitions filed on behalf of your clients Miami Crab Corporation (Miami Crab), on July 19, 2002, and Blue Star Food Products (Blue Star), on March 7, 2003.[1] Miami Crab and Blue Star contend: (1) that the Food and Drug Administration's (FDA) methodology for detecting chloramphenicol in crabmeat is not validated and deficient; (2) that chloramphenicol is a naturally occurring substance in crabmeat and is not added at any stage from harvest through packing; (3) that there is no health hazard from exposure to levels of chloramphenicol at less than 5.0 parts per billion (ppb); and (4) that FDA is acting in restraint of international trade and in violation of United States (U.S.) treaty obligations.

The Citizen Petitions request that FDA take seven actions: (1) immediately cease and desist from using unvalidated testing methodology to evaluate crabmeat, especially imported crabmeat, for the presence of chloramphenicol; (2) reinstate previous testing limits of 5.0 ppb using existing testing methodology; (3) perform a health hazard evaluation relating to the exposure to naturally occurring chloramphenicol at levels of less than 5.0 ppb before taking any action against crabmeat and revise or clarify Import Alert Nos. 16-124 and 68-01[2] to specify limits on allowable chloramphenicol in crabmeat; (4) provide public assurances that the presence of naturally occurring chloramphenicol in crabmeat at levels of less than 5.0 ppb does not result in such crabmeat being adulterated; (5) recognize and accept expert testimony and compelling scientific evidence that there is no established likelihood of any health risk from the ingestion of

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[1]Pursuant to a letter dated May 5, 2003, FDA notified you that the above-referenced Citizen Petitions were consolidated for review in docket number 02P-0321, because they both presented the same issues, and that the clock was restarted as of the date that the second petition was filed (Tab A).

[2]A new import alert has been drafted to make clear that FDA's actions with respect to chloramphenicol in crabmeat are based on sections 402(a)(2)(C)(i) and (a)(1) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 342(a)(2)(C)(i) and (a)(1). If appropriate, FDA may also bring a new animal drug charge; however, in this case, such a charge is unnecessary because the presence of detectable levels of chloramphenicol in crabmeat renders this crabmeat adulterated under sections 402(a)(2)(C)(i) and (a)(1), 21 U.S.C. § 342(a)(2)(C)(i) and (a)(1).

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crabmeat containing less than 5.0 ppb chloramphenicol; (6) recognize and accept that recently instituted testing methodology has not been shown to reliably and accurately identify chloramphenicol as opposed to possible cross-reactivity with the known and lawful presence of authorized food contact surface indirect additives containing chlorine; and (7) enforce current World Trade Organization treaty obligations that prohibit differential treatment of foreign goods based on spurious and unscientific safety standards. Citizen Petitions at 1-2. [3]

After reviewing the Citizen Petitions, the information presented at the April 7, 2003, meeting with you and your clients, and the entire record herein, FDA concludes that:

- its methodology for detecting chloramphenicol in crabmeat is scientifically valid, because it has been properly validated for crabmeat, the development and implementation of its methodology is scientifically supportable, and the method's criteria are capable of distinguishing chloramphenicol from other structurally similar compounds;

- crabmeat containing detectable levels of chloramphenicol (i.e., at the time of the Citizen Petitions, 0.5 parts per billion (ppb) and higher[4]) is an adulterated food, pursuant to sections 402(a)(2)(C)(i) and 402(a)(1) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 342(a)(2)(C)(i) and (a)(1), in that it (1) contains an unapproved, unsafe food additive, and (2) bears or contains an added poisonous or deleterious substance that may render the food injurious to human health. The known potential human health risks from exposure to chloramphenicol at low dietary levels include: (1) aplastic anemia, a potentially fatal illness that takes the form of suppression of all blood cell types by the bone marrow; (2) genetic toxicity (i.e., chromosome breaks and DNA damage) and carcinogenicity (i.e., leukemia); and (3) reproductive toxicity (i.e., potentially fatal harm to fetuses during late gestation and to infants during breastfeeding);

- FDA is not acting in restraint of international trade or in violation of any U.S. treaty obligations. Given the agency's need to prioritize its regulatory objectives to accommodate its resource limitations, FDA began the chloramphenicol testing program for crabmeat with imported product because of the evidence of a greater public health threat from these imported products, but FDA plans to expand its testing program to include domestic product

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[3]The Citizen Petitions also note in passing a "voluntary recall" of some of the Miami Crab crabmeat, and an import detention of some of the Blue Star crabmeat in Florida due to findings of the presence of chloramphenicol in these products. Miami Crab Citizen Petition at 2; Blue Star Citizen Petition at 4. Because these Citizen Petitions do not seek in their "Action Requested" sections any particular relief with respect to this detained or recalled product, these actions will not be formally treated as part of the Citizen Petitions' objections. See 21 CFR 10.30(b).

[4]FDA is now capable of testing with a limit of detection at 0.3 ppb. However, this new detection limit was established after these Citizen Petitions were filed and was not used on the crabmeat at issue.

in the near future.

For these reasons, the requests in your Citizen Petitions on behalf of Miami Crab and Blue Star are denied.

I. FDA's Methodology for Detecting Chloramphenicol in Crabmeat is Scientifically Valid

FDA's methodology for detecting chloramphenicol in crabmeat – the Electrospray Liquid Chromatography Mass Spectroscopy (LC/MS) method[5] – was developed by FDA's Denver District Office in the summer of 2002. This methodology is fully validated and can distinguish chloramphenicol from other structurally similar substances that may be present in crabmeat samples (Tab B, set 1). Moreover, given that chloramphenicol is being detected in crabmeat, testing for its presence is obviously appropriate. As set forth more fully below, FDA's methodology for detecting chloramphenicol in crabmeat is scientifically valid.

A. The LC/MS Methodology Has Been Properly Validated for Crabmeat

The Citizen Petitions assert that FDA's method for detecting chloramphenicol in crabmeat has not been properly validated. Miami Crab Petition at 3-4; Blue Star Petition at 9. Specifically, the Petitions claim that the validation assessment for this chloramphenicol test was performed using only shrimp meat, rather than crab. Miami Crab Petition at 3; Blue Star Petition at 9. In fact, the test that FDA uses to detect chloramphenicol in crab has been properly validated using crabmeat.[6] The Denver District laboratory performed a method validation that complied with their standard operating procedure (SOP) DEN-LB.46 Quality Control Program for Method Verification, Validation, and Modifications (Tab C). With respect to the Laboratory Information Bulletin (LIB) 4294 (Tab D) mentioned in the Citizen Petitions as "evidence" that FDA's method is not validated,[7] that publication was merely intended to identify for the public the steps used in FDA's methodology. It was not intended to detail the validation determinations or the confirmation criteria. As explained above, FDA's LC/MS methodology as developed by the Denver laboratory has been fully validated for crabmeat at 0.5 ppb (Tab B, set 2).

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[5]The Citizen Petitions refer to the Electrospray Liquid Chromatography Mass Spectroscopy method as "LCEMS"; however, for consistency with other relevant FDA publications, this testing method is abbreviated "LC/MS" in this document and in the entire record herein.

[6]DEN-LB.46 Quality Control Program for Method Verification, Validation, and Modifications (Tab C); see also DEN-LB.80 Chloramphenicol Residue in Food by Electrospray LC/MS (Tab E).

[7]At an April 7, 2003, meeting, you and your clients asserted that the FDA's method as an LIB publication is not validated as evidenced by the disclaimer applied to all LIB publications (i.e., "Users must assure ...by appropriate validation procedures that LIB methods . . . are reliable and accurate. . . .").

B. *The Development and Implementation of the LC/MS Methodology, Including the 0.5 ppb Detection Limit, is Scientifically Supportable*

One critique of FDA's LC/MS methodology given in the Citizen Petitions is that it is not scientifically supportable. Specifically, the Citizen Petitions contend that: (1) FDA investigators did not consider whether the positive test results of some of the samples resulted from naturally-occurring chloramphenicol; (2) false positive outcomes occurred; and (3) FDA should be using a 5.0 ppb detection limit, rather than the 0.5 ppb limit used by FDA, for chloramphenicol testing of the crabmeat at issue. Miami Crab Petition at 1-4; Blue Star Petition at 12-13, 17-18.

