October 5, 2023

Office of Food Additive Safety, CFSAN
5001 Campus Drive
College Park, Maryland 20740
United States

Re: Supplement to Disclosable Safety Narrative for CCC 000002 - Updated Heavy Metal Specifications

To Whom it May Concern:

On behalf of UPSIDE Foods, Inc. (the "Company"), we write to update the heavy metal specifications set forth in the Company's submission for Cell Culture Consultation (CCC) 000002. Consistent with a discussion the Company had with the Office of Food Additive Safety in April 2023, the Company has lowered the levels of and specifications for heavy metals in the product that is the subject of CCC 000002.

As the Company has implemented stricter raw material controls and generated additional data, we have obtained reproducible results that show that we have routinely achieved lower levels of lead, arsenic, mercury, and cadmium than were measured in the data presented in CCC 000002. These results were achieved without significant production process changes. Below, we provide a summary of these results as well as our updated heavy metal specifications.

Table 1 lists the Company's updated heavy metal specifications, as well as the original heavy metal specifications filed in CCC 000002 and in the Company's September 16, 2022 amendment.

Table 2 summarizes the results for heavy metals analysis for harvested culture poultry meat (CPM) from three nonconsecutive production runs conducted via inductively coupled plasma with mass spectrometry detection (ICP-MS) by a third-party laboratory. These results demonstrate that the level of lead in the product, on average, is 13.3 parts per billion (ppb), which is equivalent to 0.33 µg of lead per day for a 25 g serving of the product. For arsenic, 2 of the 3 lots yielded a non-detect (<10 ppb) result, and 1 of the 3 lots yielded a 10 ppb result. Levels of mercury and cadmium were non-detectable (<10 ppb) in all three lots.

Best regards,

Terry Reyes, PhD
Senior Manager Global Regulatory and Public Policy
UPSIDE Foods

Table 1. Heavy Metal Specifications

	Lead (Pb)	Arsenic (As)	Cadmium (Cd)	Mercury (Hg)
UPSIDE CCC 000002 premarket notice to the FDA (10/1/2021)	<2000 ppb	<1000 ppb	<2000 ppb	<2000 ppb
UPSIDE's amendment to CCC 000002 premarket notice (9/16/2022)	<100 ppb	N/A	N/A	N/A
UPSIDE current commercial release specifications	<100 ppb	<20 ppb	<20 ppb	<10 ppb

Table 2. Heavy Metal Analysis

Representative batch (RB)	Lead (ppb)*	µg of Lead per day, 25 g portion per day	Arsenic (As), ppb*	µg of As per day, 25 g portion per day	Mercury (Hg), ppb*	µg of Hg per day, 25 g portion per day	Cadmium (Cd), ppb*	µg of Cd per day, 25 g portion per day
RB1	20	0.5	<10	<0.25	<10	<0.25	<10	<0.25
RB2	<10	<0.25	<10	<0.25	<10	<0.25	<10	<0.25
RB3	10	0.25	10	0.25	<10	<0.25	<10	<0.25
Average of all lots	**13.3**	**0.33**	**≤10**	**≤0.25**	**<10**	**<0.25**	**<10**	**<0.25**

*For lead, arsenic, mercury, and cadmium values below the detection level (<10 ppb), to calculate the daily exposure and average, it was assumed that the highest detected level is the limit of detection (10 ppb). Heavy metals were analyzed using EPA 6020B.

Ashley E. Nazario-Toole, PhD.
Office of Food Additive Safety, CFSAN
5001 Campus Dr, College Park
MD 20740, United States

Re: Request for Additional Information re: UPSIDE Foods, October 5, 2023, Supplement to CCC 000002

Dear Dr., Nazario-Toole:

This letter responds to the Food and Drug Administration's (FDA) request for additional information regarding UPSIDE Foods' (UPSIDE) October 5, 2023, supplement to Cell Culture Consultation No. CCC 000002. Responses to FDA's substantive information requests are provided below. Questions from FDA are presented below in blue text and corresponding responses from UPSIDE are shown in black.

