From: Tao, Xin
To: Morissette, Rachel
Cc: Steinborn, Steven B.; Harry, Molly; Hall, Karen
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900
Date: Friday, May 1, 2020 5:42:04 PM
Attachments: image001.png
Response to U.S. Food and Drug Administration (FDA)'s Question on Intended Use for GRAS Notices 898, 899, and 900.pdf

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Dear Rachel,

Attached, please find our response to the over-arching question regarding the subpopulation. It supplements the telephone conference we had with the agency on April 24, 2020, and provides a more detailed written narrative of the sub-population that we hope is helpful for the agency's on-going review of GRAS Notices 898, 899, and 900.

If you have any other questions, please do not hesitate to contact us.

Best regards,
Steve and Xin

Xin Tao
Senior Associate

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Friday, April 24, 2020 2:20 PM
To: Tao, Xin
Cc: Steinborn, Steven B.; Harry, Molly; Hall, Karen
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Xin and Steven,

Thank you again for meeting with us today. We all felt it was a very productive discussion. As mentioned, we'll be expecting to see your response to our over-arching question first regarding the subpopulations for GRN 898-900. If you can have that response to us as soon as possible (within 10 business days), we will be able to continue our reviews and will be generating an additional set of questions for each notice. You can expect to receive copies of those questions from Molly, Karen, and myself as the project managers of the three notices. In the meantime, please let us know if you have any further questions.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Friday, April 24, 2020 11:49 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel – Here is an updated version with one typo fixed on Slide #8. Sorry about that.

Regards,
Xin

From: Tao, Xin
Sent: Friday, April 24, 2020 11:46 AM
To: 'Morissette, Rachel'
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

That would be great if you can lead the meeting and advance the slides Rachel. Sorry for the delay on our end, and yes, our plan is to go through them very quickly with the agency on the call and please note we plan to stop at Slide #8 for the quick presentation. The remaining slides are backup slides just in case we need to reference them during the discussion with the agency.

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Friday, April 24, 2020 11:41 AM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Thank you. We will not have a chance to fully review these in time for the meeting, but I sent them

to the review team to take a look in case they are able to review them. I can share my screen when the time comes and advance the slides for you. I will give some introductory remarks and then ask you to briefly go through the slides. We want to spend as much time as possible on the discussion.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Friday, April 24, 2020 11:25 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900
Importance: High

Dear Rachel,

Attached, please find our short presentation (10-15 mins) to provide clarification on the infant subpopulation. Please note we also have one more attended and the following is the final list for your easy reference:

- Miguel Del Toro, Danone North America/Nutricia North America
- Madeline Jurch, Danone North America/Nutricia North America
- Caitlin Krekel, Danone North America/Nutricia North America
- Nga Tran, Exponent
- Mary Murphy, Exponent
- Steve Steinborn, Hogan Lovells
- Xin Tao, Hogan Lovells

We look forward to our call.

Best regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Tuesday, April 21, 2020 9:39 AM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Xin,

The following staff were invited to the meeting, though not all have accepted it yet. I won't know for sure until the meeting starts who will be able to join us, but this gives you an idea.

- Rachel Morissette, Ph.D. – Regulatory Review Scientist (RRS), Office of Food Additive Safety (OFAS)/Division of Food Ingredients (DFI)
- Molly Harry, M.S. – RRS, OFAS/DFI
- Karen Hall, M.S. – RRS, OFAS/DFI
- Sue Anne Assimon, Ph.D. – Toxicologist, OFAS/DFI
- Kotaro Kaneko, Ph.D. – Toxicologist, OFAS/DFI
- Danica DeGroot, Ph.D. – Toxicologist, OFAS/DFI
- Alison Edwards, Ph.D. – Chemist, OFAS/DFI
- Jeremy Mihalov, M.S. – Chemist, OFAS/DFI
- Perry Wang, Ph.D. – Chemist, OFAS/DFI
- Shayla West-Barnette, Ph.D. – Regulatory Review Team Lead, OFAS/DFI
- Negash Belay, Ph.D. – Regulatory Review Team Lead, OFAS/DFI
- Supratim Choudhuri, Ph.D. – Toxicology Team Lead, OFAS/DFI
- Janet Zang, Ph.D. – Toxicology Team Lead, OFAS/DFI
- Jannavi Srinivasan, Ph.D. – Chemistry Team Lead, OFAS/DFI
- Diana Doell, Ph.D. – Chemistry Team Lead, OFAS/DFI
- Megan Kulas – Consumer Safety Officer, Office of Nutrition and Food Labeling (ONFL)/Infant Formula and Medical Foods Staff (IFMFS)
- Carrie Assar, Pharm. D. – Team Lead, ONFL/IFMFS
- Andrea Lotze, M.D. – Medical Director, ONFL/IFMFS

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 6:29 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

As promised, following is the list of attendees and their afflation from our end for the Friday meeting:

- Miguel Del Toro, Danone North America/Nutricia North America
- Madeline Jurch, Danone North America/Nutricia North America
- Nga Tran, Exponent
- Mary Murphy, Exponent
- Steve Steinborn, Hogan Lovells
- Xin Tao, Hogan Lovells

If possible, could you please provide a list of FDA attendees so we can be better prepared?

Best regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 12:19 PM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Sure, that would be fine.

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 12:11 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Rachel,

We received your invitation, and yes, we will provide a list of attendees and affiliations shortly.

Quick question: can we present a couple of slides to guide the subpopulation discussion during the call using WebEx? We can send them to you before the call as well.

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 11:58 AM
To: Tao, Xin; Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Please let me know if you didn't receive the WebEx info. Also, please send me a list of attendees and affiliations the day before the meeting.

Thanks,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 11:45 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Great, thanks!

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 11:43 AM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Hi Xin,

It looks like that slot is still available. I'll send you a meeting invite with call-in info shortly.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 10:56 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

Thank you, and I will call you at 11:30 am.

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 10:49 AM
To: Tao, Xin
Cc: Steinborn, Steven B.

Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Xin,

Yes, I'm available from 11:15 am-3 pm today. My desk number is 240-402-1212.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 10:14 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

May I give you a quick call today at your convenience to discuss the meeting?

Regards,
Xin

Xin Tao
Senior Associate

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

From: Tao, Xin
Sent: Monday, April 20, 2020 8:44 AM
To: 'Morissette, Rachel'
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

Thank you for the reminder. Sorry for the delay as we are trying to make sure we have the right people to attend the requested meeting and have been coordinating on our end. I will get back to you today.

Best regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 8:35 AM
To: Tao, Xin; Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Steve and Xin,

I have not received a list of meeting dates that would work for you as of yet; therefore, I cannot guarantee that the options I listed below are still available. Due to the 180-clock for a GRAS notice review, we are requesting to have this meeting as soon as possible to ensure we can meet that deadline and move forward with our review of these three notices. Please let me know by COB today, if at all possible. You might also suggest some dates and times next week that could work in the event that the options I presented last week are no longer available.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Morissette, Rachel
Sent: Wednesday, April 15, 2020 11:16 AM

To: Tao, Xin <xin.tao@hoganlovells.com>; Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Thank you. The more options you can provide, the easier it will be to accommodate.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Wednesday, April 15, 2020 10:54 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>; Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

Here is to acknowledge the receipt of your email. I will coordinate on our end and get back to you with our preferred date. Thank you!

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Wednesday, April 15, 2020 9:47 AM
To: Steinborn, Steven B.; Tao, Xin
Subject: request for teleconference to discuss GRNs 898, 899, and 900

Dear Steve and Xin,

We have reviewed your GRAS notices GRNs 000898, 000899, and 000900 for the intended use of dried milk fat, citric acid esters of mono- and diglycerides, and corn oil, respectively, in exempt infant

formulas for “term infants requiring a calorically dense formula and/or fluid restriction.” We request a teleconference with you to discuss all three notices. To provide some context, the over-arching question we have is to clarify the sub-population of term infants that may consume calorically dense or fluid restrictive infant formula. The rest of the discussion hinges on the answer to this question, as we have other issues that depend on clarifying the intended use and infant population. Please let me know if you are available for a teleconference during any of the following 1.5 hour slots. Since this teleconference involves three different notices and three different review teams, I’ve been asked to take the lead in coordinating this meeting as our office’s infant formula liaison to the Infant Formula and Medical Foods Staff in the Office of Nutrition and Food Labeling, who will also be attending the meeting. This is the group that administers the 412 Infant Formula submission process.

Monday April 20th 2-3:30 pm

Wednesday April 22nd 12-1:30 pm

Thursday April 23rd 9-10:30 am

Thursday April 23rd 9:30-11 am

Friday April 24th 9-12 pm

Friday April 24th 1-4 pm

If these dates don’t work, I can look into the following week, as well. Please note that schedules fill up very quickly for us, so please let me know as soon as possible your availability so we can secure a time.

Thank you for your attention to this matter.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

About Hogan Lovells
Hogan Lovells is an international legal practice that includes Hogan Lovells US LLP and Hogan Lovells International LLP. For more information, see www.hoganlovells.com.

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

May 1st, 2020

By Electronic Mail

Rachel Morissette, Ph.D.
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

Re: Response to U.S. Food and Drug Administration (FDA)'s Question on Intended Use for GRAS Notices 898, 899, and 900

Dear Dr. Morissette:

In this letter we are responding to the agency's question on the intended use for GRAS Notices 898, 899, and 900 which we submitted for anhydrous milk fat (AMF), citric acid esters of mono- and diglycerides (CITREM), and corn oil's use in exempt infant formulas for "term infants requiring a calorically dense formula and/or fluid restriction." In particular, the agency would like us to *clarify the sub-population of term infants that may consume calorically dense or fluid restrictive infant formula*. This letter supplements the telephone conference we had with the agency on April 24, 2020, and provides a more detailed written narrative of the sub-population that we hope is helpful for the agency's on-going review of GRAS Notices 898, 899, and 900.

Before we address the agency's particular question regarding the sub-population, we first provide a quick overview for the exempt infant formula to which the three ingredients AMF, CITREM, and corn oil will be added. The infant formula is a nutritionally complete and nutrient dense formula intended for use among full-term infants from birth and up to 18 months of age (or 9 kg) with increased energy requirements and/or fluid restrictions. The infant formula will be used under medical supervision as a ready-to-feed formulation. CITREM serves as an emulsifier in the formulation, whereas AMF and corn oil are sources of fat that serve as an energy source.

Regarding the particular question from the agency, the sub-populations of infants consuming the formula include the full term infants who are appropriate for oral or enteral feeding, with increased energy and nutrient requirements, fluid restrictions and/or limited ability to take oral feeds. As discussed in the GRAS notices, the nutrient dense formula is a high-energy formulation intended for use in term infants with a functional or partially functional gastrointestinal tract in the absence of comorbidities affecting metabolism. Full term infants with these special nutritional needs include infants with:

- Congenital heart disease (CHD)
- Chronic lung disease
- Respiratory syncytial virus (RSV)

- Neurological syndrome or neuro-disabilities
- Non-organic cause of growth failure

Among the above medical conditions, we note that certain infants with CHD or chronic lung disease may need to limit their fluid intake to avoid stress to their organs. While we recognize the standards of care for the above medical conditions may differ, all of these are conditions that do not signify altered gastrointestinal function or nutrient metabolism. As such, term infants consuming the calorically dense formula with the three ingredients – AMF, CITREM, and corn oil added would reasonably digest and metabolize them, as do other term infants consuming similarly structured components in human breast milk or standard infant formula.

