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CITIZEN PETITION

The undersigned submits this petition under the Federal Food, Drug, and Cosmetic Act (FDC Act), 21 U.S.C. § 342, and 21 C.F.R. § 10.30 to request the Commissioner of Food and Drug to grant relief from inaccurate and unwarranted testing for de minimis and/or naturally occurring levels of chloramphenicol in imported crabmeat. This petition is submitted on behalf of John Keeler & Co., Inc., d/b/a Blue Star Food Products, 3000 NW 109th Avenue, Miami, Florida 33172, a company that imports and distributes wild-raised crabmeat for human consumption.

A. ACTION REQUESTED

Blue Star Food Products requests that the U.S. Food and Drug Administration (FDA):

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 parts per billion (ppb) using existing testing methodology.

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3. Perform a health hazard evaluation relating to the exposure to naturally occurring chloramphenicol at levels of less than 5 ppb before taking any action against crabmeat containing such levels and revise or clarify Import Alert Nos. 16-124 and 68-01 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 ppb does not result in such crabmeat being deemed 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 crabmeat containing less than 5 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.

7. Enforce current World Trade Organization treaty obligations that prohibit differential treatment of foreign goods based on spurious and unscientific "safety" standards.

On July 19, 2002, a citizen petition with supporting documents was submitted on behalf of Miami Crab Corporation (Miami Crab). The petition, assigned Docket No. 02P-0321, seeks much of the same relief sought by this petition and is relevant to the issues presented here. Accordingly, we hereby incorporate by reference the documents submitted in support of the Miami Crab petition and ask that the contents of Docket No. 02P-0321 be incorporated as part of the record supporting this petition and vice versa.

B. STATEMENT OF GROUNDS

1. Summary

The recently instituted Liquid Chromatography Electrospray Mass Spectroscopy (LCEMS) methodology for testing for chloramphenicol residues is not valid, as a matter of regulatory science,

for its intended purpose. Therefore, the methodology cannot be used to identify crabmeat as adulterated as a matter of law. Thus, there is no rationale for this testing program as applied to crabmeat. First, as supported by attached affidavits from a chemistry expert, the test method employed by the FDA has not been properly validated to ensure against false positive results and thus positive test results do not confirm the presence of chloramphenicol. (See section 4 infra). But, more importantly, even if the tests were determinative of chloramphenicol content, there has never been and cannot be a health hazard from exposure to de minimis levels of chloramphenicol at less than 5 ppb. Third, even if the test were accurate and there were some evidence to support a health risk (which there is not), crabmeat from wild-raised crabs containing very low levels of naturally occurring chloramphenicol is not adulterated within the meaning of the FDC Act.

This petition further notes that the European Commission has already undertaken the requested action for the aforementioned reasons. Thus, other international authorities have recognized that such testing should not be conducted. Finally, we believe that the agency actions are in restraint of international trade, since our understanding is that this testing is applied only to crabmeat of foreign origin and is without basis in any rational or legally authorized health or safety standard, and thus represent a violation of the nation's treaty commitments.

2. Background

As noted in the prior citizen petition and confirmed in this petition, FDA has begun testing samples of crabmeat imported from China for chloramphenicol residues using an unvalidated LCEMS method. This test methodology has been widely instituted for imported crabmeat notwithstanding the failure to conduct any validation of the test method in crabmeat. Since the filing

of the prior citizen petition on July 19, 2002, and possibly in response thereto, the agency published new experimental data on the use of this test method in crabmeat. (See Tab A). This additional experimental work remains, however, inadequate under generally accepted scientific standards to validate the test method for use in crabmeat.

This test method was applied to imported crabmeat owned by Blue Star Food Products and, subsequently, FDA's Florida District Office detained the crabmeat based on LCEMS test results that purport that the samples "met confirmation criteria for chloramphenicol." (See Tab B). Under the false or unproven assumptions that, first, the LCEMS test reliably detected chloramphenicol as opposed to some other permissible chloride-containing substance; second, that such chloramphenicol was given to the crabs as an animal drug; and third, that such levels represent a health hazard, the agency concluded that such crabmeat was adulterated within the meaning of the FDC Act. (See Tab C). These events are causing serious economic injury to Blue Star Food Products. This harm will continue unless FDA grants the relief sought by this petition.