Substantive Information Requests

Product Characterization

Heavy Metal Specifications

Information Requested

In Table 2 of your October 5, 2023, supplement, you report lead levels for three lots of the harvested cell material with an average lead level of 13.3 µg/kg. **In Table 1 of the supplement, you indicate a specification for lead of <100 µg/kg. Given FDA's interest in lowering exposure to lead in the diet, and the fact that you have reported levels much lower than your proposed specification, we request that you lower your lead specification to at least 50 µg/kg.**

We established the lead specification as <100 µg/kg (or <100 ppb) because this level is consistent with FDA's *Closer to Zero* initiative, while providing appropriate flexibility as we continue to optimize our processes for commercial purposes. We note that this lead specification is consistent with the amendment to CCC 000002 that UPSIDE submitted on September 16, 2022.[1] This specification assures that the level of lead in UPSIDE's cultivated poultry meat (CPM) that is the subject of CCC 000002 is as low as reasonably possible given current production processes and, critically, is below a level that would present safety concerns. Indeed, 0.1 ppm (or 100 ppb) is the recommended maximum level of lead that FDA identified for candy likely to be consumed frequently by small children.[2] In a document supporting this recommended maximum lead level, the agency explained that the potential exposure of small children to lead in candy produced in accordance with the 0.1 ppm guidance level would not constitute a health hazard.[3]

As noted in our October 5, 2023, supplement, UPSIDE has been working to achieve lower levels of lead,

[1] Disclosable Safety Narrative of CCC 000002, at 94 (stating that UPSIDE has reduced the lead specification to ≤ 0.1 ppm (or 100 ppb)).
[2] FDA, Guidance for Industry: Lead in Candy Likely to Be Consumed Frequently by Small Children: Recommended Maximum Level and Enforcement Policy (Nov. 2006).
[3] FDA, Supporting Document for Recommended Maximum Level for Lead in Candy Likely to Be Consumed Frequently by Small Children (Nov. 2006).

arsenic, mercury, and cadmium by implementing stricter raw material controls. For CPM produced using serum-containing growth media, UPSIDE has achieved a decrease in the average level of lead from 16.9 ppb to 13.3 ppb. The average level of lead in CPM produced using serum-free growth media, as reported in Table 5.5-1 of the September 3, 2021, disclosable safety narrative and on page 27 of the March 25, 2022, amendment to the disclosable safety narrative, is 4.76 µg/100g (or 47.6 ppb). To assure adequate flexibility, we believe it is appropriate to retain the lead specification for CPM as <100 ppb. This is a level that UPSIDE can ensure will not be exceeded in CPM, and of particular note, has already been evaluated and accepted by FDA in the context of a food product likely to be consumed frequently by small children.

In addition, as recently as March 2023, FDA evaluated the heavy metal specifications for a cultivated poultry product (CCC 000001) that included a higher specification for lead, "to ensure [the specifications] were as low as reasonably possible and were consistent with food safety," and confirmed that the agency did not have questions regarding the notifier's safety conclusions pertaining to the product.[4] Notably, the lead specification for this product (<0.20 ppm or <200 ppb) is twenty-fold higher than the lead levels demonstrated by batch analyses reported in CCC 000001 (<0.01 ppm or <10 ppb) and twice as high as UPSIDE's lead specification for CPM.[5]

For these reasons, we continue to believe that a lead specification of <100 ppb for UPSIDE's CPM does not present safety concerns and is appropriate in light of the average levels in CPM.

Information Requested

In Table 5.5-1 of the September 3, 2021, disclosable safety narrative, and on page 27 of the March 25, 2022, amendment to the disclosable safety narrative of CCC 000002 you provided data for cultured chicken cells produced from both serum-containing and serum-free processes. **Please indicate if the data provided on heavy metal levels in the October 5, 2023, supplement are for serum-free or serum containing cultured chicken cells. If you are producing both serum-free and serum-containing cultured chicken cells, we would want to receive updated analytical results from the analysis of toxic heavy metals and heavy metal specifications for the harvested cell material from both processes. If you are only producing the serum-free cultured chicken cells, please provide written confirmation that your intent is to abandon the serum-containing cultured chicken cell process, and that we should no longer consider it part of the consultation.**

The data provided on heavy metal levels in the Oct. 5, 2023, supplement are for CPM produced using serum-containing growth media. To date, our commercialized product has been CPM produced using serum-containing growth media. When we make CPM using serum-free growth media for commercialization, we will provide data confirming that those products meet the updated specifications.

Information Requested

Please provide the **certificates of analysis (COA)** for the heavy metal testing provided in Table 2 of the October 5, 2023, supplement.