The sub-population also includes full term infants with cystic fibrosis (CF). While unlike other conditions listed above, CF is a chronic condition with known involvement of the gastrointestinal tract, human milk or standard infant formula is recommended for this infant population under the current standards of care, with pancreatic enzyme supplementation (if indicated). This product would be used under medical supervision.

It is important to note that the formula may not be appropriate for all full term infants requiring a calorically dense formula and/or fluid restriction. Specifically, it is not recommended for conditions including:

- Malabsorption due to causes other than cystic fibrosis,
- Conditions that impact gastrointestinal function or metabolism,
- Significant cow milk protein allergy.

In all, the sub-population of term infants requiring a calorically dense formula and/or fluid restriction that may consume formula containing AMF (GRAS Notice 898), CITREM (GRAS Notice 899), and corn oil (GRAS Notice 900) are term infants with a functional or partially functional gastrointestinal tract in the absence of comorbidities affecting metabolism and would be expected to handle these three ingredients as would other term infants. The intake of the infant formula will also be under medical supervision.

* * *

If you have any other questions, please do not hesitate to contact us.

Sincerely,

Steve B. Steinborn
steven.steinborn@hoganlovells.com
+1 202-637-5969

Xin Tao
Xin.tao@hoganlovells.com
+1 202-637-6986

Cc:

Molly A. Harry
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Molly.Harry@fda.hhs.gov

Karen M. Hall
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Karen.Hall@fda.hhs.gov

From:	Tao, Xin
To:	Harry, Molly
Cc:	Steinborn, Steven B.
Subject:	RE: GRN 000898 Anhydrous Milk Fat - Additional Questions to the Notifier
Date:	Monday, June 15, 2020 6:48:28 PM
Attachments:	image001.png Response to FDA"s Additional Questions on GRN 898.pdf Attachment B (GRN 898).pdf Attachment C (GRN 898).pdf Attachment D (GRN 898).pdf Attachment A (GRN 898).pdf

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Dear Ms. Harry,

Hope you keep doing well. Attached, please find our response to the agency's additional questions for GRN 000898. Please note that our attachments contain confidential commercial and trade secret information that is protected from public disclosure under the Federal Food, Drug, and Cosmetic Act, the Freedom of Information Act, FDA's implementing regulations, and the Trade Secrets Act. In accordance with FDA's implementing regulations, if a request for disclosure is received, we would like to ask that we be notified and provided an opportunity to address why the information or materials should not be released.

We would like to thank you again for the flexibility on the timeline. We trust our response addresses all the questions raised by the agency. If any additional questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

Best regards,
Steve and Xin

Xin Tao
Senior Associate

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

From: Harry, Molly [mailto:Molly.Harry@fda.hhs.gov]
Sent: Wednesday, May 13, 2020 5:48 PM
To: Steinborn, Steven B.
Cc: Tao, Xin
Subject: RE: GRN 000898 Anhydrous Milk Fat - Additional Questions to the Notifier

Dear Mr. Steinborn,

Our review of Hogan Lovells' GRAS notice (GRN 000898) for the intended use of anhydrous milk fat is ongoing and members of the review team have identified additional questions and areas of the information provided in the notice and in the amendment provided on May 1, 2020, that the team would like you to respond to or clarify (see attached). Please provide your response to these questions within ten business days. If you think you will not be able to complete the response within this time frame, please contact us to discuss.

Please feel free to contact me if you have any questions.

Sincerely,

Molly A. Harry
Regulatory Review Scientist

Office of Food Additive Safety, Division of Food Ingredients
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Molly.Harry@fda.hhs.gov

Tel: 240-402-1075

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

Via Electronic Mail

June 15, 2020

Molly A. Harry
Regulatory Review Scientist
Office of Food Additive Safety, Division of Food Ingredients
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Molly.Harry@fda.hhs.gov

Re: Response to FDA's Questions for GRN 000898

Dear Ms. Harry,

We hereby submit our responses to FDA's questions for GRAS Notice 000898 (GRN 898), which covers the intended use of anhydrous milk fat (AMF) as a source of fat in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction.

For your ease of reference, we first copied FDA's questions below, followed by each of our response:

Question #1 (Chemistry):

- ***FDA Question #1****: We note that the terms "calorically-dense" or "energy dense formulas" are not defined in the notice or in FDA's regulations.*
    - *For the purpose of the notice, please clarify if these terms refer to infant formulas with 24 kcal per oz (81 kcal/100 mL) and above or if they are specifically 100 kcal/100mL.*
    - *Please clarify the range of energy densities for infant formulas that meet your definition of calorically-dense infant formulas.*

Response to Question 1: We hereby clarify that for purposes of GRAS Notice 898 (GRN 898), the term "calorically-dense or energy dense formulas" refers specifically to formulas that provide 100 kcal/100mL. In other words, calorically-dense or energy dense formulas that target energy densities other than 100 kcal/100mL are not subject to this notification.

Question #2 (Chemistry):

- ***FDA Question #2****: In the dietary exposure estimate, you note that fat is typically 50% of energy in infant formula and that 7% of the total fat in the calorically-dense infant formula would be anhydrous milk fat (AMF). However, this assumption is based on common levels of fat in non-exempt term infant formulas.*

    - *Please provide the maximum level of fat used in energy-dense exempt infant formulas described in the intended use.*

    - *Please include a narrative on the safe use of this ingredient if the maximum level is expected to contribute >50% of total energy, as is the case for current exempt infant formulas on the market*

Response to Question 2: The maximum level of fat used in energy-dense exempt infant formula will be 50%; the typical range of fat used is 48-50% of the formula. We recognize for current exempt infant formulas on the market, the maximum level of fat can be higher than 50%. However, we hereby clarify the intended use of AMF under this GRAS notice will only be used in energy-dense exempt infant formula with maximum level of fat at 50% of total energy.

- ***FDA Question #2 (continued)****:*

    - *It is not clear what the basis is for limiting AMF to 7% of the fat blend. Please describe the basis for this limitation and include any technological or nutritional limitations in the narrative.*

Response to Question 2 (continued): AMF is limited to 7% of the fat blend to achieve the targeted total fatty acid profile for the targeted infant population described in the intended use. As described in Table 1 of the GRN 898, AMF is a rich source of saturated fatty acids, and in particular palmitic acid (C16:0) and oleic acid (C18:0) which are a substantial components of human milk. Palm oil has been commonly used as a source of palmitic acid in infant formula though there are concerns regarding potential reduction of calcium absorption from palm oil-derived palmitic acid. 1/ Coconut oil is also used as a source of palmitic acid in infant formula but it provides relatively high concentrations of lauric acid and myristic acid. AMF therefore provides an alternative to palm oil and use of higher levels of coconut oil. The 7% rate of inclusion enables an optimal total fatty acid profile for the target infant population within the fat blend of the calorically-dense infant formula. We are not aware of technological limitations to use of AMF in infant formula. No single fat source mimics the fatty acid profile of human milk, therefore a blend of multiple fat sources is required to achieve the desired profile. We are not aware of nutritional limitations for use of AMF as a component of the fat blend to achieve a fatty acid profile in infant formula comparable to that of human milk.

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1 Koo WW, Hockman EM, Dow M. Palm olein in the fat blend of infant formulas: effect on the intestinal absorption of calcium and fat, and bone mineralization. J Am Coll Nutr. 2006 Apr;25(2):117-22. doi: 10.1080/07315724.2006.10719521.

- ***FDA Question #2 (continued)****:*
    - *Please clarify how you determined a maximum concentration of 7.0% AMF by weight in the fat blend.*

Response to Question 2 (continued): We assumed that fat accounts for 50% of total energy, fat provides 9 kcal/gram, and AMF accounts for 7% of fat in the fat blend by weight. The calculation is as follows:

$$\frac{100\ mL}{100\ kcal}\ X\ \frac{50\ kcal\ from\ fat}{100\ mL}\ X\ \frac{1\ g}{9\ kcal\ fat}\ X\ \frac{7\ g\ AMF}{100\ g\ fat} = \frac{0.39\ g\ AMF}{100\ mL}$$

Question #3 (Chemistry):

- ***FDA Question #3****: Please clarify if the intended use includes both milk-based and soy-based infant formulas. Also, clarify the intended source of the protein base (e.g., milk, soy, whey) of the infant formula that AMF would be added to.*

Response to Question 3: We hereby clarify that the intended use only includes milk-based formulas. The milk-based source is made up of whey and casein.

Question #4 (Chemistry):

- ***FDA Question #4****: In the notice, you provided specifications for AMF in Table 2, analytical results for five non-consecutive batches in Table 3, and the certificate of analyses (COAs) in Appendix C. However, the parameters in Tables 2 and 3 and in the COAs are inconsistent for the microbiological analyses. In Tables 2 and 3, specifications are listed for "Anaerobic plate count 30°C" and "Anaerobic plate count 55°C", whereas results in the COAs are listed for "Total plate count (30°C)" and "Total plate count (55°C)".*
    - *Please clarify the intended specification (i.e., anaerobic plate count or total plate count) because the intended application of the two methods is quite different.*
    - *Confirm that the results of five non-consecutive lots have been provided for the appropriate specification.*

Response to Question 4: We apologize for the discrepancy. The method listed in Table 2 and 3 analyzes total viable plate count. The specifications in Table 2 and 3 should be corrected to "total plate count" in lieu of "Anaerobic plate count". The COAs are correct and the method of analysis uses total plate count. We can confirm that the results of five non-consecutive lots have been provided for the appropriate specification.

Question #5 (Chemistry):

- ***FDA Question #5****: The COAs (Appendix C) indicate a specification for Salmonella of "absent in 250 grams," while the specifications provided in Table 2, Table 3, and the analytical report from Eurofins (Appendix A) indicate a specification of "absent in 25 grams."*
    - *Please clarify the intended specification for Salmonella.*
    - *Provide the appropriate analysis of five consecutive lots demonstrating conformance with the specification*

Response to Question 5: We apologize for the discrepancy between the specifications and the analytical report. The intended specification for *Salmonella* should be "absent in 250 grams" as reported in the COAs (Appendix C). Table 2 and Table 3 should be corrected to use "absent in 250 grams" instead of "absent in 25 grams" as intended specification for *Salmonella*. The results from five non-consecutive batches can be found in the COAs (Appendix C) and they demonstrate compliance with the intended specification.

Question #6 (Chemistry):

- ***FDA Question #6****: The specifications in Table 2 and the analytical report from Eurofins (Appendix A) list the Enterobacteriaceae method as DIN ISO 21528-1, while the COAs in Appendix C list ISO 21528-2 as the method. Please clarify this discrepancy.*

Response to Question 6: We apologize for the discrepancy. ISO 21528-1 specifies a method, with enrichment, for the detection of *Enterobacteriaceae*, whereas ISO 21528-2 specifies a method for the enumeration of *Enterobacteriaceae*. For our purpose, the appropriate method is ISO 21528-1 and the method of analysis used by the lab in Appendix C is actually ISO 21528-1, not ISO 21528-2 which was erroneously listed.