1. The Purpose of the Samples Was To Test Our Methodology, Not to Determine Background Levels of Chloramphenicol

The Citizen Petitions assert that FDA investigators rejected the idea that the positive test results of some of the unspiked samples (i.e., those samples to which chloramphenicol was not deliberately added) may derive from naturally occurring chloramphenicol. Miami Crab Petition at 4; Blue Star Petition at 12-13. This assertion appears to be derived from the fact that FDA's Denver laboratory sought crabmeat without detectable levels of chloramphenicol to initially evaluate and run the LC/MS method.

When analytical laboratories evaluate test methods, it is important to test the method using product material that does not contain the compound or analyte under investigation to ensure that the method can differentiate between samples that contain the substance and samples that do not. Since crabmeat is not aquacultured and thus no controlled source of crabmeat could be identified, the lab purchased canned crabmeat from a local retailer for use in evaluating its method. None of the crabmeat from two lots of store-bought product produced detectable levels of chloramphenicol.[8] The chloramphenicol-free crabmeat was used to evaluate the test method by spiking the samples (i.e., adding known amounts of chloramphenicol at various levels) and then testing the end product through the LC/MS method. The testing of this retail product was not done to determine environmental background levels of chloramphenicol, because, as discussed in section IIB2, these levels, if they exist at all, would be so low as to not be detectable under the LC/MS methodology. The purchase of this product was done randomly and was not intended to be a controlled study; it was merely done to obtain clean product samples for use in testing the LC/MS methodology. The Denver laboratory evaluated existing extraction and chromatographic techniques known to isolate and detect chloramphenicol in seafood tissue. The method for crabmeat was validated as a qualitative method; and the laboratory applied generally accepted scientific standards for the validation of qualitative methods (Tab B, set 1; Tab F, #6).

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[8]If, as you assert in your Citizen Petitions, crabmeat contains background levels of naturally occurring chloramphenicol at detectable levels, the Denver laboratory should have been unable to locate crabmeat that did not contain chloramphenicol at these levels. However, the Denver laboratory did in fact locate crabmeat with no detectable levels of chloramphenicol.

2. No False Positives Occurred with the LC/MS Method

The Citizen Petitions also allege that the implementation of the LC/MS method is not scientifically supportable because false positive outcomes occurred with the method applied to chloramphenicol in crabmeat. Miami Crab Petition at 4; Blue Star Petition at 13. However, these contentions are contradicted by data generated by the Denver laboratory. Testing using the LC/MS method yielded no false positive and no false negative outcomes during method validation and quality assurance determinations (Tab F, #2). The use of the qualitative method when applying the confirmation criteria uniquely identifies chloramphenicol with the highest degree of assurance.[9] The false positives observed with the r-Biopharm ELISA method or the non-specificity for florfenicol amine in LIB 4284, mentioned in the Citizen Petitions, are not relevant to the LC/MS confirmation method for chloramphenicol. The ELISA method is much less specific than the LC/MS method; it only gives a color indicator of the presence of the analyte and does not give detailed information on the structure of the analyte, which is necessary to confirm the identity of the compound (Tab F, #7). The FDA does not take enforcement action on residues using ELISA-based methods since these methods do not assure a sufficient degree of specificity when compared to the LC/MS method. Moreover, while it is true that the LIB 4284 method did not yield sufficient MS fragmentation data to allow confirmation of florfenicol amine, this is not the case when confirming the presence of CAP; the development of a unique ion fragmentation pattern using the MS method for CAP provides confirmation of identity (Tab F, #7). The LC/MS method with confirmation criteria is the sole basis for FDA legal action on chloramphenicol since this method provides confirmation of chloramphenicol detection (Tab F, #7).

3. FDA's 0.5 ppb Detection Limit is Scientifically Supportable

Finally, the Citizen Petitions argue that FDA should be using a 5.0 ppb detection limit in lieu of the 0.5 ppb limit used by FDA for chloramphenicol testing of the crabmeat at issue. Miami Crab Petition at 1-2; Blue Star Petition at 17-18. The 5.0 ppb limit was the limit of a chloramphenicol quantitation method by gas chromatography/electron capture detector (GC/ECD) that was run only on shrimp from 1996-1997 and from June 2001-June 2002. A separate mass spectroscopy confirmation method was performed when the GC/ECD method detected chloramphenicol at the level of 5.0 ppb or greater. The mass spectroscopy determination was required for enforcement purposes, because only the mass spectroscopy test provides a high degree of specificity for confirmation of the compound (Tab F, #7). However, by 2002, better scientific methods became available that allowed FDA to increase its sensitivity levels. Accordingly, FDA concentrated its resources on developing and validating a more sensitive enforcement method (the LC/MS method for chloramphenicol). This validated enforcement method is scientifically supportable and can detect chloramphenicol down to 0.5 ppb in crabmeat (Tab F, #4). The 5.0 ppb limit was a method quantitation and confirmation limit and was never a tolerance or safe level for chloramphenicol. FDA is enforcing an action level of any detectable presence of

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[9]See confirmation criteria in DEN-LB.80 Chloramphenicol Residue in Food by Electrospray LC/MS (Tab E).

chloramphenicol, and at that time, the test limit was at 5.0 ppb. However, when lower testing limits became scientifically possible and the foreign and domestic (State) testing identified lower levels of chloramphenicol in seafood, the FDA validated test methods with lower detection levels to detect chloramphenicol residues at these lower levels.

C. *The LC/MS Methodology is Not Deficient and Can Distinguish Chloramphenicol From Structurally Similar Compounds*

The Citizen Petitions also argue that FDA's LC/MS methodology is deficient because (1) it is not quantitative; (2) it cannot distinguish chloramphenicol from other structurally similar substances; and (3) trichloro-isocyanuric acid in hand sanitizers used by crab processors may be reacting with compounds in the crab to create chloramphenicol in the crabmeat. Miami Crab at 4; Blue Star Petition at 11-13. FDA disagrees.

1. FDA's Qualitative Method is Adequate for Enforcement Purposes

The Blue Star Citizen Petition objects to the non-linear and qualitative nature of FDA's LC/MS methodology and argues that, due to its non-quantitative nature, the LC/MS method cannot distinguish natural from added chloramphenicol. Blue Star Petition at 12-13. First, this distinction is irrelevant, because the law does not require FDA to distinguish the amount of the poisonous or deleterious substance that was added from any portion that may be naturally occurring. As long as some of the chloramphenicol was added, FDA need only show that the substance is an unsafe food additive, pursuant to section 402(a)(2)(C)(i), 21 U.S.C. § 342(a)(2)(C)(i), or that the entirety of the substance may render the food injurious to human health, pursuant to section 402(a)(1), 21 U.S.C. § 342(a)(1).[10]

Second, the LC/MS method was developed as a qualitative method, and linearity is not a requirement for a qualitative method. When a signal response analysis was run, the signal increased as the amount of chloramphenicol that was added increased (Tab F, #5). Consistent recoveries of chloramphenicol were observed using this signal response, which supports the use of a detection limit for regulatory purposes. In response to the argument that this method is not quantitative, quantitation methods do not necessarily provide a level of data necessary to confirm analyte identity. As a result, FDA's method was developed solely for qualitative purposes and the Liquid Chromatography/Mass Spectroscopy criteria established by the Denver laboratory are sufficiently rigorous to distinguish the chloramphenicol analyte from other compounds that may be present in a sample.

2. FDA's Test Distinguishes Chloramphenicol From Other Structurally Similar Substances

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[10] See, e.g., United States v. Anderson Seafoods, Inc., 622 F.2d 157, 161-62 (5th Cir. 1980) ("we hold that where some portion of a toxin present in a food has been introduced by man, the entirety of that substance present in the food will be treated as an added substance and so considered under the 'may render injurious to health' standard of the Act").