Recently, in correspondence signed by Associate Commissioner for Regulatory Affairs John M. Taylor III, the agency confirmed its "current testing initiative for chloramphenicol (CAP) in imported food." (Tab D (emphasis added)). This correspondence further indicates that, "[f]or crabmeat products . . . the detection (confirmation) limit was established at 0.5 ppb."

3. There Is No Evidence That Chloramphenicol, A Naturally Occurring Substance, Was Added To Crabmeat At Any Time During Growth, Harvesting, Or Processing, And Thus, Its Presence At Very Low Levels Does Not Render The Crabmeat Adulterated Under The FDC Act.

In testing for chloramphenicol at extremely low levels using the LCEMS methodology, the agency has simply missed the point. As noted in the earlier petition, chloramphenicol was originally discovered in 1947 in soil samples taken in Venezuela. Chloramphenicol is present in the environment naturally and without human intervention. The development of new testing methodologies that identify substances at extremely low levels raises the issue of what is the natural, very low-level, presence of the compound when there has been no human intervention. As set forth in the Meyer Declaration (see Tab E), this is not a new issue but one that has been ignored by FDA in instituting the LCEMS test method.

When it comes to unapproved new animal drugs or unapproved food additives, the permitted level of residues is zero. See 21 U.S.C. § 360b(a)(1)(A), § 348(a), § 342(a)(2)(C). In comparison, under § 342(a)(1), a different standard applies for any "poisonous or deleterious substance" other than a new animal drug or a food additive. For a food bearing or containing any such substance to be deemed adulterated, FDA must establish that there is a potential for injury to health (with different standards, depending on whether the substance is added or naturally occurring). FDA has completely disregarded this distinction, and has chosen to disregard the issue of the natural "presence of chlorine-containing substances in the environment and testing for their presence" (Tab E at ¶ 4). For instance, in the new experiments, the investigators summarily "rejected any samples that showed chloramphenicol in the background or non-fortified crabmeat" (Tab E at ¶ 10),

indicating that they were most likely unaware, or disregarded evidence from their own studies, that chloramphenicol is a naturally occurring compound and that the introduction of new test methods with extremely low limits of detection requires assessment of background presence of natural compounds.[1] (See Tab E). Since the LCEMS test method cannot distinguish natural from added chloramphenicol and no evaluation was done as to normal baseline levels of chloramphenicol, the LCEMS method is simply inappropriate as an assay for added chloramphenicol.

We have investigated crab production practices in Asia. (See Keeler Declaration at Tab F). Crabs are harvested from coastal waters. Crabs live in tidal areas where water originates both from the ocean (salt water) and as run-off from land (rain water or rivers) so that naturally present chloramphenicol in dirt produced by microorganisms should find its way into crabs at very low levels. Unlike shrimp, crabs are not—and cannot be—subject to aquaculture or "farming" techniques. Additionally, any such shrimp fisheries are hundreds of miles from crab harvesting areas. (See Tab F). Crabs are not exposed to antibiotics (new animal drugs) in feed or in any other manner to improve production, or to prevent or treat disease, or even by accidental contamination of their feeding waters through shrimp aquaculture.

Moreover, chloramphenicol is not added to harvested crabs or crabmeat. Blue Star Food Products has undertaken an intensive investigation of crab processing performed by our suppliers.

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[1] "Indeed, the investigators pro forma rejection of positive samples from unspiked crabmeat appears to indicate that they are unaware that chloramphenicol might be present as a natural substance at these levels." Tab E at ¶ 10.