Question #7 (Chemistry):

- ***FDA Question #7:*** *Please provide the complete citations for the analytical methods and indicate that all analytical methods are validated for their specific purpose.*

Response to Question 7: Please find the complete citations for the current analytical methods in the last column of the updated Table 2 of GRN 898 below. Other than the methods for fat and moisture levels (which we respectfully submit no validation is needed), we also hereby confirm all the other listed analytical methods are validated for the specific purpose.

Parameter	Unit	Limit	Test Method (with complete citations)
Physico-Chemical Parameters			
Fat	% (as solids)	Min 99.8	Calculate by difference
Moisture	%	Max 0.1	Karl Fischer-STD 023-2002 ISO (Karl Fischer titration method via testing lab Mettler Toledo, additional details available at: https://www.mt.com/us/en/home/library/collections/laboratory-division/karl-fischer-titration-guides.html)
Free fatty acids (as oleic acid)	%	Max 0.3	NEN-ISO 1740 | IDF6 2004 (Milkfat products and butter – Determination of fat acidity (Reference method) (ISO 1740:2004, I
Peroxide Value	Meq O_2/kg fat	Max 0.3	ISO-DIS 3976 | IDF74E 2004 (Milk fat – Determination of peroxide value)
Microbiological Parameters			
Total Plate Count 30°C	/g	< 500	NEN-EN-ISO 4833-1 (ISO 4833-1:2013 Microbiology of the food chain - Horizontal method for the enumeration of microorganisms - Part 1: Colony count at 30 degrees C by the pour plate technique)
Total Plate Count 55°C	/g	< 2500	NEN-EN-ISO 4833-1 (same as above)
Enterobacteriaceae	/g	non detectable	NEN-EN-ISO 21528-1 (ISO 21528-1:2017 Microbiology of the food chain — Horizontal method for the detection and enumeration of Enterobacteriaceae — Part 1: Detection of Enterobacteriaceae)
Mold	/g	Max 10	NEN-ISO 6611 (ISO 6611:2004 Milk and milk products - Enumeration of colony-forming units of yeasts and/or moulds - Colony-count technique at 25 degrees C)
Yeast	/g	Max 10	NEN-ISO 6611 (ISO 6611:2004 Milk and milk products - Enumeration of colony-forming units of yeasts and/or moulds - Colony-count technique at 25 degrees C)

Parameter	Unit	Limit	Test Method (with complete citations)
Staphylococcus Aureus	/g	non detectable	NEN-EN-ISO 6888-3 (Microbiology of food and animal feeding stuffs – Horizontal method for the enumeration of coagulase-positive staphylococci (Staphylococcus aureus and other species) – Part 3: Detection and PMN technique for low numbers (ISO 6888-3:2003, IDT)
Salmonella	/250 g	non detectable	NEN-EN-ISO 6579-1 (Microbiology of the food chain – Horizontal method for the detection, enumeration and serotyping of Salmonella spp. (ISO6579-1:2017, IDT)
Thermophilic aerobic sporeforming bacteria	/g	Max 100	NEN 6809 –(100°C-30min) (NEN 6809 : “MILK AND MILK PRODUCTS - ENUMERATION OF THERMOPHILIC AEROBIC SPOREFORMING BACTERIA”)
Thermophilic anaerobic sporeforming bacteria	/g	Max 100	Supplier’s ISO-certified lab’s internal method “FLMV0194”
Sulphite Reducing Clostridia	/g	Max 5	Weenk et al: Modified methods for the enumeration of spores of mesophilic Clostridium species in dried foods.
Bacillus cereus	/g	Max 50	NEN-EN-ISO 7932 (ISO 7932:2004 Microbiology of food and animal feeding stuffs - Horizontal method for the enumeration of presumptive Bacillus cereus - Colony-count technique at 30 degrees C)

Question #8 (Chemistry):

- ***FDA Question #8****: The methods used for the analyses should reflect the current versions. The following methods listed in the analytical report from Eurofins (Appendix A) are not the most current:*
    - *Yeasts and Molds – ISO 6611:2003-12*
    - *Salmonella – ISO 6579:2007-10*
    - *Cronobacter spp. – ISO 22964:2006-02*

  Please clarify if current methodology was used in the analyses.

Response to Question 8: At the outset, we note Appendix A contains testing results from Eurofins to provide typical compositions of AMF summarized in Table 1 of GRN 898; the data are not used to provide the microbial specifications of AMF summarized in Table 2 of GRN 898, which were actually based on test reports of five production lots from Appendix C. Only "yeast and molds" and "*Salmonella*" are tested per ingredient specifications.

We recognize the importance of using current methodology for ingredient specifications. Regular testing on each batch is received via COAs from the supplier noting the results and method of analysis being used. The supplier's internal Laboratory & Quality Services is ISO certified and validations are performed when choosing and executing methods. The microbiological methods are accredited and validated. We rely on the supplier to implement the latest analytical methods such as ISO standards as they change based on new and improved analysis methodology. The latest ISO methods we have been informed of are:

> Yeasts and Molds – ISO 6611:2004-10: "Milk and milk products – enumeration of colony-forming units of yeasts and/or molds – colony-count technique at 25°

There are no technical changes from the former ISO method to the more recent, only editorial changes.

> Salmonella – ISO 6579-1:2017: Salmonella detection in foodstuff; validation just finished in lab

A new agar was implemented in the latest ISO method and can be used as an alternative. The old agar is still valid and can be used for results as well.

It is reasonable to assume there might be gaps in how quickly a particular analytical lab can adapt and implement the most recent test method. We respectfully submit that even a slightly outdated ISO method, which is validated and suitable for the intended use, still provides a valid test result and does not pose a safety risk. Moving forward, the most up to date standards, once validated, will be used for analysis of each batch.

Question #9 (Chemistry):

- ***FDA Question #9****: We note that a specification for Cronobacter spp. is typically provided for ingredients used in infant formula. In the notice, a specification for Cronobacter spp. is indicated in Appendix A, but neither Table 2 nor the COAs list a specification for Cronobacter spp.*
    - *Please include a specification for Cronobacter in Part 2 of the notice and provide the results from the analysis of five non-consecutive lots demonstrating conformance with the Cronobacter specification.*
    - *For the record, please provide revised Tables 2 and 3 to reflect the new Cronobacter specification and results of the batch analyses.*
    - *Please clarify whether the provided specifications for Cronobacter spp. in AMF are performed using a 300-gram sample (Appendix A).*
    - *In addition, we request that you address how the manufacturing process controls for the presence of Cronobacter spp.*

Response to Question 9: We would like to clarify that we did not intend to have *Cronobacter spp.* as a test item for the ingredient specification. Appendix A was provided to support the typical composition (mostly nutrient) levels summarized in Table 1 of the GRAS notification. The AMF ingredient specification is provided in Table 2 of GRN 898 based on test results from Appendix C. As the agency noted, neither Table 2 nor Appendix C contains test result of *Cronobacter spp.*

We recognize the importance of ensuring that infant formulas containing AMF should be in compliance with 21 CFR 106.55, quality factor requirements for infant formula. For powdered infant formula, 21 CFR 106.55(e) provides limits for *Cronobacter spp*. in the finished infant formula product. Because AMF is an ingredient intended for use in liquid formula only, under 21 CFR 106.55(b), the manufacturer of liquid infant formula shall comply, as appropriate, with the procedures specified in part 113 of this chapter for thermally processed low-acid foods packaged in hermetically sealed containers and part 114 of this chapter for acidified foods. The liquid infant formula manufacturer, who will add AMF, will have to comply with 21 CFR 106.55 before it can legally market the infant formula in the United States using AMF. While there is no particular microbial limit under 21 CFR 106.55(b) for ingredients such as AMF used in manufacturing liquid infant formula, we respectfully submit that our current specifications for AMF in Table 2 of GRN 898 are sufficient to ensure that the liquid infant formula product can be in compliance with 21 CFR 106.55, and additional microbial limits are unnecessary.

Additionally, the calorically-dense formula undergoes several processes to ensure all contaminants of concern are eliminated, in particular a wet production process involving an ultra-heat treatment (UHT). This heat treatment is 5 seconds at 295°F (146°C), which is

expected to effectively kill *Cronobacter spp.*, *Salmonella* and other Enterobacteria present. After the UHT treatment, the process is closed and the product is filled aseptically to eliminate chances of product contamination. Additionally, every batch of the final product is tested for commercial stability at 86° F (30°C), which would detect the growth of microorganisms in the exceptional situation they would still be present. We are confident these are sufficient mitigation steps from receiving the raw material to producing and shipping of the final product as it relates to *Cronobacter spp.* in the finished product. The production site for AMF is also FSSC 22000 compliant and annual audits are conducted to ensure the highest food safety and ingredient quality. Therefore, we do not view a *Cronobacter spp.* specification necessary for AMF.

Question #10 (Chemistry):

- ***FDA Question #10****: The COAs (Appendix C) indicate the shelf life is 21 days at 45 °C when stored under nitrogen. In the manufacturing process, you indicate that the final product was stored under nitrogen, but you do not discuss storage conditions.*
    - *Please clarify the storage temperature of the final product.*
    - *Please address the anticipated shelf-life of the AMF ingredient.*

Response to Question 10: We appreciate FDA pointing out what may have been confusing to in the "Method of Manufacture" section of GRN 898. We would like to clarify that when the "final product" is referred to on page 12, we are referring to the AMF final product that is packed and not the calorically-dense formula. The use of nitrogen flushing to preserve the AMF remains accurate and is used for the liquid AMF. It is also important to clarify that the noted AMF shelf life of 21 days (45 °C) stored under nitrogen conditions is for the liquid product in bulk. However, there is another applicable storage condition utilized by the supply point producing the calorically-dense formula. Depending on the manufacturer's supply point, the AMF is received in bulk (liquid, flushed with nitrogen) using the product almost immediately. Other supply points use relatively small amounts of AMF and these are received in 10 kg crystallized blocks, not in bulk. The 10 kg blocks are packed tightly without headspace (not flushed with nitrogen) and stored at refrigeration temperatures. For these unopened blocks, a shelf life of 8 months is applicable at 12°C stored in a cool, dark and dry place. We apologize for not clarifying the various applicable storage conditions in GRN 898.

Question #11 (Chemistry):

- ***FDA Question #11:*** *On page 14 of the notice, you state that AMF meets the Codex limit for peroxide value (0.3 meq/kg). We note that this is higher than the specification for peroxide value in 7 CFR 58.347 (0.1 meq/kg). Please address this discrepancy.*

Response to Question 11: As the agency pointed out, the specification for AMF is provided as 0.3 meq/kg, the same as the Codex standard for maximum peroxide value. The COA results in Appendix C of the GRAS notification show even a lower value of 0.2 meq/kg. We recognize that the requirements for 7 CFR 58.347 relate to the finished AMF to bear a USDA Official Identification. In particular, 7 CFR Part 58 contains regulations for "grading an inspection, general specifications for approved plants and standards of grades of dairy products" and we do not view the regulations applicable for ingredient safety assessment. Due to the intended use of AMF in this case, we believe the Codex standard as a more appropriate standard to support the safety of the intended use. Further, as AMF is less than 1% of the final product, we respectfully submit our specification for peroxide value which is the same as Codex limit ensures the safety of the intended use. We will continue to monitor and evaluate the peroxide level as we undergo different levels of analysis.