The Citizen Petitions also hypothesize that FDA's test may be detecting chlorine used in approved chlorine-containing sanitizers. Miami Crab Petition at 4; Blue Star Petition at 11. However, the presence of chlorine is not the determinative structural feature that provides for the confirmation of identity of chloramphenicol using our method. We have evaluated other structurally similar compounds, including several that contain chlorine,[11] in the presence of chloramphenicol and the LC/MS method is capable of distinguishing among them (Tab F, summary). The validation of the method specificity, demonstrating that chloramphenicol can be distinguished from structurally similar compounds, is included in the data submitted by FDA's Denver laboratory (Tab B, set 2).

3. Regardless of How the Chloramphenicol is Entering the Crab, It is Added

Finally, the Citizen Petitions note the possibility that trichloro-isocyanuric acid in polychlorinated hand sanitizers used by crab processors could react with compounds in the crab tissue to essentially create chloramphenicol inside the tissues or cells of the crabmeat. Miami Crab Petition at 4; Blue Star Petition at 11. The Citizen Petitions have not provided us with sufficient information to determine which sanitizers you are referring to, so FDA cannot evaluate whether or not they are in fact approved for these uses and whether the argument you make could be sufficiently feasible with respect to these specific products. FDA's regulations require you to include in full all information referred to or relied upon in your submission. See 21 CFR 10.20(c)). Therefore, your Citizen Petitions are deficient on this point. Moreover, we do not believe that this hypothesis is scientifically credible since it is highly unlikely, and improbable at best, for a natural organic matter precursor in crabmeat to produce chloramphenicol when reacted with a polychlorinated hand sanitizer (Tab F, #3).[12] Furthermore, if it was in fact true that the trichloro-isocyanuric acid in some approved sanitizers was creating chloramphenicol in the crabs, this chloramphenicol would still be considered "added" under the applicable caselaw, because it is entering the crab through the hand of man.[13]

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[11]For example, FDA evaluated compounds in the phenicol class of drugs (thiamphenicol, florphenicol) (Tab F, summary).

[12]FDA finds it highly unlikely that a natural organic matter precursor (in crabmeat) would produce chloramphenicol when reacted with an active disinfectant that contains chlorine. Moreover, FDA has learned of an upcoming presentation entitled "Clean Hands, Dirty Data: Does the Use of Trichlor Disinfectant in Asia Cause False Positive Chloramphenicol Results in the US" by Dr. Robert Beine, Louisiana Department of Agriculture and Forestry. The data and information in this discussion will be presented on July 23, 2003 at the 40th Annual Florida Pesticide Residue Workshop & 6th Annual Foodborne Pathogen Analysis Conference, July 20-23, 2003. The presentation will provide scientific data to demonstrate that trichlor disinfectant, a polychlorinated sanitizer, when mixed into crabmeat does not produce chloramphenicol in situ, or mimic the chemical structure of chloramphenicol to yield false positive results during testing.

[13]See Anderson Seafoods, 622 F.2d at 160; Continental Seafoods, Inc. v. Schweiker, 674

D. Testing for Chloramphenicol in Crabs is Appropriate

The Blue Star Citizen Petition also asserts that crabmeat should not be subject to chloramphenicol testing because crabs are harvested in the wild and not aquacultured. Blue Star Petition at 19. The Citizen Petition correctly notes that on December 20, 2002, the European Commission (EC) stated that "Fishery products obtained by other means than aquaculture are not concerned by risks identified above [chloramphenicol] and should therefore be exempt from monitoring." However, this statement was based on the presumption that the only route of exposure to chloramphenicol was through animal feed or some other route of administration, such as baths. After finding detectable levels of chloramphenicol in wild-caught products such as crab, it has become clear to FDA that chloramphenicol is also being added to crab products in other ways, such as through use by or on humans during processing.[14] Therefore, given that chloramphenicol is being detected in crabmeat, testing for chloramphenicol in crabs is appropriate.

In conclusion, FDA's LC/MS methodology for detecting chloramphenicol in crabmeat is fully validated, scientifically supportable, and capable of distinguishing chloramphenicol from other structurally similar substances. Moreover, the EC's 2002 determination that there is no risk of finding chloramphenicol in non-aquaculture products, such as crabmeat, is outdated and contradicted by the data derived from FDA's testing over the past year.

II. Crabmeat Containing Detectable Levels of Chloramphenicol is Adulterated

A. Chloramphenicol in Crabmeat is an Unapproved, Unsafe Food Additive

The 1958 Food Additives Amendment was enacted to give FDA the authority to protect the public from untested food ingredients. See, e.g., United States v. Ewig Bros. Co., 502 F.2d 715, 721 & n.4 (7th Cir. 1974), cert. denied, 420 U.S. 945 (1975). The amendment "permits FDA to regulate the use of substances affecting foods without first determining that they are in fact dangerous; the method is to require that such substances be established as safe before being used." Natick Paperboard Corp. v. Weinberger, 525 F.2d 1103, 1106 (1st Cir. 1975), cert. denied, 429 U.S. 819 (1976); see also Ewig Bros., 502 F.2d at 721. The term "food additive" has

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F.2d 38, 42-44 (D.C. Cir. 1982). Moreover, if any approved sanitizers are causing the production of chloramphenicol in crab this would raise questions about their safety. However, to date, there are no data in the Citizen Petitions and FDA has no other information that any FDA-approved sanitizers do in fact create chloramphenicol in crab.

[14]Other countries are also indicating concern for chloramphenicol residues in crab: "Minutes of the 3rd Meeting of the Veterinary Residues Committee, 10:30 am Tuesday 27 November 2001, Conference Room, Veterinary Medicines Directorate, New Haw Surrey" at http://www.vet-residues-committee.gov.uk/minutes/minutes271101.pdf (UK); China Business Handbook 2003, at http://www.chinaeconomicreview.com/htm/n_20020401.290998.htm (PRC).

been broadly defined as:

> any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food . . .), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use . . . .

§ 201(s), 21 U.S.C. § 321(s) (emphasis added). This definition has two parts: (1) the intended use of the substance must be such that it results or may reasonably be expected to result in the substance becoming a component of food; and (2) there must be a lack of general recognition among qualified experts of the safety of the substance under the conditions of that intended use. Monsanto Co. v. Kennedy, 613 F.2d 947, 955 (D.C. Cir. 1979). As set forth below, FDA believes that chloramphenicol in crabmeat meets both prongs and is, therefore, a "food additive."

Pursuant to section 402(a)(2)(C)(i), 21 U.S.C. § 342(a)(2)(C)(i), any unsafe food additive and any food containing an unsafe food additive are adulterated. See, e.g., United States v. An Article of Food * * * Coco Rico, 752 F.2d 11 (1st Cir. 1985). A food additive is unsafe unless FDA has: (1) promulgated a regulation prescribing the conditions under which the food additive can be safely used, or in the case of a food additive that is a food contact substance, FDA has promulgated a regulation permitting its use or there is a notification that is effective for its use; or (2) granted an investigational exemption for use. Section 409(a), (i), 21 U.S.C. §§ 348(a), (i). FDA has not issued a regulation or received an effective notification, nor has FDA issued an investigational exemption for chloramphenicol as a component of food (Tab G). Therefore, chloramphenicol in crabmeat is deemed to be unsafe under section 409, 21 U.S.C. § 348.

Accordingly, crabmeat containing detectable levels of chloramphenicol is adulterated in that it contains an unsafe, unapproved food additive.

1. The Intended Uses of Chloramphenicol May Reasonably Be Expected to Result in Its Becoming a Component of Food

Congress defined a "food additive" as "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component . . . of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food . . . .)" that is not generally recognized by qualified experts as safe (GRAS) for its intended use in food. Section

201(s), 21 U.S.C. § 321(s). Nowhere in section 201(s), 21 U.S.C. § 321(s), did Congress limit the scope of the word "component" to substances that are intended or claimed to serve particular functions or purposes in food. Ewig Bros. Co., 502 F.2d at 721 & n.4.[15] Nor does the definition place any restriction on how large or small a component of food the substance is. United States v. An Article of Food * * * FoodScience, 678 F.2d 735, 738 (7th Cir. 1982). Thus, why the substance, or how much of the substance, is part of the food is irrelevant as a matter of law when determining whether the substance is one whose intended use may reasonably be expected to become a component of food.