(See Tab F). Chloramphenicol is not present or used in any manner, whether as a hand sanitizer, surface cleaner, or adulterant in any way, shape, or form. Crabs are placed on ice when harvested. This ice is made from water without chloramphenicol. Crabmeat is removed from the crabs and exposed to equipment (tables, knives, etc.) that is cleaned with substances free of chloramphenicol. Crab pickers are gowned and gloved, and use hand washes that are free of chloramphenicol. Thus, chloramphenicol is not added to crabmeat at any time from harvest to packing and, any chloramphenicol present must derive from natural sources. (See Tab F). This investigation and the accompanying Keeler Declaration provide further evidence to support FDA's own improperly discarded test results that any chloramphenicol found in crabmeat, if that is indeed what the test is identifying, represents background "noise" from naturally occurring chloramphenicol.

Quite clearly, this test method cannot distinguish background, naturally occurring chloramphenicol from added chloramphenicol. As stated by a competent and experienced chemistry expert:

> [T]he test method is not capable of distinguishing chloramphenicol that has been added to crabmeat by the investigators (or similarly might have been added to crabmeat during processing) from chloramphenicol that might be present naturally and derived from production and release of chloramphenicol into the environment by bacteria known to produce chloramphenicol. That said, when using test methods that have very low limits of detection to test for residues of added substances, it is important to identify what levels of the substance might be present naturally. This also has not been done.

(Tab E at ¶ 9).

In sum, the facts are these:

- Chloramphenicol is a natural substance present in low levels in the environment.

- Chloramphenicol is not added to crabmeat from Asia, either as an unapproved new animal drug or a food additive.

- FDA investigators have summarily rejected and not considered the implications of LCEMS-positive unspiked crabmeat samples, apparently without awareness that chloramphenicol is a naturally occurring substance.

- The test method cannot distinguish naturally occurring chloramphenicol from added chloramphenicol.

Thus, given the known absence of added chloramphenicol in crabmeat production, the known environmental presence of chloramphenicol based on its discovery in nature, the inability of the test method to distinguish added from naturally present chloramphenicol, and the presence of positive test results from unspiked domestic crabmeat, the finding of a positive test result does not render the crabmeat adulterated.

FDA's authority to detain an imported food product is limited by statute. The FDA must rely upon authority provided by 21 U.S.C. § 342(a) and § 381(a), respectively). Under § 342(a)(1), "[a] food shall be deemed to be 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" (emphasis added). Thus, since chloramphenicol is not an "added substance," its presence does not make the crabmeat adulterated. There is no evidence that chloramphenicol is "ordinarily . . . injurious to health" at the levels being assessed. (See section 5 infra).

In this circumstance, because chloramphenicol is a naturally occurring compound produced by soil organisms (Streptomyces sp.) with likely run-off into coastal waters where crabs are captured

as the source of chloramphenicol,[2] and there is no evidence that the substance was administered to crabs or added to crabmeat at any time during growth, harvesting, or processing, the crabmeat is simply not adulterated within the statutory meaning of the term regardless of FDA's test results and regardless of how well the test has been validated.

4. The Electrospray Liquid Chromatography/Mass Spectroscopy Methodology Has Not Been Validated For Use In Crabmeat And The Agency Cannot Legally Or Scientifically Rely On The Test Method To Detect Chloramphenicol In Crabmeat.

The new testing methodology was first described in a paper authored by FDA scientists, "Confirmation of Multiple Phenicol Residues in Shrimp by Electrospray LC/MS." (Tab G). At that time, and notwithstanding that the method was already in use for imported crabmeat, no validation had been performed to assess accuracy for assessment of chloramphenicol residues in crabmeat.

FDA has now implicitly conceded as much as they have recently conducted and posted on their website additional studies using the test method in crabmeat. However, this experimental work failed to undertake the basic controls and analyses that are required by experts before acceptance and use. A brief review of the technology itself is required to understand the deficiencies in the test method evaluation.

Chloramphenicol interferes with bacterial protein synthesis. Chloramphenicol acts by binding to the 50S ribosomal subunit and blocking the formation of a peptide bond by inhibiting peptidyl transferase activity. It accomplishes this as such: first, by mimicking amino acid structure

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[2] This assumes that the test method does indeed detect reliably chloramphenicol at these levels and is not confounded by the presence of interfering approved chemicals from sanitizers (see section 4 infra), which has yet to be proven.

but, second, by donating chlorine atoms at a critical point in protein synthesis and thus blocking completion of the peptide bond. The structure of chloramphenicol demonstrates the presence of two chlorine atoms as in Figure 1.