Question #12 (Chemistry):

- ***FDA Question #12****: 7 CFR 58.347 provides specifications for iron (NMT 0.2 mg/kg) and copper (NMT 0.05 mg/kg). You provide batch data for iron and copper but did not provide specifications for the metals.*
    - *Please provide specifications for iron and copper.*
    - *Indicate these specifications in the revised Table 2.*
    - *Include the batch analyses results for the metals in a revised Table 3.*

Response to Question 12: We agree with the agency iron and copper should be established as part of the ingredient specifications for AMF. We also agree the iron (NMT 0.2 mg/kg) and copper (NMT 0.05 mg/kg), which are consistent with the Codex standard, are appropriate maximum limits. Indeed, when we reached out to the supplier, we learned that iron and copper levels are routinely monitored. The revised Table 2 (partial table) is provided below, with changes highlighted in red.

Parameter	Unit	Limit	Test Method
Physico-Chemical Parameters			
Fat	% (as solids)	Min 99.8	Calculate by difference
Moisture	%	Max 0.1	Karl Fischer-STD 023-2002 ISO
Free fatty acids (as oleic acid)	%	Max 0.3	IDF 6B 1989
Peroxide Value	Meq O_2/kg fat	Max 0.3	IDF 74A 1991
Iron	mg/kg	Max 0.2	FC-method using AOAC 984.27
Copper	mg/kg	Max 0.05	FC-method using AOAC 984.27

While the test results of iron and copper levels for the five batches discussed in Table 3 are not available, the supplier believes the copper and iron levels are in compliance with the specs (iron (NMT 0.2 mg/kg) and copper (NMT 0.05 mg/kg)) based on historical data. A copy of a COA for AMF showing levels of copper and iron complying with the specs is also provided (**Attachment A**). Going forward, we will ensure AMF complies with the iron and copper specifications.

Question #13 (Chemistry):

- ***FDA Question #13:*** *Food-grade milk products are produced in compliance with 21 CFR 1240.61 (mandatory pasteurization for all milk and milk products in final package form intended for direct human consumption)*
    - *Please confirm that the milk used in the manufacture of AMF is pasteurized in accordance with the provisions of the Pasteurized Milk Ordinance (PMO). The PMO is the milk sanitation standard for Grade "A" milk and milk products used by the National Conference on Interstate Milk Shipments program.*

Response to Question 13: We recognize the importance of PMO in addressing the US industry requirements for dairy food safety. The supplier has confirmed the milk used in the manufacture of AMF is pasteurized under conditions equivalent with the applicable provisions of the PMO. The supplier site manufacturing the AMF is also certified under FSSC 22000 and is audited annually.

Question #14 (Chemistry):

- ***FDA Question #14:*** *For clarity of the record, please provide the units for non-dioxin like PCBs in the contaminant results summary (Table 5).*

Response to Question 14: The units for Table 5 should be nanograms per gram of fat.

Question #15 (Chemistry):

- ***FDA Question #15:*** *Please note that standards and regulations for environmental contaminants, animal drugs, and pesticides in foods such as milk are outlined in 21 CFR 109.30 (tolerances for PCBs), 21 CFR Part 556 (tolerances for residues of new animal drugs in food), and 40 CFR Part 180 (tolerances for pesticides in food and feed). FDA also has action levels for several pesticides (listed in Compliance Policy Guide (CPG) 575.100) 2 and for aflatoxin M1 (FDA's CPG Section 527.400). In addition to tolerances and action levels, FDA also may use "target testing levels" as guidelines for certain drug residues, including those with a tolerance of zero in milk (e.g., erythromycin, penicillin). In accordance with Appendix N of the PMO, target testing levels have been communicated via Memoranda of Information (M-I) from FDA, most recently M-I-18-9, issued February 12, 2018.3 In the notice, you note that you analyzed for persistent environmental contaminants (i.e., dioxins, furans, PCBs, pesticides) and radioactivity (Cs-134/137).*

    - *Please provide additional information to support the safety of the AMF and to demonstrate that the regulatory limits are met.*

Response to Question 15: We recognize the importance of ensuring all applicable standards and regulations for environmental contaminants, animal drugs, and pesticides are met. The supplier has confirmed that the AMF and milk used to manufacture AMF comply with tolerance levels established for milk and milk fat under 21 CFR Part 556 (tolerances for residues of new animal drugs in food), and 40 CFR Part 180 (tolerances for pesticides in food and feed).

Table 5 of GRN 898 provides the maximum limits of environmental contaminants including dioxin and PCBs, which are partially copied below.

Parameter	**Unit**	**Limit**
Aflatoxin M1	ppb	Max 0.1
Mercury	ppb	20
Lead	ppb	50
Cadmium	ppb	10
Total arsenic	ppb	100
Inorganic arsenic	ppb	75
Non dioxin like PCBs (ndl PCBs), sum of	Ndl/g fat	Max 20
Dioxins and Furans WHO (2005)-PCDD/F TEQ (upper bound)	pg TEQ/g fat	Max 2.5
Sum WHO(2005)-PCDD/F + dl-PCBs TEQ (upper bound)	pg TEQ/g fat	Max 5.5
Activity Cs 134	Bq/kg	Max 370
Activity Cs 137	Bq/kg	Max 370

Further as discussed in GRN 898, milk and dairy products produced by the supplier providing the AMF are routinely monitored as demonstrated in Appendix D of the GRAS notification to ensure that potential contaminants of concern, including metals (e.g., lead, arsenic, cadmium, mercury), aflatoxins, radioactive substances, PCB compounds, dioxins, PAHs, and veterinary

drugs meet appropriate specifications to ensure that all milk and milk-derived products are food-grade. We further requested the supplier to issue a statement on the compliance of the AMF and the milk used to manufacture AMF with the test results reported in the monitoring program. (**Attachment B**). More recent monitoring data from the environmental monitoring are also provided in **Attachment C**.

Under 21 CFR 109.30 (tolerances for PCBs), the maximum limits of PCB in milk and manufactured dairy products is 1.5 ppm. As reported in Appendix D, the ingredient is subject to a monitoring program which has a limit for PCB compounds at 40 ppb. Under FDA's guidance CPG Sec 527.400 Whole Milk, Lowfat Milk, Skim Milk - Aflatoxin M1, the agency established a 0.5 ppb action guideline for aflatoxin contamination of fluid milk products. As listed in Table 5 of GRN 898, the maximum limit for aflatoxin M1 in the ingredient is 0.1 ppb. Regarding FDA action levels for the following pesticides under Compliance Policy Guide (CPG) 575.100, we have summarized them below for easy reference.

Aldrin & Dieldrin	Milk (fat basis)	0.3 ppm
Benzene Hexachloride (BHC)	Milk (fat basis)	0.3 ppm
DDT, DDE, & TDE	Milk (fat basis)	1.25 ppm
Heptachlor & Heptachlor Epoxide	Milk (fat basis)	0.05 ppm
Lindane	Milk (fat basis)	0.3 ppm

As demonstrated in Appendix D of GRN 898, all of the above have been subject to monitoring with detection limits or actual reported results lower than the FDA action levels summarized above. As for the FDA "target testing levels" provided in Appendix N of the PMO, via Memoranda of Information (M-I) from FDA, most recently M-I-18-9, issued February 12, 2018, we have reviewed the individual limits and many of these levels are the same as those provided in 21 CFR Part 556. For those antibiotic target testing levels not covered by 21 CFR Part 556, according to Appendix D of GRN 898, as well as the **Attachment C**, the vast majority of the samples tested under the monitoring program show the farm milk are in compliance with limits for beta-lactam antibiotics and other (non beta-lactam antibiotics). The supplier further represents the AMF ingredient and milk used to manufacture AMF comply with EU regulation EU/37/2010, which contains similar limits for most of the veterinary drug residues.

In light of the above, we respectfully submit the current limits and monitoring of the environmental contaminants, pesticides, and veterinary drug residues ensure the intended use is safe and all the applicable regulatory limits are met.

Question #16 (Chemistry):

- ***FDA Question #16:*** *Please confirm:*

    - *The starting material for AMF (i.e., heavy cream and butter) is made from fluid milk which has been produced in accordance with good agricultural practices and meets applicable US regulations.*

Response to Question 16: The supplier has confirmed the fluid milk used to manufacture AMF has been produced in accordance with good agricultural practices and meet all applicable US regulations.

FDA Question #16 (continued):

- *The starting material for AMF (i.e., heavy cream and butter) is made from food-grade fluid milk that complies with derived intervention levels (DILs) for radionuclides (CPG 560.750). While you provide data to support radioactivity limits for Cs-134/137 (p. 18 and Appendix D), please confirm that the fluid milk complies with additional DILs for radionuclides listed in CPG 560.750.*

Response to Question 16 (continued): We understand the importance of using food-grade milk that complies with DILs under FDA's guidance CGP 560.750, which are copied below. We understand these DILs, which were initially first issued after the Chernobyl nuclear incident, help the agency determine whether foods present a safety concern due to radionuclide activity. Our supplier is based in the Netherlands, where there is a long track record of safety when coming to radionuclide food safety issues. Instead of testing every radionuclide listed below for every batch of fluid milk used to manufacture AMF, our supplier monitors Cesium-134 + Cesium-137 with much lower limits than those provided in CGP 560.750 (i.e., 1200 Bq/kg vs. 370 Bq/kg). As the presence of Celisum-134 and Celcium-137 are good indicators of the general levels of radionuclides, we trust by setting the lower limits for these two particular radionuclides through the monitoring program, the supplier can also ensure the fluid milk will also comply with the other additional DILs listed in CPG 560.750.

- Strontium-90 (DIL, 160 Bq/kg)
- Iodine-131 (DIL, 170 Bq/kg)
- Cesium-134 + Cesium-137 (1200 Bq/kg)
- Plutonium-238 + Plutonium-239 + Americium-241, (DIL, 2 Bq/kg)
- Ruthenium-103 + Ruthenium-106, (DIL, (C3 / 6800) + (C6 / 450) < 1Bq/kg)

FDA Question #16 (continued):

- *The starting material for AMF (i.e., heavy cream and butter) is made from fluid milk that meets pesticide tolerances specified in 40 CFR Part 180 for milk and milk fat. We note that, in Appendix D you cite limits and analytical results for persistent, lipophilic organochlorine pesticides (which include those listed in CPG 575.100),5 from a 2017 monitoring program of the Dutch dairy industry.*

However, we request that you also state compliance with tolerances specified in US regulations (40 CFR Part 180) for milk and milk fat.

Response to Question 16 (continued): The supplier has confirmed the AMF ingredient and milk used to manufacture AMF comply with tolerance specified in US regulations or milk and milk fat under 40 CFR Part 180.