Please see the attached COAs.

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[4] FDA's Scientific Memorandum for CCC 000001 (Mar. 17, 2023), at 11 and 13.

[5] Disclosable Safety Narrative of CCC 000001, at 73 (Table 45) and 85 (Table 56).

Ashley E. Nazario-Toole, PhD.
Office of Food Additive Safety, CFSAN
5001 Campus Dr, College Park
MD 20740, United States

Re: Request for Clarification – UPSIDE Foods, 10/5/2023 Supplement to CCC 000002

Dear Dr. Nazario-Toole,

This letter responds to the Food and Drug Administration's (FDA) request for clarification regarding UPSIDE Foods' (UPSIDE) December 1, 2023 amendment to the October 5, 2023 supplement to Cell Culture Consultation No. CCC 000002. Our response to FDA's request is provided below. FDA's request is presented below in italicized blue text and UPSIDE's response is provided in non-italicized black text.

FDA's Request for Clarification

In your December 1, 2023, amendment, you state, "For CPM produced using serum-containing growth media, UPSIDE has achieved a decrease in the average level of lead from 16.9 ppb to 13.3 ppb. The average level of lead in CPM produced using serum-free growth media, as reported in Table 5.5-1 of the September 3, 2021, disclosable safety narrative and on page 27 of the March 25, 2022, amendment to the disclosable safety narrative, is 4.76 µg/100g (or 47.6 ppb). To assure adequate flexibility, we believe it is appropriate to retain the lead specification for CPM as <100 ppb." We note that you report the average level of lead in the harvested cell material produced using serum-containing growth media as 13.3 ppb, while your proposed specification for lead in the harvested cell material produced using serum-containing growth media is <100 ppb. Given FDA's interest in lowering exposure to lead in the diet, the lower lead levels in harvested cell material produced using serum-containing versus serum-free media, and the fact that you have reported levels much lower than your proposed specification for harvested cell material produced using serum-containing media, we request that you lower your lead specification for the harvested cell material produced using serum-containing growth media to at least <50 µg/kg.

UPSIDE's Response

We established our lead specification of <100 ppb (or <100 µg/kg) for the harvested cell material produced using serum-containing growth media to allow for appropriate flexibility as we continue to optimize our processes and to account for potential process variability as we scale our commercial processes. While the average lead content reported in the October 5, 2023 supplement was <13.3 ppb, lowering the lead specification to <50 ppb (or <50 µg/kg) would not provide adequate flexibility to account for inherent variability in the process, particularly as UPSIDE transitions to a larger-scale production process.

UPSIDE has compiled data on lead levels from all of our commercial production runs to date, which utilized our small-scale production process. Please see **Appendix 1** for a summary of the data.

For each production run (PR) of CPM produced using serum-containing growth media, we measured the lead levels in: (1) the work in progress (WIP) material, which is the harvested cell material; and (2) the finished product. For production runs where the lead levels were higher than the <13.3 ppb average calculated from three representative production runs, the levels were significantly below a level that would present safety concerns. Overall, the data from our commercial production runs show that UPSIDE has been able to routinely achieve lead levels at the lower range.

We note, however, that these data and the <13.3 ppb average are based solely upon our small-scale production process. Therefore, the data might not fully reflect a large-scale production process and the flexibility that UPSIDE will need to account for potential process variability as we move towards large-scale production.

Based upon the data available to us at this time and consideration of lead levels that are consistent with food safety, we believe it would be appropriate to build in a little more flexibility in the lead specification, especially as UPSIDE optimizes its process for large-scale production. To support FDA's *Closer to Zero* initiative while ensuring that we have adequate flexibility to accommodate a reasonable amount of process variability that does not affect food safety, we propose lowering the lead specification from <100 ppb to <75 ppb. In addition, to better reflect the CPM production process, we believe it would be more appropriate for the <75 ppb lead specification to apply to the finished product rather than the WIP material. The finished product is the product that will be introduced into commerce, whereas the WIP material is the unformulated biomass at the point of harvest. Unlike the finished product, the WIP material has not been formulated and therefore would not contain ingredients added to the biomass at the last steps in the production process.