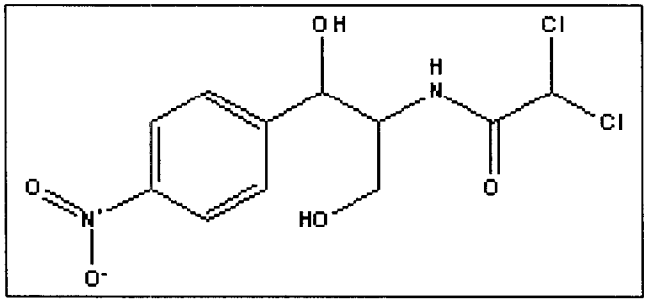

Figure 1

The LCEMS test method involves, first, the separation of chemical constituents by high-pressure liquid chromatography. (See Tabs A and G). The products are then analyzed by mass-spectrometry with electrospray ionization and an ion trap for performing MS^2 experiments. A chemical constituent with the mass/charge ratio expected for chloramphenicol is detected, $[M-H]^-$ = 321 and 323. The 323 species corresponds to the ion that contains one ^{35}Cl and one ^{37}Cl isotope while the 321 peak corresponds to the ion where both chlorine atoms are the ^{35}Cl isotope. These products were stored in an ion trap and subsequently fragmented to form daughter ions for the MS^2 experiments. Four specific daughter ions were assigned. A specifically useful daughter ion was observed that corresponds to the loss of one hydrogen, carbon, chlorine and oxygen atom, $[M-H-(HCOCl)]^-$ - 257/259. The daughter ions obtained from the 321 ion give a single peak at 257, while the daughter ions of the 323 give two peaks at 257 and 259 with the intensities expected for statistical loss of ^{37}Cl and ^{35}Cl respectively. Clearly, and as set forth in the accompanying affidavit

from a university professor and chemist who specializes in physico-chemical assays of this kind (see Tab E), any organic (i.e., containing carbon) compound with this mass that contains two chlorine atoms would give the same signature whether it was derived from "chloramphenicol" or not.

However, contrary to FDA's implication in its correspondence that the action level was validated "based on the method developed and published" (see Tab D), the test method used by FDA has not met, in the opinion of a competent expert, standard criteria and evaluations required before use. As stated by a chemistry expert, "the work does not adequately investigate the possibility of interfering peaks in the control experiments." (Tab E at ¶ 8). FDA has approved the use of chlorine-containing hand washes and sanitizers for use in the food industry to clean surfaces, equipment, and the hands of workers as contact surface food additives. (See Tab H (21 C.F.R. § 178.1010(b))). Many of these washes and cleaning solutions are in use in Asia in the crabmeat industry. This list includes polychlorinated substances such as di- and tri-chloroiscyanuric acid. As stated by a chemistry expert, "polychlorinated sanitizers, such as di- and tri-chloroisocyanuric acid, are potent oxidants that could react or associate with crabmeat to give similar masses and isotopic signatures" in the LCEMS test method. (See Tab E at ¶ 8). Stated differently, the LCEMS test might be positive merely because of the presence of these approved substances.

The agency has undertaken no evaluation to provide assurances that such false positives are not present. Testing for cross-reactivity with known substances to be sure that they do not interfere with the assay or the limits of detection before using such a test is standard practice. As stated by a chemistry expert, the published work on the method is inadequate because "the test validation work did not include purposefully adding known and approved food sanitizers which might mimic the

appearance of chloramphenicol in the test method to be sure that the test method can distinguish chloramphenicol from residues of these known and approved sanitizers." (Tab E at 8.) To the best of our knowledge, this has not been done and was certainly not published. Furthermore, while a review by a chemist of the approved sanitizer compounds might suggest that some of them might not be detected by this method, based solely on the chemistry, the interaction of these approved compounds with crabmeat and subsequent behavior in the electrospray and ion trap cannot be predicted without actual testing. Fresh crabmeat represents a complex "matrix" with many active compounds and enzymes that may change or otherwise affect chemical entities that might make them appear as falsely positive under this test method. In further support of the necessity of undertaking an evaluation of the source of false positives, we note that the ELISA method has been shown to produce false positives as a result of interference from sanitizers. (See Tab E).