FDA Question #16 (continued):

- *The starting material for AMF (i.e., heavy cream and butter) is made from fluid milk that meets U.S. regulatory limits for veterinary drug residues in milk and milk fat,6 and is tested regularly for contaminants as outlined in the Grade "A" PMO (2017). We note that, in Appendix D you cite limits and analytical ranges for two classes of antibiotics (β-lactam antibiotics and other) and for antihelmintics in fluid milk (Appendix D), from a 2017 monitoring program of the Dutch dairy industry. Although you address a few of the veterinary drugs that are listed in US regulations, there are several that you have not addressed. Further, US limits for antibiotics are expressed individually, rather than as classes of antibiotics. We request that you state compliance with tolerances specified in US regulations (21 CFR Part 556) for milk and milk fat, and also specifically address drug residues that may partition into the milk fat phase of milk,7 and the ability of the method of manufacture and relevant production controls to assure removal of these contaminants.*

Response to Question 16 (continued): Our supplier, which is based in EU, has confirmed compliance with applicable tolerance levels in 21 CFR Part 556. We recognize the Appendix D only contains lists of total antibiotics, instead results for individual antibiotic. The supplier has further confirmed the raw milk incoming for the AMF is in compliance with EU/37/2010, which covers a large number of veterinary drugs with maximum residue limits on individual substances. All raw milk is tested with a screening method and in case positive results are found, the milk is not allowed to be used in the ingredient manufacturer's factories. After evaluating US regulations in 21 CFR Part 556, the supplier confirms that the AMF ingredient subject of GRN 000898 is in compliance with tolerances specified under 21 CFR Part 556. *See* (**Attachment D**).

Question #17 (Chemistry):

- ***FDA Question #17****: In the notice, you based the dietary exposure estimates on the "highest achieved formula intake" level of 175 kcal/kg bw/d from a single published study (Clarke et al., 2007) aiming for intake levels up to 200 kcal/kg bw/d. We have seen calculations of pseudo-90th percentile dietary exposures for ingredients added to infant formula based on the assumption that the 90th percentile dietary exposure is approximately 1.2 times of the mean,8 while your cited value is approximately 1.5-1.7 times the mean.*

    - *Please address whether the cited level of caloric intake (175 kcal/kg bw/d) is reasonable and/or sustainable in the subpopulations that would consume calorically-dense formula. Please consider your response to this question in the response to the following question regarding exposure.*

Response to Question 17a: As there are currently no similar products in the US market today, the estimates of dietary exposure presented in the GRAS notification correspond to the mean level of intake of a calorically-dense infant formula achieved across several clinical studies (i.e., 120 kcal/kg bw/day) and the highest achieved formula intake per 24 h in a 6-week intervention (i.e., 175 kcal/kg bw, as cited in Clarke et al., 2007). While we noted in GRN 900 that 200 kcal/kg bw/day could be the highest use level, we believe 175 kcal/kg bw/day is a more representative conservative estimate for the purpose of a safety assessment. As the agency noted, even 175 kcal/kg bw/day may be achieved only by some infants as reported in the referenced clinical trial but is not necessarily a level representative of a 90th percentile intake. The actual representative 90th percentile intake could be lower than the 175 kcal/kg bw/day. We also note the exempt infant formula will be administered under the supervision of doctors, and the dosage will necessarily vary depending on the infant conditions and duration needed. However, by using the 175 kcal/kg bw/day during our dietary exposure assessment, we are able to establish the intended use to be safe with an extra level of conservatism.

- ***FDA Question #17b****: Please provide estimates of the mean and 90th percentile dietary exposures for infants less than 6 months of age, and for older infants 6-12 months of age consuming this ingredient. Please base your estimates on reference data for caloric needs of the subpopulation(s) of infants consuming energy-dense formulas. You may base caloric needs on published estimates of energy needs for catch-up growth or use other reference data to support your discussion.*

Response to Question 17b: Published estimates of recommended energy intakes, in particular recommended intakes for infants with elevated nutrient requirements to address faltering growth, provide an alternate approach for estimating formula intake by the target population of infants that may consume the calorically-dense infant formula. Guidance for care of critically ill pediatric patients recommends use of a predictive equation such as the Schofield equation to estimate nutrient needs (Mehta et al., 2017). The Schofield equation provides a basis to calculate resting energy requirements with a stress factor to adjust for an infant's particular needs. The equations for male and female infants to 3 years of age are as follows (weight in kg, height in cm):

Male: (0.167 x weight) + (15.174 x height) – 617.6

Female: (16.252 x weight) + (10.232 x height) – 413.5

The resulting estimate of resting energy requirements is then multiplied by a stress factor corresponding to an infant's condition:

Table 1. Schofield Stress Factors

Fever	12% per degree >37C
Cardiac Failure	1.15 – 1.25
Major Surgery	1.2 – 1.3
Sepsis	1.4 – 1.5
Catch-up growth	1.5 – 2
Burns	1.5 - 2

Using a median height for male infants ages 1 to 12 months and assuming a weight at the 3rd percentile to represent an infant at risk for growth faltering, the estimated energy needs based on the Schofield equation and a range of stress factors representative of conditions infants consuming a calorically dense formula may experience are summarized in Table 2. The stress factors selected for these calculations include 1.25, which corresponds to the midpoint of infants undergoing surgery (and the upper end of the range for infants with cardiac failure), and factors of 1,5, 1.75, and 2.0, which correspond to the lower bound, midpoint, and upper bound of the recommended range for catch-up growth of 1.5-2.0.

Table 2. Estimated energy requirements for male infants with stress factors for surgery and catch-up growth

Age (months)	Reference height (cm, 50th percentile)	Reference weight (kg, 3rd percentile)	Basal Energy Requirement kcal/day	Energy Requirement by Stress Factor kcal/kg bw/day			
				1.25	1.5	1.75	2.0
1	54.7	3.2	213	83	100	116	133
2	58.1	4.0	265	83	99	116	132
3	60.8	4.7	306	81	98	114	130
4	63.1	5.3	341	80	96	113	129
5	65.2	5.8	373	80	96	112	129
6	67	6.3	400	79	95	111	127
7	68.7	6.8	426	78	94	110	125
8	70.2	7.2	449	78	94	109	125
9	71.6	7.5	470	78	94	110	125
10	73	7.8	491	79	95	110	126
11	74.3	8.1	511	79	95	110	126
12	75.5	8.4	529	79	95	110	126

Body weight and height for infants, IOM, 2005 (based on CDC Growth Charts: United States. National Center for Chronic Disease Prevention and Health Promotion, 2000).

For infants ages 1 to 6 months, the highest estimated energy requirement at the midpoint for catch-up group is 116 kcal/kg bw/day, which is similar to the reported intakes of approximately 120 kcal/kg bw/day from the clinical studies. The Institute of Medicine (IOM) identifies the reference energy needs for catch-up growth at 113 to 123 kcal/kg bw/day assuming a rate of gain of 10 g/kg bw/day in children, which likewise is consistent with values calculated with the Schofield equation (IOM, 2005; Table 5-32). The value also is consistent with mean formula intake for formula-fed infants with the highest intake per kg bw as reported by Fomon (1993), namely 121.1 kcal/kg bw/day for boys age 14-27 days. Collectively, energy intakes as reported in clinical trials of infants consuming calorically dense formula and estimated energy needs for infants who may be recommended for use of the formula suggest that intake of 120 kcal/kg bw/day is representative of mean energy intake for the target population of infants up to 6 months of age.

Assuming a factor of 1.2 times the mean intake for a pseudo-90th percentile intake, the pseudo-90th percentile intake by infants with a mean energy intake of 120 kcal/kg bw/day is 144 kcal/kg bw/day. This pseudo-90th percentile intake is close to the cited value of 141.3 kcal/kg bw/d from Fomon (1993) for 90th percentile intake by male infants 14-27 days of age.

The estimated mean energy needs for infants age 6-12 month requiring catch-up growth is approximately 110 kcal/kg bw/day assuming a stress factor corresponding to the midpoint of the range for catch-up growth (Table 2), which is slightly lower than the estimated needs for catch-up growth for an infant in the first 6 months of life. Assuming a mean energy intake of 110 kcal/kg bw/day, the pseudo-90th percentile intake is 132 kcal/kg bw/day for infants 6-12 months of age assuming a factor of 1.2 times the mean intake for a pseudo-90th percentile intake.

Multiplying the energy intake discussed above with the maximum proposed use level of AMF, we calculated the estimated daily intake of AMF below:

Table 3. Estimated Daily Intake of AMF from the Maximum Proposed Use of AMF

Calorically Dense Formula Intake		Total Fat Intake	AMF Intake
Population and intake	kcal//kg bw/day	g/kg bw/day	g/kg bw/day
Infants 0-6 months			
Typical	120	6.7	0.47
Pseudo-90th percentile	144	8.0	0.56
Infants 6-12 months			
Typical	110	6.1	0.43
Pseudo-90th percentile	132	7.3	0.51

Assumptions: 100 kcal per 100 mL; fat accounts for 50% of kcal, and 9 kcal per gram of fat; maximum use of 7.0% AMF in fat blend

Toxicology Questions

Question #1 (Toxicology):

- ***FDA Question #1:*** *On pg. 45 of the notice, you state: "Infant formulas containing palm olein as a predominant source of fat have been demonstrated to reduce absorption of fat and calcium and decrease bone mineralization compared to formulas without palm olein (Koo et al., 2006)."*

    - *Please provide the reference for Koo et al. (2006), since it was not listed in Part 7.*

    - *Please discuss whether AMF will be used with palm olein in a blended oil formulation, and if so, why its use will not negatively impact higher fecal fat excretion and/or calcium malabsorption associated with palm olein.*

Response to Question 1: The reference in the first part of the question is: Koo WW, Hockman EM, Dow M. Palm olein in the fat blend of infant formulas: effect on the intestinal absorption of calcium and fat, and bone mineralization. J Am Coll Nutr. 2006 Apr;25(2):117-22. doi: 10.1080/07315724.2006.10719521.

As the agency noted, evidence suggests that palm olein may adversely impact fecal fat excretion and/or calcium malabsorption due to a high proportion of free palmitic acid (Koo et al., 2006). The intended use of AMF under GRN 898 was to replace palm (olein) oil completely as the main source of Palmitic acid (C16:0) in the exempt infant formula. 2/ As such, we respectfully submit the use of AMF will not negatively impact higher fecal fat excretion and/or calcium malabsorption associated with palm olein.

- ***FDA Question #2****: In your supplemental letter (dated May 1, 2020) that provided information on the subpopulation of term infants intended to consume your calorically dense or fluid restrictive infant formula, you indicate that the "current standard of care" recommended for infants with cystic fibrosis (CF) is "human milk or standard formula…with pancreatic enzyme supplement (if indicated)" (emphasis added). This statement appears to suggest the use of typical, non-exempt infant formula in infants with CF.*

    - *Please clarify and explain the intended use of your exempt, calorically dense infant formula in CF infants.*

    - *Also, please briefly discuss the safety of the intended use of your ingredient, AMF, in a calorically dense formula (i.e., expected to provide more fat per feeding) considering the gastrointestinal abnormalities often found in infants with CF (Green et al., 1995; Wouthuyzen-Bakker et al., 2011).*

2/ We note palm oil or coconut oil may also be present in the infant formula as part of the Medium-Chain Triglycerides oil.