Based on the evidence currently available, FDA concludes that chloramphenicol is becoming a component of your crabmeat in one, if not several, of the following ways: (1) through shrimp feed or by direct addition to shrimp ponds, holding tanks, or other containment areas; or (2) in a wash, dip, spray, or other treatment used during processing, such as the hand treatments documented by the Chinese government as late as June of 2002 (Tab H, #4, #5, #6, #7).

The Miami Crab Citizen Petition acknowledges that, prior to June 2002, chloramphenicol was used in shrimp aquaculture in coastal pens and that traces of chloramphenicol could have gotten into the adjacent waters from which crab are harvested. Miami Crab Petition at 10, footnote 6. While the Petition asserts that this use of chloramphenicol has ceased as of June 2002,[16] no evidence is provided to substantiate this claim. In fact, the EC Report[17] on China explaining the widespread use of chloramphenicol and the absence of any regulatory controls, meetings between FDA and government officials from China in June 2002 and Vietnam in March 2003, and FDA's own knowledge of the seafood industry in Asia all argue to the contrary.

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[15]The Seventh Circuit has explained:

> Since Congress used broad language . . ., we should not construe it narrowly. The language defined a food additive as any substance, 'the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of food . . . .' Although Congress was primarily concerned with substances used by a food processor, neither the language nor the history of the 1958 Act limits its application to such substances. The words 'the intended use of which' are not confined, as they easily could have been, to use in food processing.

Id. (emphasis in original; footnote omitted).

[16]See Miami Crab Petition at 10, footnote 6.

[17]European Commission Final Report: http://europa.eu.int/comm/food/fs/inspections/vi/reports/china/vi_rep_chin_3280-2001_en.pdf.

The EC Final Report on the mission carried out in China from November 8-22, 2001, in order to evaluate the control of residues in live animals and animal products, found that chloramphenicol, and other veterinary drugs which are totally banned in food producing animals in the EU because of their carcinogenic and mutagenic potential, are still legally in use in China.[18] (Tab I, p. 22-27) The Report explained that not only is there no general prohibition on the use of non-approved veterinary drugs in the Chinese regulations, there are also no legal provisions on extra-label use of veterinary drugs in the Chinese legislation (Tab I, p. 19). Consequently, livestock medicines, such as chloramphenicol, are freely available in China as over the counter drugs. (Tab I, p. 19)

Moreover, during recent meetings with FDA officials, government officials from the Peoples Republic of China (Tab H, #6) and from Vietnam (Tab H, #4; Tab J) have acknowledged that chloramphenicol has been added to their seafood products. During a June 5-7, 2002 meeting between the Chinese government and FDA, Chinese government officials described having performed their own investigation in which they traced chloramphenicol contamination in shrimp to the use of chloramphenicol-containing solution on the hands of shrimp peelers at processing facilities (Tab H, #6). This solution was reportedly widely-used as a treatment for cuts to the hands caused by shrimp shells. As the exoskeleton of most crabs is thicker, more brittle and sharper when broken than is that of most shrimp, it is also inherently more difficult to pick the flesh from a crab during processing than it is to peel a shrimp. Therefore, workers processing crabs would be at least as likely to seek similar treatment for cuts to the hands from picking crabs (Tab H, #6).

Similarly, during a March 5, 2003 meeting with Vietnam, Vietnamese government officials reported that they continue to have problems with chloramphenicol being used in the production of shrimp in their country, and they have acknowledged the use of chloramphenicol in shrimp farming (Tab J). With the significant tidal flux that influences many shrimp ponds,[19] water containing chloramphenicol from these ponds could be expected to flow into near-shore, intercoastal areas where indigenous crabs could also become contaminated prior to harvest.

Given this evidence and FDA's knowledge of seafood practices in Southeast Asia, FDA believes that the following are the potential routes of contamination by chloramphenicol: (1) through shrimp feed or by direct addition to shrimp ponds, holding tanks, or other containment areas; or (2) in a wash, dip, spray, or other treatment used during processing, such as the hand treatments documented by the Chinese government as late as June of 2002 (Tab H, #4, #5, #6).

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[18]"China is an important producer of bulk drugs and pharmaceutical raw materials. Many Chinese companies, manufacturers, and exporters of these goods, offer their services via the Internet. Among the bulk drugs offered there are e.g., . . . chloramphenicol and many other drugs banned for food producing animals in the EU." (Tab I, p.22; Tab H, #5)

[19]Effluent from contaminated areas may be introduced to crabs (Tab H, #4) as a result of tidal flux that influences many shrimp ponds.

Chloramphenicol used in shrimp aquaculture in shrimp feed or through direct addition to shrimp ponds, holding tanks, or other containment areas, may be introduced to crab beds through the effluent from such areas and would become a component of the crabmeat as crabs feed from the sediment in these surrounding areas (Tab H, #4). Chloramphenicol used in a wash, dip, spray, or other treatment during processing would become a component of the crab by direct contact with the edible portion (Tab H, #5, #6). Therefore, these intended uses of chloramphenicol would reasonably be expected to result in the chloramphenicol becoming a component of the crabmeat (Tab H, #7)

2. Chloramphenicol is Not GRAS

Once FDA establishes that chloramphenicol is a substance whose intended use may reasonably be expected to result in its becoming a component of food, the burden shifts to your clients to establish that chloramphenicol is not a "food additive" because it is "generally recognized among experts qualified by scientific training and experience to evaluate its safety" as safe for use under the conditions of its intended use, i.e., as a component of crabmeat. Sections 201(s) and 409(i), 21 U.S.C. §§ 321(s) and 348(i); Coco Rico, 752 F.2d at 15; FoodScience, 678 F.2d at 739.

To establish that chloramphenicol is GRAS as a component of food, your clients must show that: (1) there is published in the scientific literature at least the same quantity and quality of scientific data showing the safety of chloramphenicol for use as a component of food as would be necessary for approval of a food additive petition for chloramphenicol under section 409, 21 U.S.C. § 348, and (2) chloramphenicol is generally recognized as safe among experts who are qualified by scientific training and experience to evaluate its safety. See 21 CFR § 170.30. To date, your clients have not satisfied either requirement.

The first prong of the test for general recognition requires that there exist, in the published scientific literature, the same quantity and quality of data on the substance's safety as is required for approval of a food additive petition for the substance. 21 CFR §§ 170.30(a), (b); see, e.g., Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 652 (1973) (general recognition of safe use established by controlled studies published in recognized scientific literature); Coco Rico, 752 F.2d at 15 & nn. 4, 6 (general recognition requires published safety studies); United States v. Articles of Food and Drug (Coli-Trol 80), 518 F.2d 746 (5th Cir. 1975) (expert opinion must be based on adequate studies meeting requirements of food additive regulations). The Citizen Petitions do not include the necessary published scientific evidence of the safety of chloramphenicol for use in a manner that can reasonably be expected to result in its becoming a component of food.

Because chloramphenicol was not marketed as a component of food before 1958, general recognition must be based on "scientific procedures," section 201(s), 21 U.S.C. § 321(s), which are defined as "human, animal, analytical and other scientific studies . . . appropriate to establish the safety" of the two components. 21 CFR § 170.3(h). Thus, your clients cannot rely on an absence of reports of adverse events from the consumption of crabmeat. Moreover, the scientific

data to support a GRAS determination must pertain specifically to the component and its intended use.. See section 201(s), 21 U.S.C. § 321(s); Coco Rico, 752 F.2d at 15. Therefore your clients cannot claim that data relating to other uses of chloramphenicol (e.g., ophthalmic drug uses) supports a finding that chloramphenicol is GRAS for use as a component of food. See e.g., Coco Rico, 752 F.2d at 15 & n. 5 (claimant cannot rely on food uses of potassium nitrate to raise a genuine issue of material fact as to the lack of GRAS status of potassium nitrate in beverages); United States v. Articles of Food . . . Buffalo Jerky, 456 F. Supp. 207, 209 (D. Neb. 1978), aff'd mem., No. 78-1648 (8th Cir. 1979) (evidence of other GRAS uses of sodium nitrate and sodium nitrite does not refute government's showing or raise factual issue as to their lack of GRAS status in buffalo meat).