Second, the limits of detection of the LCEMS method and the relationship of that limit to background low levels of natural chloramphenicol have not been investigated. A test method without such validation work should not be used to investigate low levels of substances. To that end, as noted supra, the LCEMS method cannot distinguish between chloramphenicol added or spiked into samples and naturally occurring, low levels of chloramphenicol. (See Tab E). This issue is exacerbated by the fact that the new experimental results specifically point out that all the chloramphenicol deliberately added to crabmeat, and then tested in the method, cannot be fully recovered.[3] Stated differently, the method is not quantitative – if 1 microgram is added, less than

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[3] "The recoveries ranged from 53% to 71%." (Tab A at page 8).

1 microgram is detected. In many test methods, as the spiked amount is reduced, the proportional amount measured in the test is anomalously reduced. For example, if 1 microgram is added, let us say that 0.5 microgram is detected. But if 1 nanogram is added, only 0.1 nanogram might be recovered. Since the level of background or baseline substance might be at the 0.1 nanogram level, such a test would not be capable of detecting even an additional 1 nanogram because the test method could not distinguish natural from added substance at that level. Since the investigators summarily rejected unspiked samples that were qualitatively positive, they apparently did not recognize that these crabmeat samples might contain naturally occurring chloramphenicol at these levels.[4]

The non-linearity at added low levels, the inability to distinguish natural from added chloramphenicol, and the apparent failure of the investigators to recognize that there are background natural levels, work together to make the LCEMS unsuitable for use without more experimental work. A limit of detection for added chloramphenicol should be established first. Establishing a limit of detection requires both an assessment of the linearity or quantitative recovery (or measurement) of added substances at multiple low levels and an assessment of background noise or the presence of natural substance at that low level. In contrast to good scientific practices, the FDA investigators plainly report that the test is "non-linear" when extremely low levels of chloramphenicol are added but apparently did no further investigation. The investigators also summarily rejected the idea that the positivity of some spiked samples may represent normal background noise or derive from naturally occurring chloramphenicol.

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[4] We cannot overemphasize our belief that the agency has failed to recognize that chloramphenicol can be present without being added since it is a naturally occurring substance.

The experimental work presented at Tabs A and G is further flawed because, as stated by a chemistry expert:

> [T]he report does not establish the limits of detection or the linearity of the response in the crabmeat matrix. The publications do not provide sufficient information to establish a limit of detection. In fact, the investigators' stated intention was the qualitative detection of chloramphenicol in crabmeat. Thus, any use of the methodology to detect and quantify extremely low levels of chloramphenicol in crabmeat is unwarranted.

(Tab E at ¶ 7).

The current FDA work does not meet standards of practice in physicochemical testing, notwithstanding Associate Commissioner Taylor's claim that "[t]his is the first reported test limit for crabmeat by ORA." (Tab D).

In sum, the facts are these:

- Approved sanitizers containing chlorine are used throughout the crab processing industry.
- Some of these sanitizers contain polychlorinated substances that interact with crabmeat and might interfere with the LCEMS test method and produce false positive results.
- The agency investigators have not validated whether such sanitizers produce false positive results using the LCEMS test method.
- The investigators have not established a limit of detection.
- The investigators ignored false positive results in unspiked samples.
- The investigators set out to establish a qualitative test and not one that can quantitate the amount of added chloramphenicol above naturally occurring levels.

Given the inadequate background work to establish the validity of the test and the systematic disregard of the possibility that low levels of chloramphenicol are present as a natural background substance with consequent disregard of appropriate tests to evaluate the test method, the test method should simply not be used.