Response to Question 2: The current standard of care recommended for feeding infants with CF is to use human milk or standard infant formula with pancreatic enzyme supplementation (if indicated). 3/ For infants with CF who demonstrate weight loss or inadequate weight gain, calorie-dense feedings are recommended. 4/

Currently, in the United States, these infants with CF who are indicated for feeding with a calorically-dense infant formula would be fed a standard (non-exempt) infant formula prepared at a higher caloric concentration (i.e. higher ratio of powder or liquid concentrate to water than standard directions by the manufacturer to prepare the infant formula at standard caloric concentration of 65 – 67 kcal/ml) in order to achieve the higher caloric density recommended. This would be done at the direction of the infant's health care team (i.e. as directed by physician or dietitian).

Standard (non-exempt) infant formulas typically provide 48-50% of calories from fat. When prepared at a higher caloric density, the percent energy from fat remains constant at 48-50%. The calorically-dense infant formula described in this GRAS will provide 48-50% with kcal from fat not to exceed 50%. Therefore, the fat load will be comparable to when to the current practice. (See example table below).

As described by Wouthuyzen-Bakker et al., 2011, CF impacts the gastrointestinal system and high energy diets and pancreatic enzyme replacement therapy (PERT) are typical parts of treatment throughout the patient's lifespan. Nonetheless, in infants with CF, specialized hydrolyzed formulas have not been shown to confer improved nutrition or health benefits and the Cystic Fibrosis Foundation continues to recommend that when infant formulas are used, standard infant formulas should be used (in conjunction with PERT if indicated). Furthermore, if inadequate growth or weight gain is observed, increasing calorically density of feedings is recommended. In cases where a calorie-dense feeding is recommended, the fat load of feeding with the calorie-dense formula described in this GRAS will be comparable to calorie-dense feedings with standard infant formula and therefore, would not be expected to be tolerated differently than the current practice. As always, this formula should only be used under medical supervision.

Formula Type	Caloric Density	Percent Calories from Fat
Standard Infant Formula	65 – 67 kcal/100 ml	48 – 50% of calories from fat
Calorically – Dense	100 kcal/100 ml	<50% of

3/ Cystic Fibrosis F, Borowitz D, Robinson KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *The Journal of pediatrics*. 2009;155(6 Suppl):S73-93.

4/ *See id*.

Formula		calories from fat

As noted in GRN 898, AMF provides fat in the form of triglycerides and as such would be subject to the same fate as triglycerides from other dietary sources of fat. For infants with CF who have gastrointestinal abnormalities, high energy diets and pancreatic enzyme replacement therapy are recommended. When consumed by an infant with CF, the AMF component within the energy dense formula can reasonably be assumed to be hydrolyzed into common dietary components as are other triglycerides. As noted above, the fat load provided by the energy dense formula will be comparable to what is provided in current practice.

As reviewed in GRN 898 and, based on the intended use of AMF, AMF is safe and GRAS based on the totality of data and information provided in the GRAS notice.

* * *

If any additional questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

Sincerely,

Steven B. Steinborn
Partner
Hogan Lovells US LLP
steven.steinborn@hoganlovells.com
202 637 5969

[redacted]

Rapport Nr. C00065253-F01
Datum verzending 27 mei 2020
Pagina 1 van 1

Confidential

[redacted]

ANALYSERAPPORT

[redacted]

Datum monsterneming: 11 mei 2020

[redacted]

Barcode: 5010191444
Product: WV melkvet
Productiedatum: 11 mei 2020
Klant referentie: BB11JVB 931315

ANALYSERESULTATEN

Parameter	Code	Eenheid	Resultaat	Declaratie / opm.
Vetvrije droge stof in boterolie	CD0431E	% m/m	<0.05	
Vetgehalte (berekening)	CX0083	% m/m	99.9	
Vochtgehalte (KF)	CD0600E	% m/m	0.04	
IJzer [redacted]	CE6260D	mg/kg	<0.050	
Koper [redacted]	CE6265D	mg/kg	<0.020	
Melkvr	CE5120E		Niet aantoonbaar	
L. monocytogenes	BF7963E	in 1 g	Afwezig	
Salmonella	BF5970E	in 5 x 25 g	Afwezig	

In bijlage 4 van het reglement module Gezondheids- en andere productcertificaten is het indienen van een klacht geregeld. Klacht tegen de resultaten binnen 4 dagen na ontvangst van het analyseresultaat.

[redacted]

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[redacted]

CONTAMINANTS AND RESIDUES IN DUTCH FARM MILK AND DAIRY PRODUCTS

RESULTS OF THE MONITORING PROGRAM OF THE DUTCH DAIRY INDUSTRY IN 2019

This monitoring program covers all sorts of Dutch raw cow milk, including but not limited to regular milk, meadow milk, organic milk and VLOG milk.

Component	Unit	Limit	2019			2018			2014 up to and including 2018
			No. of samples	Median value [1]	Max. value	No. of samples	Median value [1]	Max. value	Median value [1]
Aflatoxin M1									
Farm milk, composite sample [2]	µg/kg milk	0,05	480	<0,010	<0,010	480	<0,010	<0,010	<0,010
Heavy metals									
Farm milk, composite sample [3]			20			20			
Cadmium	µg/kg milk	-		<0,5	<0,5		<0,5	<0,5	<0,5
Lead	µg/kg milk	20		<5	<5		<5	<5	<5
Mercury	µg/kg milk	-		<0,2	<0,2		<0,2	<0,2	<0,2
Arsenic	µg/kg milk	-		<2	<2		<2	<2	<2
Radioactive substances									
Farm milk, composite sample [4]			12			12			
^{134}Cs and ^{137}Cs	Bq/kg milk	370		<10	<10		<10	<10	<10
Organochlorine pesticides									
Farm milk, composite sample [5]			270			270			
HCB	mg/kg fat	0,125		<0,01	<0,01		<0,01	<0,01	<0,01
α-HCH	mg/kg fat	0,25		<0,01	<0,01		<0,01	<0,01	<0,01
β-HCH	mg/kg fat	0,25		<0,01	0,01		<0,01	<0,01	<0,01
γ-HCH (lindane)	mg/kg fat	0,25		<0,01	<0,01		<0,01	<0,01	<0,01
Heptachlor (sum of heptachlor, cis-heptachlor epoxide, trans-heptachlor epoxide)	mg/kg fat	0,10		<0,03	<0,03		<0,03	<0,03	<0,03 [6]
Chlordane (sum of cis-chlordan, trans-chlordan, oxychlordan)	mg/kg fat	0,05		<0,03	<0,03		<0,03	<0,03	<0,03 [6]
DDT (sum of p,p'-DDE, p,p'-DDD (TDE), p,p'-DDT, o,p'-DDT)	mg/kg fat	1,00		<0,04	<0,04		<0,04	<0,04	<0,04 [6]
Aldrin and dieldrin	mg/kg fat	0,15		<0,02	<0,02		<0,02	<0,02	<0,03
ß- Endosulfan	mg/kg fat	1,25		<0,025	<0,025		<0,025	<0,025	<0,025 [6]
Endrin	mg/kg fat	0,02		<0,01	<0,01		<0,01	<0,01	<0,01 [6]
Chloroform									
Butter	mg/kg butter	[7]	24	<0,02	<0,02	24	<0,02	0,03	0,02
PCB-compounds									
Farm milk, composite sample [5]			270			270			
Sum of PCB28, PCB52, PCB101, PCB138, PCB153 and PCB180 [8]	ng/g fat	40		12,0	12,0		12,0	12,4	12,0
Dioxins and dioxin-like PCB's									
Farm milk, composite sample [9]			72			72			
Total dioxins (sum dioxins and furans)	pg TEQ/g fat	2,5		0,23	0,36		0,23	0,30	0,24
Total dioxins and dioxin-like PCB's	pg TEQ/g fat	5,5		0,47	0,81		0,46	0,55	0,47
Polyaromatic hydrocarbons									
Farm milk, composite sample [10]			20			20			
Benzo(a)pyrene	µg/kg fat	2,0		<0,10	<0,10		<0,10	0,13	<0,10
Sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene	µg/kg fat	10,0		<0,40	<0,40		<0,40	<0,40	<0,40

Component	Unit	Limit	2019			2018			2014 up to and including 2018
			No. of samples	Median value [1]	Max. value	No. of samples	Median value [1]	Max. value	Median value [1]
Melamine and cyanuric acid									
Farm milk, composite sample [4]			36			36			
Melamine	mg/kg milk	2,5		<0,010	<0,010		<0,010	<0,010	<0,010
Cyanuric acid	mg/kg milk	-		<0,010	0,031 [11]		<0,010	0,020 [11]	<0,010
Veterinary drugs									
Anthelmintics									
Farm milk, composite sample [12]			360			360			
Avermectines									
Abamectin	µg/kg milk	-		<0,05	<0,05		<0,05	<0,05	<0,1
Doramectin	µg/kg milk	[13]		<0,05	<0,05		<0,05	0,05 [14]	<0,1
Eprinomectin	µg/kg milk	20		<4	<4		<4	<4	<10
Ivermectin	µg/kg milk	[13]		<0,05	0,19 [15]		<0,05	<0,05	<0,1
Moxidectine	µg/kg milk	40		<2	3,6		<2	<2	<2
Benzimidazoles/levamisole/triclabendazoles									
Albendazole (sum of albendazole sulfoxide albendazole sulfone albendazole 2-amino sulfone)	µg/kg milk	100		<3	<3		<3	<3	<3 [6]
Flubendazole (sum of flubendazole 2-amino flubendazole)	µg/kg milk	-		<2	<2		<2	<2	<2 [6]
Levamisole	µg/kg milk	[13]		<1	<1		<1	<1	<1
Mebendazole (sum of mebendazole amine mebendazole 5-hydroxymebendazole)	µg/kg milk	-		<3	<3		<3	<3	<3 [6]
Oxfendazolesulfone (sum of fenbendazole oxfendazole oxfendazolesulfone)	µg/kg milk	10		<3	<3		<3	<3	<3 [6]
Oxibendazole (sum of oxibendazole-amine oxibendazole)	µg/kg milk	-		<2	<2		<2	<2	<2 [6]
Thiabendazole (sum of thiabendazole 5-hydroxythiabendazole)	µg/kg milk	100		<2	<2		<2	<2	<2 [6]
Triclabendazole (sum of triclabendazole triclabendazolesulfone triclabendazolesulfoxide ketotriclabendazole)	µg/kg milk	10		<3	<3		<3	<3	<3
Antibiotics				% non-compliant [16]			% non-compliant [16]		% non-compliant [16]
Farm milk			2,0 x 10^6			2,0 x 10^6			
ß-lactam antibiotics	% non-compliant			0,012			0,013		0,013
Other (non ß-lactam antibiotics)	% non-compliant			<0,001			<0,001		<0,001

1) The median is the middle value in a set of numbers that are arranged by size. This means that 50% of the numbers is below the median and 50% of the numbers is above the median.
2) A composite sample of farm milk was prepared from 4 individual farm milk samples.
3) A composite sample of farm milk was prepared from 15 individual farm milk samples.
4) A composite sample of farm milk was prepared from 50 individual farm milk samples.
5) A composite sample of farm milk was prepared from 8 individual farm milk samples.
6) Median value of 2017 up to and including 2018.
7) In Germany a limit for food of 0,1 mg/kg is applied.
8) Calculated as upper bound concentration according to Regulation (EC) No 1881/2006. Upper bound concentrations are calculated on the assumption that all the values of the different congeners below the limit of quantification are equal to the limit of quantification.
9) A composite sample of farm milk was prepared from 25 individual farm milk samples.
10) A composite sample of farm milk was prepared from 20 individual farm milk samples.
11) For cyanuric acid there is no regulatory limit. Nevertheless, follow-up action has been taken.
12) A composite sample of farm milk was prepared from 3 individual farm milk samples.
13) Not allowed for administration to animals which produce milk for human consumption.
14) In 1 of the 360 samples doramectin was detected (0,05 µg/kg). Follow-up action has been taken.
15) In 2 of the 360 samples ivermectin was detected (0,07 and 0,19 µg/kg). Follow-up action has been taken.
16) % samples non-compliant with limit in milk payment testing instead of median value.