In addition, the "theoretical evaluation" of the safety of a substance by a scientist, no matter how qualified, is not legally competent: "an inference that safety might be shown by scientific testing and procedure . . . is not addressed to the critical test of general recognition in the scientific community that the compound has been shown through scientific procedure to be safe." United States v. Seven Cartons . . . Ferro-Lac, 293 F. Supp. 660, 666 (S.D. Ill. 1968), aff'd, 424 F.2d 1364 (7th Cir. 1970). Moreover, because expert recognition of the substance's safety must be "general," your clients cannot merely prepare the data necessary for approval of a food additive petition for chloramphenicol. Unless the data are made generally available to the community of experts and are subjected to peer evaluation, criticism, and review, a consensus among experts cannot be reached. Consequently, the requisite studies on chloramphenicol's safety must have been published in the scientific literature before they can support a GRAS determination. 21 CFR § 170.30(b); Bentex Pharmaceuticals, 412 U.S. at 652. Your clients have not submitted the requisite published data to support a GRAS determination for the use of chloramphenicol in a manner that can reasonably be expected to result in its becoming a component of food. Moreover, FDA has searched the scientific literature and has not found any published data to support the safety of chloramphenicol in crabs for the uses identified above (Tab K, #15).

Furthermore, the Citizen Petitions fail to provide support for the second prong of the general recognition test because they provide no evidence of an expert consensus in the scientific community that chloramphenicol is generally recognized as safe for use in a manner that can reasonably be expected to result in its becoming a component of food.[20] Moreover, FDA believes that chloramphenicol is not and cannot currently be generally recognized as safe for use in a manner that can reasonably be expected to result in its becoming a component of food.[21]

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[20]Although there need not be unanimity among qualified experts that a substance is safe for "general recognition" of its safety to exist, an "expert consensus" is required. Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 632 (1973). Accordingly, there must be no genuine difference of opinion among qualified experts as to the substance's safety.

[21]Chloramphenicol has been reviewed three times by the WHO/FAO Joint Expert Committee on Food Additives (JECFA). The JECFA consistently concluded that there is no

(Tab G; see also Tab K, #16) A genuine dispute among experts precludes a finding of general recognition of safety. See, e.g., Coco Rico, 752 F.2d at 15 n. 6; United States v. Articles of Drug * * * 5,906 Boxes, 745 F.2d 105, 119 n. 22 (1st Cir. 1984), cert. denied, 470 U.S. 1004 (1985). FDA concludes that the data do not support the safety of chloramphenicol for use in crabs through shrimp feed or by direct addition to shrimp ponds, holding tanks or other containment areas; or in a wash, dip, spray, or other treatment during processing, such as a hand treatment. Thus, chloramphenicol is not generally recognized as safe for these uses in crabs.

Because chloramphenicol is a substance the intended use of which may reasonably be expected to result, directly or indirectly, in its becoming a component of food and because it does not meet the two requirements for general recognition of safety, it is a "food additive" that needs an approved food additive petition to be lawfully marketed. Without such approval, crabmeat containing detectable levels of chloramphenicol is deemed unsafe and is adulterated under section 402(a)(2)(C)(i), 21 U.S.C. § 342(a)(2)(C)(i).

B. Crabmeat Containing Chloramphenicol Bears or Contains a Poisonous or Deleterious Substance Which May Render It Injurious to Health

Under section 402(a)(1) of the Act, 21 U.S.C. § 342(a)(1), a food shall be deemed adulterated if it "bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health." Thus, if a substance is deemed "added," then food containing the substance is deemed adulterated if the substance "may render (the food) injurious to health." Anderson Seafoods, Inc., 622 F.2d at 159; Continental Seafoods, 674 F.2d at 42-43.

After carefully reviewing the information provided in your Citizen Petitions, as well as all other publicly available information on this subject, FDA concludes that crabmeat containing detectable levels of chloramphenicol is adulterated, because chloramphenicol is an added poisonous or deleterious substance that may render the crabmeat injurious to human health under section 402(a)(1) of the Act, 21 U.S.C. § 342(a)(1).

1. Crabmeat Testing Positive Using FDA's Methodology Bears or Contains Chloramphenicol

As discussed above,[22] FDA's LC/MS methodology for detecting chloramphenicol in crabmeat is fully validated, scientifically supportable, and capable of distinguishing chloramphenicol from other structurally similar substances (Tab F, summary). Thus, crabmeat

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acceptable daily intake for chloramphenicol in the human diet (12th JECFA, 1968; 32nd JECFA, 1987; 42nd JECFA, 1994).

[22]See, infra, section I.

found to contain detectable levels of chloramphenicol using FDA's methodology "bears or contains" chloramphenicol for purposes of section 402(a)(1), 21 U.S.C. § 342(a)(1).

2. Chloramphenicol in Crabmeat is Added

The Citizen Petitions assert that chloramphenicol in crabmeat must be naturally occurring because crabs are wild and not subject to aquaculture and that there is no opportunity for the chloramphenicol to be artificially added to the crabs. Miami Crab Petition at 5; Blue Star Petition at 6-8. To support this proposition, the Citizen Petitions point out that chloramphenicol was originally discovered in soil samples taken in Venezuela in 1947. Miami Crab Petition at 5; Blue Star Petition at 5. Thus, the Citizen Petitions contend that, since the chloramphenicol is naturally occurring and not added, FDA must prove that the chloramphenicol in crabmeat is "ordinarily injurious" to health rather than merely proving that it "may render" the crabmeat injurious to health. Miami Crab Petition at 9; Blue Star Petition at 8.

In order to be subject to the "may render injurious" standard in section 402(a)(1) of the Act, 21 U.S.C. § 342(a)(1), a portion of the chloramphenicol in crabmeat must be found to be "added." The term "added" as used in section 402(a)(1), 21 U.S.C. § 342(a)(1), means "artificially introduced, or attributable in some degree to the acts of man." Anderson Seafoods, 622 F.2d at 160; see also Continental Seafoods, 674 F.2d at 43. In other words, "where some portion of a toxin present in a food has been introduced by man, the entirety of that substance present in the food will be treated as an added substance and so considered under the 'may render injurious to health' standard of the Act." Anderson Seafoods, 622 F.2d at 161; see also Continental Seafoods, 674 F.2d at 43. The amount of the added substance contributed by man "need not be substantial"; the FDA need show only that some portion of the toxin is attributable to the acts of man and that the total amount may be injurious to health. Anderson Seafoods, 622 F.2d at 162; see also Continental Seafoods, 674 F.2d at 43 ("In light of FDA's broad authority to prohibit import of any food that 'appears' to be adulterated, the agency need not prove that substances present in a particular lot were introduced by man").

Based on evaluation of its method, published literature, and consultations with its expert on the issue, FDA concludes that the chloramphenicol being detected in crabmeat is added and is not naturally occurring (Tab L, #12; also see Tab F, #2). Given the short half-life (Tab L, #9) of chloramphenicol, the bioaccumulation of chloramphenicol in the soil would occur, if at all, at extremely low levels and would not be responsible for the levels being detected in crab by FDA using its current method (Tab F, #2; also see Tab L, #10, #11c). Moreover, to FDA's knowledge, chloramphenicol has never been detected in natural, unpolluted soil samples (Tab L, #11b, #11e); it has only been detected in soil samples exposed to artificial conditions (Tab L, #11b). While it is true that the bacterium which produces chloramphenicol, *Streptomyces venezuelae*, was originally discovered in 1947 in Venezuela, the antibiotic chloramphenicol was not detected directly in natural soil samples. The discovery of antibiotic activity attributable to chloramphenicol was observed from extracts of the *Streptomyces* bacterium that were grown, or cultured, in a laboratory setting. If chloramphenicol were to be detected directly in natural soil

samples, it would be necessary to have rigorous extraction and concentration steps to make laboratory detection possible.[23] However, FDA's detection methodology does not involve such a concentration step that is sufficiently refined to detect the extremely low levels of chloramphenicol that would be present if the chloramphenicol were coming solely from soil run-off (Tab F, #2). Therefore, FDA's method would not detect chloramphenicol in crabmeat following dilution of soil run-off into coastal waters; consequently, the chloramphenicol being detected by FDA's method is not coming from a natural source such as soil run-off. Moreover, if the chloramphenicol detection using FDA's methodology revealed a naturally-occurring substance, FDA would expect to find chloramphenicol in most, if not all, product from affected areas. However, this simply is not the case. In fact, only six of twelve crabmeat samples taken between June 2002 and June 2003 tested positive for chloramphenicol (five from Vietnam and one from China) (Tab M). Therefore, FDA does not believe that the chloramphenicol being detected in crabmeat is naturally occurring.