Hice, Stephanie

From: Terry Reyes <treyes@upsidefoods.com>
Sent: Tuesday, June 25, 2024 2:07 PM
To: Animal Cell Culture Foods
Cc: Sean Edgett; Kulkarni, Deepti; Hice, Stephanie
Subject: [EXTERNAL] Re: Request for Clarification – UPSIDE Foods, 10/5/2023 Supplement to CCC 000002

Dear Dr. Nazario-Toole,

On behalf of UPSIDE Foods (UPSIDE), please find our response below to FDA's request for clarification regarding information in the April 11, 2024, amendment to the October 5, 2023, supplement to CCC 000002. Please let us know if you have additional questions.

Best regards,

Terry Reyes

FDA Request for Clarification 06-13-2024

1.
2.
3. **Has the analytical data for toxic**
4. **heavy metal analyses UPSIDE Foods (UPSIDE) provided up to the April 11, 2024, amendment to the supplement to CCC 000002 (including in the October 5, 2023, supplement to CCC 000002 and in the October 1, 2021, dossier), been based on the "work-in-progress" (WIP;**
5. **i.e., the harvested cell material) or the final food product?**
6.

All analytical data for toxic heavy metal analysis provided up to and since the April 11, 2024, amendment to the supplement to CCC 000002 (including in the October 5, 2023, supplement to CCC 000002 and in the October 1, 2021, dossier) are based on "Work In Progress" ("WIP") material, *i.e.* the harvested cell material.

In the April 11, 2024, amendment, UPSIDE states, "Unlike the finished product, the WIP material has not been formulated and therefore would not contain ingredients added to the biomass at the last steps in the production process." What are the "… ingredients added to the biomass at the last steps in the production process" that appear to increase the lead levels? At what point in the production process are these substances added (e.g., added to the bioreactor, added after removal from the bioreactor)?

We would like to clarify that our conclusion that it would be appropriate for the lead specification to apply to the finished product, rather than the WIP, is **NOT** based on the possibility that ingredients added to the biomass in the last steps of the production process could increase lead levels. In fact, we can confirm that none of the ingredients added to the biomass during the last steps of the production process contains lead, and we have obtained COAs from our suppliers confirming this.

Rather, our determination is based on the fact that the formulated finished product is the product that will be introduced into commerce, and is therefore most reflective of the actual product consumers will consume. Thus, from a public health standpoint, we believe it is more appropriate to establish a lead specification for the finished product, not the WIP. As noted in response to FDA's third question below, however, and given FDA's continued position on this issue, we plan to continue conducting heavy metal testing on the WIP product at this time.

In the April 11, 2024, amendment, UPSIDE states, "To support FDA's Closer to Zero initiative while ensuring that we have adequate flexibility to accommodate a reasonable amount of process variability that does not affect food safety, we propose lowering the lead specification from <100 ppb to <75 ppb." For the administrative record, please clarify whether this is for both the serum-containing and serum-free formulations, or only for the serum-containing formulation. Further, UPSIDE states, "In addition, to better reflect the CPM production process, we believe it would be more appropriate for the <75 ppb lead specification to apply to the finished product rather than the WIP material." As FDA's premarket consultation ends at harvest, we consider specifications for the harvested cell material (i.e., the "WIP material"). As such, within the context of FDA's premarket consultation, the provided specifications should be for the harvested cell material and not the final food product.

At this time, we are proposing to establish a <75 ppb lead specification for the serum-containing formulation only since, to date, we have only produced commercial product using the serum-containing formulation. As previously noted, we will notify FDA when we begin producing commercialized product using the serum-free formulation and, at that time, we will provide data confirming that those products meet the applicable specifications.

As noted in our response to FDA's second question, we continue to believe that it would be appropriate for the lead specification to apply to finished product, rather than WIP product, since finished product is most reflective of the actual product consumers will consume. That said, given FDA's continued position on this issue, we plan to continue conducting heavy metal testing on the WIP product at this time.

On Thu, Jun 13, 2024 at 1:09 PM Terry Reyes <treyes@upsidefoods.com> wrote:

Hello Dr. Nazario-Toole,

We confirm receipt of your email. We will provide a response soon.

Best regards,

Terry Reyes

On Thu, Jun 13, 2024 at 1:03 PM Animal Cell Culture Foods <AnimalCellCultureFoods@fda.hhs.gov> wrote:

Good afternoon, Dr. Reyes –

Below, please find a request for clarification regarding information in the April 11, 2024, amendment to the October 5, 2023, supplement to CCC 000002. Your response will be appended to the CCC 000002 disclosable safety narrative as an amendment and will subsequently be treated as part of the disclosable safety narrative in the administrative record for CCC 000002 unless we specifically note otherwise. We expect to proactively disclose the October 5, 2023, supplement to CCC 000002, the December 1, 2023, and April 11, 2024, amendments, and your response to this request for clarification upon completion of this supplement.