5. Chloramphenicol At Levels Below 5 ppb Does Not Represent A Health Risk

Associate Commissioner Taylor has recently re-affirmed the "FDA policy regarding the presence of CAP [chloramphenicol] in food. Because of our public health concerns, no residues of CAP are permitted at any level." (Tab D). Disregarding the issue that chloramphenicol could be found in all food at some very low level given its natural presence, there is simply no scientific substantiation for the agency's public health concern. FDA's public health concern is ostensibly related to the development of aplastic anemia, a fatal disease, from exposure to therapeutic doses of chloramphenicol. There is no corresponding risk associated with ingestion of crabmeat containing less than 5 ppb of chloramphenicol.[5] In the agency Import Alerts and in the Taylor correspondence, the agency persists in its unfounded belief that there is no dose relationship between chloramphenicol and risk of aplastic anemia.[6]

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[5] This discussion assumes, without conceding, that the test method accurately measures very low levels of added chloramphenicol.

[6] Import Alert 68-01 states incorrectly that "[t]his irreversible aplastic anemia does not seem to be related to the frequency or level of exposure to the drug." (See Tab J). Mr. Taylor's letter states that "ORA will respond immediately to findings of [chloramphenicol] at any level consistent with this policy and our public health mission" (Tab D), notwithstanding that the FDA mission is protection from adulteration of food products as defined in statute and not from any and all assumed threats to public health.

We first note that, as stated in Dr. Murphy's declaration, "[t]here is a background rate of cases of aplastic anemia in persons without any known exposure to bone marrow toxins." (Tab I at ¶ 8). This rate must be used to calculate risk related to chloramphenicol. As stated by Dr. Murphy, "[t]he risk of death from the baseline incidence of aplastic anemia is estimated at 1/500,000 population per year. Most of these cases are of unknown etiology." (Tab I at ¶ 8). When a cause can be identified, most cases of aplastic anemia are caused by viruses that are endemic and common throughout the United States. (See Tab I at ¶ 9). Certain chemicals other than chloramphenicol are also known to cause aplastic anemia. (See Tab I at ¶ 10). These causes of aplastic anemia create confusion because a patient may have both a common viral infection, or exposure to another chemical, and also have received chloramphenicol. In this setting, it is common for physicians to ascribe the case to chloramphenicol.

Studies were performed to identify the actual risk from chloramphenicol. As stated by Dr. Murphy:

> The studies that associated the use of chloramphenicol with aplastic anemia were undertaken precisely because there was a perception that patients on therapeutic doses of chloramphenicol developed aplastic anemia more commonly. This perception was tested by comparing the incidence of aplastic anemia on therapeutic doses – a cut-off of 3 grams of exposure was selected – with the general incidence of aplastic anemia. These studies demonstrated that, for chloramphenicol used in doses measured in grams, the incidence of aplastic anemia is about 13 times the background rate. In other words, between one in 20,000 and one in 60,000 people treated with therapeutic (more than one gram) doses of chloramphenicol will develop aplastic anemia.

(Tab I at ¶ 12).

However, subsequent studies have looked at the risk of aplastic anemia from smaller doses of chloramphenicol, such as those delivered by chloramphenicol eyedrops. These studies have led to conflicting opinions. Some experts believe that there is no increased risk of aplastic anemia from chloramphenicol eyedrops but others believe that there may be some risk, although it is substantially lower than the risk from therapeutic doses. (See Tab I at ¶ 16). In any event, the dose of chloramphenicol in a complete treatment course of eyedrops is about 5.25 mg. These data on reduced risk from eyedrop doses demonstrate that there is a dose-relationship to risk of aplastic anemia from chloramphenicol. (See Tab J at ¶ 20; highest estimated risk from eyedrops is 1/150,000 or 1/3 to 1/10 that of therapeutic oral doses). As stated by Dr. Murphy:

> While it is often stated that there is no relation between the dose of chloramphenicol and the development of aplastic anemia, this is not an accurate statement when addressing sub-therapeutic doses of chloramphenicol. Generally, studies have only looked at variations of therapeutic oral and intravenous doses and, then, have had to estimate dose exposure based on limited and often inaccurate information. Since each therapeutic dose is likely in the range of 13-fold increased risk, it would require extremely precise knowledge of actual dose exposure to identify a difference between, say 13-fold increased risk and 14- or 12-fold increased risk. It is not surprising that such data failed to yield a dose-response curve. The fact that chloramphenicol eye drops are either safe or minimally dangerous, however, means that there is in fact a dose-response curve for chloramphenicol and its relationship to aplastic anemia.