Moreover, while we appreciate your clients' asserted efforts to investigate crab production practices,[24] FDA cannot agree that there is no possibility that chloramphenicol was added to the crabmeat at some time during growth, harvest, or processing. As discussed above,[25] given the evidence of widespread use of chloramphenicol and the absence of any regulatory controls in China,[26] the previous acknowledgments by the governments of China and Vietnam that chloramphenicol has been added to seafood products,[27] and FDA's knowledge of seafood practices in Southeast Asia,[28] FDA concludes that there are several potential routes of contamination by chloramphenicol: (1) through shrimp feed or by direct addition to shrimp ponds, holding tanks, or other containment areas; or (2) in a wash, dip, spray, or other treatment used during processing, such as the hand treatments documented by the Chinese government as

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[23]Thomashow LS, Bonsall RF, Weller DM. Antibiotic Production by Soil and Rhizosphere Microbes In Situ. *In* Hurst CJ, Knudsen GR, McInerney MJ, Stetzenbach LD, Walter MV (eds.), *Manual of Environmental Microbiology*. ASM Press, 1997; p. 493. Even indirect molecular genetics approaches, such as identifying genetic material required for antibiotic production which are far more sensitive than FDA's analytical chemistry methods, have been unreliable in detecting naturally-occurring antibiotics in the soil. Id.

[24]See Miami Crab Petition at 5; Blue Star Petition at 6.

[25]See infra IIA1.

[26]See European Commission Final Report (Tab I, p. 27).

[27]See Tab H, #4, #6; see also Tab J.

[28]See Tab H, #4, #5, #6; see also Tab I.

late as June of 2002 (Tab H, #4, #5, #6). Due to its apparent ready availability, low price,[29] and broad anti-spectrum antibiotic activity,[30] it is reasonably likely that chloramphenicol is added to crabmeat in these ways.

3. Chloramphenicol in Crabmeat is a Poisonous or Deleterious Substance that May Render the Crabmeat Injurious to Human Health

Since crabmeat testing positive for chloramphenicol bears or contains chloramphenicol and since this substance is added for purposes of section 402(a)(1), 21 U.S.C. § 342(a)(1), crabmeat containing detectable levels of chloramphenicol is adulterated if chloramphenicol in crabmeat may render the food injurious to health. The "may render injurious" standard has been interpreted to mean that there is a reasonable possibility of injury to the consumer. See United States v. Lexington Mill & Elevator Co., 232 U.S. 399 (1914); Berger v. United States, 200 F.2d 818, 821 (8th Cir. 1952). "It may be consumed . . . by the strong and the weak, the old and the young, the well and the sick and it is intended that if any . . . [crabmeat], because of any added poisonous or deleterious ingredient, may possibly injure the health of any of these, it shall come within the ban of the statute." Lexington Mill, 232 U.S. at 340-41. The absence of documentation of any reported instances of illnesses or deaths associated with the particular food product at issue does not mean that there does not exist a reasonable possibility that the poisonous or deleterious added substance may be injurious to the health of those who consume it. Continental Seafoods, 674 F.2d at 200; see also Seabrook Internatl. Foods, Inc. v. Harris, 501 F. Supp. 1086, 1092 (D.D.C. 1980) ("This claim rests entirely upon the apparent absence of any reported instances of salmonellosis specifically attributable to shrimp. . . . This absence of documentation does not foreclose the Administrator's discretion to determine that salmonella in shrimp may be injurious to the health of those who consume it."), aff'd, 674 F.2d 38 (D.C. Cir. 1982). Given the evidence of human health risks associated with chloramphenicol, FDA disagrees with the assertion in the Citizen Petitions that there is no health hazard from exposure to chloramphenicol in crabmeat.

There are at least three known potential human health risks from exposure to chloramphenicol at low dietary levels: (1) aplastic anemia, (2) carcinogenicity, and (3) reproductive toxicity. Concern for these three health risks currently exists at all levels of exposure.

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[29]The website, http:www.expresspharmapulse.com/20030522/drug.shtml, lists chloramphenicol for 1325 Rupees ($28.29) per kilogram; for comparison to some other widely available antibiotics, ciproflaxacin is 1300 Rupees ($27.75), ampicillin is 1700 Rupees ($36.29) and nalidixic acid is 2350 Rupees ($50.17).

[30]Sande MA, Mandell GL. Tetracyclines, chloramphenicol, erythromycin, and miscellaneous antibacterial agents. Goodman and Gillman's The Pharmacological Basis of Therapeutics. 8th edition. Editors: Goodman Gillman A., Rall TW, Nies AS, Taylor P. McGraw-Hill, Inc. New York. 1993.

a. Chloramphenicol Associated Aplastic Anemia

Aplastic anemia, a potentially fatal illness associated with chloramphenicol, generally takes the form of suppression of all blood cell types by the bone marrow (Tab K, #6; Tab N). Patients with aplastic anemia with all blood cell types suppressed are susceptible to infections and bleeding complications because they lack the necessary blood cell types to respond to these infections or bleeding events. Infections and bleeding events are common causes of death in patients with aplastic anemia. Aplastic anemia with suppression of all blood cell types has been reported to be associated with fatality in more than 50% of patients (Tab N). The anemia is frequently described as idiosyncratic, meaning that some individuals may be more susceptible to chloramphenicol associated aplastic anemia than others, and as being unpredictable based on the magnitude, dose, or frequency of the administered dose (Tab K, #7).[31]

One possible method by which chloramphenicol may cause aplastic anemia is through nitro-reduction, or removal of a nitro group (NO_2) of the chloramphenicol, possibly by bacteria in the gastrointestinal tract, resulting in reactive products that may damage DNA in the bone marrow which prevents the stem cells in the bone marrow from developing into normal blood cell types. Studies have also reported the metabolism of chloramphenicol to dehydrochloramphenicol by gastrointestinal bacteria or through metabolism of the chloramphenicol by the liver (32nd JECFA, 1987). The dehydrochloramphenicol, in turn, can undergo nitro-reduction in the bone marrow, resulting in DNA strand breaks (10th Annual Report of Carcinogens, 2002).

Chloramphenicol has been reviewed three times by the WHO/FAO Joint Expert Committee on Food Additives (JECFA).[32] The JECFA consistently concluded that there is no acceptable daily intake for chloramphenicol in the human diet.

While it is true that the only human data that exist on aplastic anemia measure exposure at therapeutic doses of chloramphenicol, it does not follow that there is no corresponding risk associated with ingestion of crabmeat containing subtherapeutic levels (including residue concentration levels at and below 5.0 ppb in edible tissue) of chloramphenicol. The reason that there are no data at the lower levels is that useful animal models do not exist for chloramphenicol-induced aplastic anemia and it is considered unethical to subject humans to

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[31]Settipani, JAVMA 184 (8): 930-931, 1984; 50 FR 27059 (July 1, 1985); 12th JECFA, 1968; 32nd JECFA, 1987; 42nd JECFA, 1994.