Request for Clarification

1. Has the analytical data for toxic heavy metal analyses UPSIDE Foods (UPSIDE) provided up to the April 11, 2024, amendment to the supplement to CCC 000002 (including in the October 5, 2023, supplement to CCC 000002 and in the October 1, 2021, dossier), been based on the "work-in-progress" (WIP; i.e., the harvested cell material) or the final food product?
2. In the April 11, 2024, amendment, UPSIDE states, "Unlike the finished product, the WIP material has not been formulated and therefore would not contain ingredients added to the biomass at the last steps in the production process." What are the "… ingredients added to the biomass at the last steps in the production process" that appear to increase the lead levels? At what point in the production process are these substances added (e.g., added to the bioreactor, added after removal from the bioreactor)?
3. In the April 11, 2024, amendment, UPSIDE states, "To support FDA's Closer to Zero initiative while ensuring that we have adequate flexibility to accommodate a reasonable amount of process variability that does not affect food safety, we propose lowering the lead specification from <100 ppb to <75 ppb." For the administrative record, please clarify whether this is for both the serum-containing and serum-free formulations, or only for the serum-containing formulation. Further, UPSIDE states, "In addition, to better reflect the CPM production process, we believe it would be more appropriate for the <75 ppb lead specification to apply to the finished product rather than the WIP material." As FDA's premarket consultation ends at harvest, we consider specifications for the harvested cell material (i.e., the "WIP material"). As such, within the context of FDA's premarket consultation, the provided specifications should be for the harvested cell material and not the final food product.

We are happy to discuss this request should you have questions about how to convey substantive safety information without disclosing other details that may contain confidential commercial information or trade secrets, or if you believe that we are directly requesting you to disclose such information.

Sincerely,

Ashley

Ashley E. Nazario-Toole, Ph.D.

Biologist

Office of Food Additive Safety

Center for Food Safety and Applied Nutrition

U.S. Food and Drug Administration

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U.S. FOOD & DRUG ADMINISTRATION

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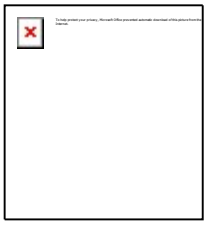

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Winner Best and Brightest Companies to Work For 2019 - 2022

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Winner Best and Brightest Companies to Work For 2019 - 2022

Jessica Mills, PhD.
Office of Food Additive Safety, CFSAN
5001 Campus Dr, College Park
MD 20740, United States

Re: Request for Clarification – UPSIDE Foods, 10/5/2023 Supplement to CCC 000002

Dear Dr. Mills,

This letter responds to the Food and Drug Administration's (FDA) request for clarification regarding UPSIDE Foods' (UPSIDE) October 5, 2023 supplement to Cell Culture Consultation No. CCC 000002. Response to Q1 from FDA's request is provided below. Question 1 from FDA is presented below in black text and corresponding responses from UPSIDE are shown in blue.

1. In the April 11, 2024, amendment, UPSIDE states, "Unlike the finished product, the WIP material has not been formulated and therefore would not contain ingredients added to the biomass at the last steps in the production process." While the post-ingredients added to the harvested cell material fall outside the scope of FDA's human foods made with cultured animal cells premarket consultation program, please note any substance that is added to conventional food must be one of the following before it can be lawfully used in products marketed in the U.S.:

    A. An approved food additive;
    B. An approved color additive;
    C. GRAS as determined by qualified experts for the intended conditions of use;
    D. Prior sanctioned for that use by FDA or the U.S. Department of Agriculture (USDA)
    E. Fall into another category exempt under Section 201(s) if the FD&C Act.

    If you have questions about the regulatory status of any post-harvest ingredient added to the harvested cell material, please consult with our Division of Food Ingredients (DFI) by submitting a request to premarkt@fda.hhs.gov.

    All substances added to formulated products during manufacturing under USDA inspection (*i.e.*, post-harvest) are safe and suitable for their intended use in compliance with all applicable USDA FSIS requirements.