[redacted]

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[redacted]

To whom it may concern

Subject: Compliance with EU/37/2010

We, [redacted], herewith inform you as follows, in answer to your request d.d. 12 June 2020.

We comfirm that [redacted] is compliant with REGULATION (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. Based on an assessment of 21 CFR 556 and additional documentation, we confirm that the product [redacted] is seen to fulfil the stated requirements and reference lists regarding to the listed substances there in.

We trust to have informed you sufficiently.

[redacted]

[redacted]

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[redacted]

From: Tao, Xin
To: Harry, Molly
Cc: Steinborn, Steven B.
Subject: RE: GRN 000898 Anhydrous Milk Fat - Additional Clarifications Needed
Date: Friday, July 17, 2020 4:20:25 PM
Attachments: image001.png
Response to FDA's Additional Questions for GRN 000898.pdf
GRAS_AMF Appendix C. Certificates of Analysis on AMF.PDF

Dear Molly,

Please find our response to your additional questions re GRN 898 attached. As always, please do not hesitate to reach out if you have any follow-up questions.

Best regards,
Steve and Xin

Xin Tao
Senior Associate

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

From: Harry, Molly [mailto:Molly.Harry@fda.hhs.gov]
Sent: Tuesday, July 07, 2020 10:39 AM
To: Steinborn, Steven B.
Cc: Tao, Xin
Subject: RE: GRN 000898 Anhydrous Milk Fat - Additional Clarifications Needed

Dear Mr. Steinborn,

The review team would like you to clarify the following information that you provided in GRN 000898 (AMF):

1. Please clarify that the provided specifications for *Salmonella serovars* in AMF are performed using a 250-gram sample.
2. Please clarify if the analysis for *S. serovars* is performed using a pooled sample of 250 grams of AMF. If so, please provide results of analyses of three non-consecutive batches for *S. serovars* in a sample size of 25 grams of AMF.

3. In your response to FDA question #7, you stated that the method used to detect *Staphylococcus aureus* is NEN-EN-ISO 6888-3, which corresponds to Microbiology of Food and Animal Feeding Stuffs – Horizontal Method for the Enumeration of Coagulase-Positive *Staphylococci* (*Staphylococcus aureus* and Other Species) – Part 3: Detection and PMN Technique for Low Numbers. We note that the appropriate title is Microbiology of Food and Animal Feeding Stuffs – Horizontal Method for the Enumeration of Coagulase-Positive *Staphylococci* (*Staphylococcus aureus* and Other Species) – Part 3: Detection and MPN Technique for Low Numbers. Please provide a statement that corrects this reference.

Please provide your response with ten days, and feel free to contact me if you have any questions.

Sincerely,

Molly A. Harry
Regulatory Review Scientist

Office of Food Additive Safety, Division of Food Ingredients
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Molly.Harry@fda.hhs.gov

Tel: 240-402-1075

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

Via Electronic Mail

July 17, 2020

Molly A. Harry
Regulatory Review Scientist
Office of Food Additive Safety, Division of Food Ingredients
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Molly.Harry@fda.hhs.gov

Re: Response to FDA's Additional Questions for GRN 000898

Dear Ms. Harry,

We hereby submit our responses to FDA's additional questions for GRAS Notice 000898 (GRN 898), which covers the intended use of anhydrous milk fat (AMF) as a source of fat in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction.

For your ease of reference, we first copied FDA's questions below, followed by each of our response:

- ***FDA Question #1****: Please clarify that the provided specifications for Salmonella serovars in AMF are performed using a 250-gram sample.*

Response to Question 1: The intended specification for *Salmonella* should be "absent in 250 grams" as reported in the COAs (Appendix C of the GRN 898 submission). As discussed in our response to FDA's questions on June 15, Table 2 and Table 3 of GRN 898 should be corrected to use "absent in 250 grams" instead of "absent in 25 grams" as intended specification for *Salmonella*. The results from five non-consecutive batches can be found in the COAs (attached for your easy reference) and they demonstrate compliance with the intended specification.

We note that according to the test method ISO 6579, if 10 test portions of 25 g are to be examined, the lab should combine the 10 units to form a composite test portion of 250 g. However, this is not how we conducted the *Salmonella* testing. We would likely to clarify that instead of using pooled samples for *Salmonella* testing, 250 gram is directly taken from the

AMF. In other words, the 250 gram represents the direct sample volume, not the pooled sample volume from 10 units of 25 gram samples.

- ***FDA Question #2****: Please clarify if the analysis for S. serovars is performed using a pooled sample of 250 grams of AMF. If so, please provide results of analyses of three non-consecutive batches for S. serovars in a sample size of 25 grams of AMF*

Response to Question 2: As discussed above, we hereby clarify that the analysis for *S. serovars* is not performed using a *pooled* sample. Instead, 250 grams of AMF is directly used for the testing.

- ***FDA Question #3****: In your response to FDA question #7, you stated that the method used to detect Staphylococcus aureus is NEN-EN-ISO 6888-3, which corresponds to Microbiology of Food and Animal Feeding Stuffs – Horizontal Method for the Enumeration of Coagulase-Positive Staphylococci (Staphylococcus aureus and Other Species) – Part 3: Detection and PMN Technique for Low Numbers. We note that the appropriate title is Microbiology of Food and Animal Feeding Stuffs – Horizontal Method for the Enumeration of Coagulase-Positive Staphylococci (Staphylococcus aureus and Other Species) – Part 3: Detection and MPN Technique for Low Numbers. Please provide a statement that corrects this reference.*

Response to Question 3: We hereby confirm the appropriate title of the method is "Microbiology of Food and Animal Feeding Stuffs – Horizontal Method for the Enumeration of Coagulase-Positive Staphylococci (*Staphylococcus aureus* and Other Species) – Part 3: Detection and MPN Technique for Low Numbers" as noted by the agency. We apologize for the typo.

* * *

If any additional questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

Sincerely,

Steven B. Steinborn
Partner
Hogan Lovells US LLP
steven.steinborn@hoganlovells.com
202 637 5969

[redacted]

[redacted]

CERTIFICATE OF ANALYSIS

Order information	
Customer	[redacted]

Product information	
Product description	Anhydrous Milk Fat IFT Tank truck
Lot number	BB0XW1H
Production date	05-06-2019

Chemical and physical analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Fat *	%	99.9	Min. 99.8	Calculated
Moisture *	%	0.1	Max. 0.1	IDF 23
FFA (as oleic acid) *	%	0.2	Max. 0.3	IDF 6
Peroxide value *	Meq O_2/kg	0.2	Max. 0.3	IDF 74

Microbiological analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Total plate count (30ºC)	CFU/g	<500	<500	ISO 4833
Total plate count (55ºC)	CFU/g	<2500	<2500	ISO 4833
Enterobacteriaceae	/g	Absent	Absent	ISO 21528-2
Yeast & moulds *	CFU/g	<10	<10	ISO 6611
Staphylococcus Aureus *	/g	Absent	Absent	ISO 6888-3
Salmonella	/250g	Absent	Absent	ISO 6579
Thermophilic aerobic and anaerobic spores *	CFU/g	<100	<100	
Sulphite Reducing Clostridia	CFU/g	<1	<1	Weenk
Bacillus Cereus	CFU/g	<10	<10	ISO 7932

Remarks
Results of parameters marked with * are based on monitoring program. Shelf life: Out of direct sunlight: 21 days at 45 °C when stored under nitrogen (During filling the product is flushed with nitrogen E 941)

Signing	
Date	14-06-2019
Name	H. Pel

[redacted]

[redacted]

[redacted]

CERTIFICATE OF ANALYSIS

Order information	
Customer	[redacted]

Product information	
Product description	Anhydrous Milk Fat IFT Tank truck
Lot number	BB0Z9ZN
Production date	18-07-2019

Chemical and physical analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Fat *	%	99.9	Min. 99.8	Calculated
Moisture *	%	0.1	Max. 0.1	IDF 23
FFA (as oleic acid) *	%	0.2	Max. 0.3	IDF 6
Peroxide value *	Meq O_2/kg	0.2	Max. 0.3	IDF 74

Microbiological analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Total plate count (30ºC)	CFU/g	<500	<500	ISO 4833
Total plate count (55ºC)	CFU/g	<2500	<2500	ISO 4833
Enterobacteriaceae	/g	Absent	Absent	ISO 21528-2
Yeast & moulds *	CFU/g	<10	<10	ISO 6611
Staphylococcus Aureus *	/g	Absent	Absent	ISO 6888-3
Salmonella	/250g	Absent	Absent	ISO 6579
Thermophilic aerobic and anaerobic spores *	CFU/g	<100	<100	
Sulphite Reducing Clostridia	CFU/g	<1	<1	Weenk
Bacillus Cereus	CFU/g	<10	<10	ISO 7932

Remarks
Results of parameters marked with * are based on monitoring program. Shelf life: Out of direct sunlight: 21 days at 45 °C when stored under nitrogen (During filling the product is flushed with nitrogen E 941)

Signing	
Date	25-07-2019
Name	W de Haan

[redacted]

[redacted]

[redacted]

CERTIFICATE OF ANALYSIS

Order information	
Customer	[redacted]

Product information	
Product description	Anhydrous Milk Fat IFT Tank truck
Lot number	BB0XJBS
Production date	09-05-2019

Chemical and physical analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Fat *	%	99.9	Min. 99.8	Calculated
Moisture *	%	0.1	Max. 0.1	IDF 23
FFA (as oleic acid) *	%	0.2	Max. 0.3	IDF 6
Peroxide value *	Meq O_2/kg	0.2	Max. 0.3	IDF 74

Microbiological analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Total plate count (30ºC)	CFU/g	<500	<500	ISO 4833
Total plate count (55ºC)	CFU/g	<2500	<2500	ISO 4833
Enterobacteriaceae	/g	Absent	Absent	ISO 21528-2
Yeast & moulds *	CFU/g	<10	<10	ISO 6611
Staphylococcus Aureus *	/g	Absent	Absent	ISO 6888-3
Salmonella	/250g	Absent	Absent	ISO 6579
Thermophilic aerobic and anaerobic spores *	CFU/g	<100	<100	
Sulphite Reducing Clostridia	CFU/g	<1	<1	Weenk
Bacillus Cereus	CFU/g	<10	<10	ISO 7932