[32]12th JECFA, 1968; 32nd JECFA, 1987; 42nd JECFA, 1994.

testing, even at very low levels, because of the serious and potentially fatal nature of this disease. Chloramphenicol-associated aplastic anemia remains an extremely serious and potentially fatal disease (see Tab K, #6; Tab N). Consequently, chloramphenicol's oral and intravenous use in the U.S. is limited to treatment of life threatening infections when all less potentially dangerous alternative antimicrobial drugs will be ineffective or cannot be used.[33] Indeed, all oral and intravenous forms of chloramphenicol marketed for human use in the U.S. must include a black box warning explaining the risk of aplastic anemia; dictating that this drug must not be used in the treatment of trivial infections, where it is not indicated, or as a prophylactic agent to prevent bacterial infections; and stating that in the rare instances in which it is used, it is essential that adequate blood studies be made during treatment with chloramphenicol and that hospitalization during treatment is recommended.[34]

The Blue Star Citizen Petition asserts that the data on reduced risk from doses of chloramphenicol in eye drops demonstrate that there is a dose-response relationship to risk of aplastic anemia from chloramphenicol. Blue Star Petition at 17. FDA agrees that there are epidemiological data to suggest that the frequency of aplastic anemia following the use of eye drops containing chloramphenicol is not above the frequency for aplastic anemia from all causes among the non-U.S. populations examined; but FDA disagrees with the Citizen Petition's conclusion that this information can be used to establish the safety of chloramphenicol residues in food (Tab K, #9, #11). First, case studies and adverse event reports of aplastic anemia in people that have used chloramphenicol eye drops have been reported (Tab K, #9). Second, in contrast to the ingestion of chloramphenicol residues in food, only a fraction of the dose of chloramphenicol administered through eye drops is actually swallowed; most of the absorbed dose enters through the eye (Tab K, #10). Third, there is no evidence that the likelihood of aplastic anemia following exposure to chloramphenicol eye drops can be used as a model to predict the likelihood of aplastic anemia in people who consume chloramphenicol residues in food, particularly considering the increased likelihood of aplastic anemia following the oral use of chloramphenicol in human medicine (Tab K, #11). The human toxicity data available for chloramphenicol follow relatively acute (short term) exposure at relatively high doses intended to have a therapeutic impact on the user (Tab K, #12). Most therapeutic uses, including eye drops, involve only days or weeks of use of the drug (Tab K, #12). Dietary consumption, on the other hand, would be anticipated to continue for a lifetime (Tab K, #12).

While there may be, as pointed out in the Blue Star Citizen Petition, a background rate of cases

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[33] Despite the risks of chloramphenicol therapy, for patients with certain types of life threatening infections for which there is no other available acceptable treatment, chloramphenicol may be an appropriate therapeutic option (Tab N).

[34] See Tab O; see also 1998 Physician Desk Reference Entry for Chloramycetin (sterilechloramphenicol sodium succinate, USP) for IV administration, 1996 Warner-Lambert Co.

of aplastic anemia in persons without any known exposure to bone marrow toxins,[35] this does not necessarily mean that these persons were not subjected to chloramphenicol or other toxic materials, but only that it was not documented. Moreover, the fact that aplastic anemia may also result from other causes, as mentioned in the Blue Star Petition,[36] is irrelevant to the issue at hand. The question is whether chloramphenicol in crabmeat may cause fatal aplastic anemia. FDA has substantial evidence based on the oral and injected medical use of chloramphenicol that exposure to chloramphenicol is known to cause a fatal aplastic anemia, that the likelihood of a fatal aplastic anemia occurring cannot be predicted from the chloramphenicol dose, and that studies have shown that fatal aplastic anemia is 13 times more likely to occur after use of chloramphenicol.[37] Under these circumstances, there is a reasonable possibility of injury to the health of the consuming public from detectable chloramphenicol residues in crabmeat.

Finally, we cannot agree with the proposition in the Blue Star Citizen Petition that eating one 1/4 pound crabcake per day results in safe consumption for 54 years. Blue Star Petition at 18. This proposition is based on the evidence of decreased risk of aplastic anemia through eye drop administration. There is no evidence to support the safety of chronic human dietary exposure to chloramphenicol residues. While the bulk of human toxicity data available for chloramphenicol follows relatively acute (short term) exposure at relatively high doses intended to have a therapeutic impact on the user, toxic effects are commonly seen at lower doses in long term studies (Tab K, #13). The maximum dose tested in a long term study typically results in only mild effects in a short term study.[38] Moreover, fatal aplastic anemia following oral exposure to chloramphenicol in human medicine is recognized to be idiosyncratic, and so the likelihood and severity of aplastic anemia cannot be predicted from the administered dose of chloramphenicol. It is not possible, therefore, to conclude that the consumption of measurable amounts of

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[35]See Blue Star Petition at 16.

[36]Id.

[37]Wallerstein RO, et al. "Statewide Study of Chloramphenicol Therapy and Fatal Aplastic Anemia." JAMA 1969 June 16; 208(11): 2045-050. Wallerstein RO. "Chloramphenicol Toxicity." Lancet, 1969, ii: 695. Kucers A, et al., "Chloramphenicol and Thiamphenicol" in The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal and Antiviral Drugs 5th Edition, ©1997, Butterworth-Heinemann. pp. 548-579. Feder HM, Osier C, Maderazo EG. "Chloramphenicol A Review of Its Use in Clinical Practice." Rev. Infect. Dis. 1981, Vol. 3, No. 3, pp. 479-491. Nagao T, Mauer AM. "Concordance for Drug-induced Aplastic Anemia in Identical Twins." NEJM 1969, 281:7-11. Yunis AA. "Chloramphenicol Toxicity: 25 Years of Research." Am. J. Med. 1989, Vol. 87, 3-44N - 3-48N. Best WR. "Chloramphenicol-Associated Blood Dyscrasias." JAMA 1967 July17; 201(3) 181-188.

[38]Casarett and Doull's Toxicology. The Basic Science of Poisons. 5th ed., 1996. CD Klaassen, editor. MO Amdur and J. Doull, Editors Emeriti. McGraw-Hill. N.Y.

chloramphenicol in crabmeat is safe and may not cause harm to the public health.

Based on the evidence currently available, FDA concludes that chloramphenicol at detectable levels in crabmeat subjects consumers to a reasonable possibility of developing fatal aplastic anemia.

b. Carcinogenicity

There are also data that cause significant concern for genetic toxicity, (i.e., chromosome breaks and DNA damage), and carcinogenicity, (i.e. leukemia), associated with chloramphenicol. The 1994, 42nd JECFA and the US National Toxicology Program's current Tenth Annual Report on Carcinogens (2002) reviewed the available data on effects of chloramphenicol on the DNA. They found chloramphenicol to cause chromosomal damage and concluded that it was therefore genotoxic. In addition, the 1990 World Health Organization International Agency for Research on Cancer concluded that chloramphenicol is likely carcinogenic to humans (category Group 2A, IARC vol. 50: 169, 1990). Finally, chloramphenicol is listed in the U.S. Tenth Annual Report on Carcinogens, which classifies chloramphenicol as "reasonably anticipated to be a human carcinogen, based on limited evidence of carcinogenicity from studies in humans."[39] As with the concern for aplastic anemia, there are insufficient data to establish a relationship between the magnitude, frequency, or duration of the administered chloramphenicol dose and the likelihood and severity of cancer. Because it is not possible to predict which individuals will be susceptible, concerns exist for any level of chloramphenicol exposure, including levels of chloramphenicol residues found in crabmeat.

c. Chloramphenicol Associated Reproductive Toxicity

Finally, in addition to the risks of aplastic anemia and carcinogenicity, chloramphenicol also presents a risk of reproductive toxicity. There are data to show that chloramphenicol crosses the placenta and is thus a danger to fetuses during late gestation.[40] In addition, there are animal data to show that exposure to high doses of chloramphenicol (500 mg/kg per day) during pregnancy can result in the death of fetuses and there is an absence of animal data to show a dose that will

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[39]10th Annual Report on Carcinogens, 2002.