(Tab I at ¶ 22).

As further stated by Dr. Murphy, "there is a low dose of chloramphenicol which is safe and it is likely to be close to, at, or just below the dosage available in chloramphenicol eyedrops (5 mg)." (Tab I at ¶ 23).

Blue Star Crab and, as stated in its petition, Miami Crab are completely comfortable with the historic limit of 5 ppb using the ELISA test notwithstanding that any chloramphenicol in crabmeat must derive from natural sources that does not render the crabmeat adulterated under the FDC Act. As noted by Dr. Murphy, that level of chloramphenicol would result in a maximum dose of 1 microgram of chloramphenicol in an all-meat crabcake of 200 grams or about one-half pound. (We note that this is an unusually large crabcake and many crabcakes are only half meat.) (See Tab I at ¶ 26). As stated most succinctly by Dr. Murphy:

> To reach a dose with possibly increased risk (5 mg), an individual would have to consume 5000 such crabcakes. By eating three ½ lb crabcakes per day every day, an individual would reach this threshold of [marginally] increased risk in 1,667 days, or approximately 4.5 years. If the crabcake is only 50% meat, as is usual, it would take 9 years of this restricted diet.

(Tab I at ¶ 27).

This is obviously an unrealistic hypothesis, especially since dropping to one realistic ¼ lb crabcake per day results in safe consumption of a crabcake per day for 54 years. As concluded by Dr. Murphy, "I am not aware of any scientific data, after a thorough search, that suggests that exposure to a dose of less than 1 μg of chloramphenicol represents a risk to human health or is likely to increase the incidence of aplastic anemia." (Tab I at ¶ 30).

In short, FDA's zero tolerance policy, regardless of its lack of foundation in statutory authority, also lacks any foundation in science and medicine. Thus, this policy also is not an appropriate action even if FDA in fact had unlimited discretion to act to protect the public health.

6. There Has Been International Recognition That Testing For Chloramphenicol Residues In Wild-Raised Crabmeat Is Unwarranted

We have attached at Tab K a copy of the European Commission Decision on protective measures with regard to animal products imported from China. This document notes that: "Fishery products obtained by other means than aquaculture are not concerned by risks identified above [chloramphenicol] and should therefore be exempt from monitoring." This decision was taken after due consideration of the facts which, heretofore, FDA has disregarded in its single-minded determination to ignore such issues as the absence of adding chloramphenicol to crabmeat, the presence of low levels of naturally occurring chloramphenicol as found in FDA's own test, and the absence of any known health risk. We cannot understand, in light of this international recognition of the lack of risk related to chloramphenicol in wild raised crab, why the FDA persists in its LCEMS testing program for crabmeat, and, indeed, apparently expends large sums in continuing experimentation on a test method that serves no health or safety purpose and, furthermore, results in detention actions in excess of FDA's legal authority over adulterated food products.

In sum, we are not aware of any evidence establishing – or even suggesting – that there is an established health risk from exposure to naturally occurring chloramphenicol in soil samples or in coastal water run-off from such soil. There is no evidence that a level of exposure of less than 5 ppb in crabmeat represents any health risk.

7. Clarification Of Import Alerts

FDA has heretofore issued two relevant Import Alerts. Import Alert 16-124 indicates that FDA may detain "aquaculture seafood products" due to the "use of unapproved new animal drugs."

This Import Alert is not applicable to crabmeat, which is not an aquaculture seafood product. FDA should clarify that this Import Alert is not applicable to crabmeat. This was the Import Alert cited in the detention of Blue Star Food Products crabmeat.