Remarks
Results of parameters marked with * are based on monitoring program. Shelf life: Out of direct sunlight: 21 days at 45 °C when stored under nitrogen (During filling the product is flushed with nitrogen E 941)

Signing	
Date	29-08-19
Name	E. Modderman

[redacted]

[redacted]

[redacted]

CERTIFICATE OF ANALYSIS

Order information	
Customer	[redacted]

Product information	
Product description	Anhydrous Milk Fat IFT Tank truck
Lot number	BB0Z7VD
Production date	08-07-2019

Chemical and physical analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Fat *	%	99.9	Min. 99.8	Calculated
Moisture *	%	0.1	Max. 0.1	IDF 23
FFA (as oleic acid) *	%	0.2	Max. 0.3	IDF 6
Peroxide value *	Meq O_2/kg	0.2	Max. 0.3	IDF 74

Microbiological analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Total plate count (30ºC)	CFU/g	<500	<500	ISO 4833
Total plate count (55ºC)	CFU/g	<2500	<2500	ISO 4833
Enterobacteriaceae	/g	Absent	Absent	ISO 21528-2
Yeast & moulds *	CFU/g	<10	<10	ISO 6611
Staphylococcus Aureus *	/g	Absent	Absent	ISO 6888-3
Salmonella	/250g	Absent	Absent	ISO 6579
Thermophilic aerobic and anaerobic spores *	CFU/g	<100	<100	
Sulphite Reducing Clostridia	CFU/g	<1	<1	Weenk
Bacillus Cereus	CFU/g	<10	<10	ISO 7932

Remarks
Results of parameters marked with * are based on monitoring program. Shelf life: Out of direct sunlight: 21 days at 45 °C when stored under nitrogen (During filling the product is flushed with nitrogen E 941)

Signing	
Date	29-08-2019
Name	E. Modderman

[redacted]

[redacted]

[redacted]

CERTIFICATE OF ANALYSIS

Order information	
Customer	[redacted]

Product information	
Product description	Anhydrous Milk Fat IFT Tank truck
Lot number	BB0ZLR2
Production date	19-08-2019

Chemical and physical analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Fat *	%	99.9	Min. 99.8	Calculated
Moisture *	%	0.1	Max. 0.1	IDF 23
FFA (as oleic acid) *	%	0.2	Max. 0.3	IDF 6
Peroxide value *	Meq O_2/kg	0.2	Max. 0.3	IDF 74

Microbiological analysis				
Parameter	**Unit**	**Result**	**Standard**	**Method**
Total plate count (30ºC)	CFU/g	<500	<500	ISO 4833
Total plate count (55ºC)	CFU/g	<2500	<2500	ISO 4833
Enterobacteriaceae	/g	Absent	Absent	ISO 21528-2
Yeast & moulds *	CFU/g	<10	<10	ISO 6611
Staphylococcus Aureus *	/g	Absent	Absent	ISO 6888-3
Salmonella	/250g	Absent	Absent	ISO 6579
Thermophilic aerobic and anaerobic spores *	CFU/g	<100	<100	
Sulphite Reducing Clostridia	CFU/g	<1	<1	Weenk
Bacillus Cereus	CFU/g	<10	<10	ISO 7932

Remarks
Results of parameters marked with * are based on monitoring program. Shelf life: Out of direct sunlight: 21 days at 45 °C when stored under nitrogen (During filling the product is flushed with nitrogen E 941)

Signing	
Date	29-08-2019
Name	E. Modderman

[redacted]

From: Tao, Xin
To: Harry, Molly
Cc: Steinborn, Steven B.
Subject: RE: [Confidential and Privileged] FW: GRN 000898 - Request for Clarification
Date: Thursday, August 13, 2020 4:06:50 PM
Attachments: image001.png
Response to FDA's Follow-up Question for GRN 000898.pdf

Dear Ms. Harry,

We hereby submit our attached responses to FDA's follow-up question for GRAS Notice 000898 (GRN898). We also wonder can we set up a time for a quick conversation on the review timeline and next steps?

Best regards,
Steve and Xin

Xin Tao
Senior Associate

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

From: Harry, Molly [mailto:Molly.Harry@fda.hhs.gov]
Sent: Monday, August 03, 2020 6:24 PM
To: Steinborn, Steven B.
Cc: Tao, Xin
Subject: RE: GRN 000898 - Request for Clarification

Hi Mr. Steinborn,

In the original submission of GRN 000898 for AMF, the notice provides specifications for AMF in Table 2 (page 14). However, this table does not include specifications for heavy metals. In Table 5 (on page 18) you have provided limits for potential contaminants in samples of AMF. It is not clear to us if the parameters provided in the third column (Limits) are specifications for the ingredient AMF since these were not included in Table 2. We believe some of these parameters (e.g., heavy metals) could be specifications. Please confirm if you have set specifications for any of the parameters in Table 5 or if the limits in Table 5 are intended to be specifications. If these are not specifications, please provide specifications for the parameters listed in Table 5, including heavy metals.

Thanks,

Molly A. Harry
Regulatory Review Scientist

Office of Food Additive Safety, Division of Food Ingredients
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Molly.Harry@fda.hhs.gov

Tel: 240-402-1075

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

Via Electronic Mail

August 13, 2020

Molly A. Harry
Regulatory Review Scientist
Office of Food Additive Safety, Division of Food Ingredients
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Molly.Harry@fda.hhs.gov

Re: Response to FDA's Follow-up Question for GRN 000898

Dear Ms. Harry,

We hereby submit our responses to FDA's follow-up question for GRAS Notice 000898 (GRN 898), which we received on August 3.

For your ease of reference, we first copied FDA's question below, followed by our response:

- ***FDA Question****: In the original submission of GRN 000898 for AMF, the notice provides specifications for AMF in Table 2 (page 14). However, this table does not include specifications for heavy metals. In Table 5 (on page 18) you have provided limits for potential contaminants in samples of AMF. It is not clear to us if the parameters provided in the third column (Limits) are specifications for the ingredient AMF since these were not included in Table 2. We believe some of these parameters (e.g., heavy metals) could be specifications. Please confirm if you have set specifications for any of the parameters in Table 5 or if the limits in Table 5 are intended to be specifications. If these are not specifications, please provide specifications for the parameters listed in Table 5, including heavy metals.*

Response: We hereby confirm some of the parameters provided in Table 5 (but not in Table 2) are indeed specifications, which were incidentally left out of Table 2. These include aflatoxin and heavy metals. We apologize for any confusion. To clarify, we have added these specifications to the revised Table 2 below (partial table, with changes highlighted in red):

Table 2. Updated Specifications for Anhydrous Milk Fat (AMF)

Parameter	Unit	Limit	Test Method
Mycotoxins and Heavy Metals			
Aflatoxin M1	ppb	0.1	DIN EN ISO 14501 (2007-01)
Mercury (Hg)	ppb	50	ISO 21424:2018, "Milk, milk products, infant formula and adult nutritionals — Determination of minerals and trace elements — Inductively coupled plasma mass spectrometry (ICP-MS) method"
Lead (Pb)	ppb	50	Same as above
Cadmium (Cd)	ppb	10	Same as above
Total arsenic (As)	ppb	100	Same as above

Other than mercury, for which the specification of 50 ppb is slightly higher than the limit provided in Table 5, the specifications for aflatoxin and other heavy metals are the same as those reported in Table 5 of GRN 898. 1/

For the other items listed in Table 5 including PCBs, dioxins, and Cs 134/137, while we do not treat them as specifications of AMF for the purpose of GRN 898, we do monitor these levels in the ingredient and the data of the batch analysis also show the levels are in compliance with the limits in Table 5.

* * *

If any additional questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

Sincerely,

Steven B. Steinborn
steven.steinborn@hoganlovells.com
202 637 5969

1/ Further, we treat the "total arsenic" as part of the specifications for the AMF ingredient and view it unnecessary to establish specifications for both "total arsenic" and "inorganic arsenic" for AMF.

From: Tao, Xin
To: Morissette, Rachel; Steinborn, Steven B.
Cc: Harry, Molly; Hall, Karen
Subject: RE: additional questions for GRNs 000898, 000899, 000900
Date: Wednesday, October 21, 2020 12:03:29 PM
Attachments: image001.png

Dear Rachel, Molly, and Karen,

Please see our response to the additional questions below.

1. *In your response dated May 1, 2020, you stated the following:*

"The infant formula is a nutritionally complete and nutrient dense formula intended for use among full-term infants from birth and up to 18 months of age (or 9 kg) with increase energy requirements and/or fluid restrictions."

We note that "infants" are defined as 0-12 months of age. Thus, it is not clear whether your intended use for infants/toddlers aged 12-18 months is in the form of infant formula or other types of formula. We suspect that the 12-18 months subpopulation weighing less than 9 kg as a part of your intended use likely includes infants suffering from a particular affliction that would necessitate feeding infant formula. Please briefly and clearly explain your use for toddlers aged 12-18 months.

HL Response: we hereby clarify GRNs 898, 899, and 900 only cover the intended uses of the ingredients in exempt infant formula for infants (i.e., 0-12 months).

2. *Please confirm that the intended use in GRNs 000898, 000899, and 000900 does not include non-exempt infant formula or any other types of exempt formula not specified in the notice.*

HL Response: we hereby confirm the intended use in GRNs 898, 899, and 900 does not include non-exempt infant formula. The intended uses are for the ingredients to be used in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction as specified in the notices.

We trust we are responsive to the questions, and please let us know if the agency has any further questions.

Best regards,
Steve and Xin

Xin Tao
Senior Associate

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Thursday, October 15, 2020 3:46 PM
To: Tao, Xin <xin.tao@hoganlovells.com>; Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Cc: Harry, Molly <Molly.Harry@fda.hhs.gov>; Hall, Karen <Karen.Hall@fda.hhs.gov>
Subject: additional questions for GRNs 000898, 000899, 000900

Dear Xin and Steve,

We have two additional clarification questions regarding the intended use in these three notices. Please provide a response as soon as possible, within 5 business days, to facilitate the completion of our review of these notices.

1. *In your response dated May 1, 2020, you stated the following:*

   "The infant formula is a nutritionally complete and nutrient dense formula intended for use among full-term infants from birth and up to 18 months of age (or 9 kg) with increase energy requirements and/or fluid restrictions."

   We note that "infants" are defined as 0-12 months of age. Thus, it is not clear whether your intended use for infants/toddlers aged 12-18 months is in the form of infant formula or other types of formula. We suspect that the 12-18 months subpopulation weighing less than 9 kg as a part of your intended use likely includes infants suffering from a particular affliction that would necessitate feeding infant formula. Please briefly and clearly explain your use for toddlers aged 12-18 months.

2. *Please confirm that the intended use in GRNs 000898, 000899, and 000900 does not include non-exempt infant formula or any other types of exempt formula not specified in the notice.*

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

If you would like to know more about how we are managing the impact of the COVID-19 pandemic on our firm then take a look at our brief Q&A. If you would like to know more about how to handle the COVID-19 issues facing your business then take a look at our information hub.

About Hogan Lovells
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