[40]A 1999 summary by the Teratogen Information System (TERIS, 2003) notes that there is concern for maternal use of chloramphenicol during late gestation as the drug readily crosses the placenta. Placenta transfer was also noted by the 32nd JECFA. TERIS, the Reproductive Toxicity Center (REPROTOX, 2003), and the 32nd JECFA describe the "grey baby" syndrome caused by chloramphenicol as seen in some infants and which may result in vomiting, refusal to nurse, irregular respiration, abdominal distention, an ashen-gray color, hypothermia, circulatory collapse, and death.

not have this effect.[41] Furthermore, there are data to show that chloramphenicol is excreted in breast milk and is thus a danger to breastfed babies.[42] Therefore, chloramphenicol residues in crabmeat also present a risk of reproductive toxicity.

Given the risks of aplastic anemia, carcinogencity, and reproductive toxicity, exposure to chloramphenicol in crabmeat may render the crabmeat injurious to human health. Thus, since crabmeat containing detectable levels of chloramphenicol bears or contains an added poisonous or deleterious substance that may render the food injurious to human health, such crabmeat is adulterated under section 402(a)(1) of the Act, 21 U.S.C. § 342(a)(1).

III. The Agency Has Not Acted in Restraint of International Trade or in Violation of any U.S. Treaty Obligations

The Blue Star Citizen Petition notes that the LC/MS test for chloramphenicol has to date only been applied in crabmeat of foreign origin and contends that the test is therefore a restraint of international trade and in violation of U.S. treaty obligations. Blue Star Petition at 20-21. While it is true that FDA first instituted this test with respect to crabmeat of foreign origin, this is because chloramphenicol is prohibited for extra-label animal drug uses in food animals (21 C.F.R. 530.41) and has no food animal approvals in the U.S. (including crabs).[43] Conversely, there is abundant evidence that chloramphenicol is still in widespread use abroad, particularly in Southeast Asia. As pointed out in the Petition, the WTO agreements provide that the protection of "human, animal or plant life or health" is a legitimate objective for regulation. Blue Star Petition at 20. Since, as discussed above, there are significant health and safety risks associated

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[41]The 1994, 42nd JECFA concluded that chloramphenicol was a reproductive toxicant resulting in fetotoxicity (dead fetuses) in rabbits administered 500 mg/kg bw per day.

[42]A 2002 review of the reproductive toxicity of chloramphenicol provided by the REPROTOX notes that chloramphenicol is expressed in a mother's milk, and that the American Academy of Pediatrics has expressed concern for use of the drug in lactating mothers and does not recommend breastfeeding when the drug is used.

[43]Oral chloramphenicol solution product approvals were withdrawn for use in companion animals in the U.S. primarily because of the use of the companion animal drug in food animals and concern for aplastic anemia in the human consumer. See 51 FR 1367 (Jan. 13, 1986). The approval of oral chloramphenicol solution for use in dogs was also withdrawn in 1986 because of evidence, including drug residues in meat, that the drug was being used in food-producing animals. Id. Chloramphenicol for use in dogs is still approved in other dosage forms. When used therapeutically to treat life-threatening infections in humans, the oral and intravenous use of chloramphenicol is limited to severe infections due to the potentially fatal side effect – idiosyncratic aplastic anemia (Tab N). There is no tolerance established for chloramphenicol residues in any food animals, so any detectable level is a violation.

with exposure to chloramphenicol at all levels, the agency is justified in taking regulatory action against crabmeat containing chloramphenicol under sections 402(a)(2)(C)(i) and (a)(1) of the Act, 21 U.S.C. § 342(a)(2)(C)(i) and (a)(1).[44]

Courts have long upheld agencies' "broad discretion in selecting the appropriate regulatory method to advance their prescribed objectives," even where such action is instituted solely with respect to foreign-based products. Seabrook International Foods, 501 F. Supp. at 1093, citing Pan American World Airways, Inc. v. Civil Aeronautics Board, 392 F.2d 483, 496 (D.C. Cir. 1968). Given the FDA's need to prioritize its regulatory objectives to accommodate its resource limitations, FDA began the chloramphenicol testing program for crabmeat with imported product because of the evidence that the greater public health urgency and safety threat came from these imported products. However, the agency plans to expand its testing program to cover domestic product in the near future. Consequently, FDA has not violated any international trade or U.S. treaty obligations.

IV. Conclusion

As requested in the Citizen Petitions, FDA has reviewed its assessment that crabmeat testing positive for chloramphenicol under the LC/MS methodology developed by the Denver laboratory is adulterated. As explained in more detail above, FDA concludes that its LC/MS method for detecting chloramphenicol in crabmeat has been fully validated for crab and can distinguish chloramphenicol from other structurally similar substances that may be present in the crabmeat. Additionally, given that chloramphenicol is being detected in crabmeat, testing for its presence is clearly appropriate. Moreover, FDA continues to believe that crabmeat containing chloramphenicol at detectable levels using the LC/MS methodology is adulterated under sections 402(a)(2)(C)(i) and 402(a)(1) of the Act, 21 U.S.C. §§ 342(a)(2)(C)(i) and (a)(1). Crabmeat containing detectable levels of chloramphenicol is adulterated under section 402(a)(2)(C)(i), 21 U.S.C. § 342(a)(2)(C)(i), in that it contains an unapproved, unsafe food additive, because the intended uses of chloramphenicol in shrimp feed or by direct addition to shrimp ponds, holding tanks, or other containment areas; or in a wash, dip, spray, or other treatment used during processing, such as a hand treatment, may reasonably be expected to result in the chloramphenicol becoming a component of the crabmeat and because chloramphenicol is not generally recognized as safe for any of these intended uses. Crabmeat containing detectable levels of chloramphenicol is also adulterated under section 402(a)(1), 21 U.S.C. § 342(a)(1), in that it bears or contains a poisonous or deleterious substance which may render it injurious to human health, because, as explained in more detail above, chloramphenicol at detectable levels in crabmeat is added rather than naturally occurring and there is a reasonable possibility of injury to human health from the chloramphenicol in crabmeat due to concerns of fatal chloramphenicol associated aplastic anemia, carcinogenicity, and chloramphenicol associated reproductive

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[44]Other countries, such as Canada and member countries of the EU, also prohibit the importation of meat and dairy containing chloramphenicol (Tab P).

toxicity. Finally, the agency also believes that it is acting in compliance with U.S. treaty obligations and not in restraint of international trade, because the decision to begin FDA's chloramphenicol testing program for crabmeat with imported product was based upon the need to prioritize the agency's regulatory objectives to accommodate resource limitations and the evidence before the agency that the greater public health threat came from these imported products; the agency does, however, intend to expand its testing program to include domestic product in the near future. Accordingly, the Miami Crab and Blue Star Citizen Petitions are denied.

John M. Taylor, III
Associate Commissioner
for Regulatory Affairs
Food and Drug Administration

Tabs

A - Letter to Jur T. Strobos, dated May 5, 2003

B - Validation data provided by the Division of Field Science, ORA, FDA
Data Set 1: Validation and Quality Assurance Assessment
Data Set 2: Validation of the Specificity of the Method

C - Standard Operating Procedure: DEN-LB.46 Quality Control Program for Method Verification, Validation, and Modifications

D - Laboratory Information Bulletin (LIB) 4294: Confirmation of Chloramphenicol Residue In Crab By Electrospray LC/MS

E - Standard Operating Procedure: DEN-LB.80 Chloramphenicol Residue in Food by Electrospray LC/MS

F - Memorandum from the Division of Field Science, ORA, FDA

G - Memorandum from the Office of Food Additive Safety, CFSAN, FDA

H - Declaration from Dr. William Jones, Office of Seafood, CFSAN, FDA

I - Final Report of the European Commission

J - Memorandum to the official record RE: Meeting with Vietnamese government officials of March 5, 2003

K - Declaration from Dr. Kevin Greenlees, Ph.D.

L - Declaration for Dr. Russell Hill, Center of Marine Biotechnology, University of Maryland Biotechnology Institute

M - CFSAN Internal Report on Chloramphenicol Findings

N - CDER consultation review

O - Black box warning for Chloramphenicol

P - Press release dated January 31, 2002 from the UK Food Standards Agency on the ban of imported animal product due to chloramphenicol; Advisories from the CFIA on chloramphenicol detected in various products.