8. Restraint Of International Trade In Violation Of The General Agreement On Tariffs And Trade

Blue Star Food Products also believes that it is inequitable and may be in violation of treaty obligations for FDA to maintain a testing program for imported crabmeat for the detection of chloramphenicol residues below 5 ppb when there is no health or safety risk associated with such exposure. Any such testing program should be consistent with World Trade Organization (WTO) agreements such as the Agreement on the Application of Sanitary and Phytosanitary Measures and the Agreement on Technical Barriers to Trade, both of which ensure that regulations, standards, testing, and certification procedures do not create an unnecessary burden on trade. While the WTO agreements provide that the protection of "human, animal or plant life or health" is a legitimate objective for a technical regulation such as this, again, FDA has not demonstrated that there is a health or safety risk associated with exposure at the levels for which the agency is testing.

Any requirements for imports that are different or more stringent than those applied to domestically produced products—and are scientifically unjustified—give rise to non-tariff trade barriers. We believe that the agency's maintenance of the testing program, which is applied solely to imported products, creates a stigma associated with imported product that is not valid or scientifically sound. Stated differently, U.S.-origin crabmeat also may contain low levels of chloramphenicol under the test conditions of FDA's program, particularly if the crab were to

originate from or near Caribbean coastal waters where chloramphenicol is known to be present in soil samples from natural bacterial sources. However, this crabmeat is not tested and thus the government has not tainted this product with unscientific allegations of health risk or unsubstantiated accusations of use of unapproved new animal drugs.

9. Conclusion

For the reasons stated, FDA's electrospray liquid chromatography/mass spectroscopy test methodology has not been properly validated. According to FDA's own paper, the test methodology is not sensitive or reliable below 1 ppb and yet test results below that are being used to detain crabmeat products. Further, evaluation of the test method has not included whether the test can distinguish chloramphenicol from known and approved chloride containing substances used as sanitizers. Chloramphenicol is a naturally occurring soil substance, and may be present through no activity of man in coastal waters where wild crabs are harvested. Crabs are not, and cannot be, raised through aquaculture or "farming." Thus, chloramphenicol is not intentionally fed to crabs as a drug and is not added to crabmeat. There is no factual evidence to support a charge of adulteration based on use of an unapproved new animal drug or use of an unapproved food additive. There is no scientific evidence to support the conclusion that very low levels of chloramphenicol (below 5 ppb) present any risk to human health. For these reasons, FDA has no factual or legal basis for taking regulatory action against imported crabmeat with very low levels of chloramphenicol. FDA should provide assurances that the presence of naturally occurring low levels of chloramphenicol in imported crabmeat does not result in the crabmeat being deemed adulterated. Finally, FDA's

application of this testing program to imported and not domestic crabmeat is evidence of a disparate practice not based in health or safety, which amounts to an unlawful restraint of international trade.

C. ENVIRONMENTAL IMPACT

This petition is entitled to a categorical exclusion under 21 C.F.R. § 25.30 and § 25.32.

D. ECONOMIC IMPACT

Information regarding economic impact will be submitted on request.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

Jur T Strobos MD a.e.T

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OFW:cr
Attachments

Tabs Attached to Citizen Petition

A. Liquid Chromatography Electrospray Mass Spectroscopy Methodology experimental data in crabmeat from FDA website
B. Copy of Analyst Worksheet from Miami (11-22-02) Sample No. 202758
C. Documents detailing detention based upon Import Alert and adulteration due to presence of unapproved new animal drug in food
D. Correspondence from John M. Taylor III, Associate Commissioner of Regulatory Affairs, FDA, to Robert Collette, National Fisheries Institute (2-20-03)
E. Declaration of Gerald Meyer, Ph.D.
F. Declaration of John Robbins Keeler, Sr.
G. Original LCEMS Test Method from FDA website (also attached to previous petition).
H. Copy of 21 C.F.R. § 178.1010(b)
I. Declaration of Patrick Murphy, MD, Ph.D.
J. Import Alert 68-01
K. European Commission Decision on Testing of Crabmeat