From:	Morissette, Rachel
To:	Tania Porsgaard Bayer
Subject:	memorandum of meeting for osteopontin (OPN)
Date:	Thursday, July 11, 2019 2:40:00 PM
Attachments:	GPS000010_Memorandum of Meeting_Arla_6.17.19_transmittal.pdf image002.png

Dear Tania,

Please see attached the memorandum of meeting from our June 17, 2019 discussion on the intended use of osteopontin in infant formula.

In addition, we discussed providing Arla some potential starting points to consider in its search for expertise in different fields to address the safety and general recognition concerns for this intended use. I am providing a list of potential scientific and medical disciplines as a starting point below. Please let us know if we can provide further assistance.

- Developmental immunology
- Pediatric immunology
- Clinical immunology
- Immunological cell biology and biochemistry
- Developmental toxicology
- Pediatric physiology
- Milk biochemistry
- Gut physiology (especially postnatal)/gut microbiome
- Pediatric gastroenterology
- Biochemistry of osteopontin (from a basic science perspective)
- Food ingredient safety assessment/risk assessment (including familiarity with U.S. legal standards for food safety)
- Epidemiology
- Biostatistics

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

FDA U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING (COR2018-4008)

Date: September 19, 2018

Time: 11:00 a.m. – 12:00 p.m. EST

Location: FDA, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, 5001 Campus Drive, College Park, MD 20740

Participants:

Visitors:

Cathryn Sacra	EAS Consulting Group
Robin Guy	EAS Consulting Group
Peter Budde	Glanbia Foods, Inc.
Angela Walter	Glanbia Foods, Inc.
Noreen Hobayan	Glanbia Foods, Inc.
Ankur Jhanwar	Glanbia Foods, Inc.
Brent Peterson	Glanbia Foods, Inc.
Joe Milligan	Glanbia Foods, Inc.

CFSAN/OFAS/DBGNR:

Rachel Morissette, Ph.D.	HFS-255
Jeremy Mihalov, M.S.	HFS-255
Kotaro Kaneko, Ph.D.	HFS-255
Jeremiah Fasano, Ph.D.	HFS-255
Perry Wang, Ph.D.	HFS-717

CFSAN/ONFL/IFMFS:

Andrea Lotze, M.D.	HFS-850
Carrie Assar, Pharm.D.	HFS-850
Suzanne Wolcoff, M.S., R.D.	HFS-850

Subject: Pre-submission meeting for the intended use of bovine lactoferrin (bLf) in infant and toddler formulas

In an electronic mail message dated August 13, 2018, Cathryn Sacra requested a meeting with FDA/DBGNR to discuss a GRAS conclusion for the intended use of bLf (tradename Bioferrin®) as an ingredient in infant and toddler formulas at a use level up to 1 g/L. Prior to the meeting, Ms. Sacra provided a draft copy of the proposed GRAS notice. DBGNR informed her that the notice would not be reviewed in its entirety, but if there were specific sections she wanted us to review that we could accommodate that. Glanbia Foods, Inc. (Glanbia) stated that their bLf is sourced from cow's milk whey obtained from cheese production and is in accordance with all applicable U.S. Department of Agriculture and FDA regulations for the manufacture of dairy products.

Glanbia discussed the identity of its bLf and stated that it has the same chemical properties to the subject of GRN 000465.[1] Glanbia presented Fourier-transform infrared spectroscopy (FTIR) data to support their view that their bLf is structurally equivalent to that from GRN 000465. DBGNR pointed out that FTIR is better suited for small molecules, not proteins. Therefore, DBGNR suggested that other analytical methods could be used and presented in the GRAS notice to support structural similarities to other bLf proteins. DBGNR noted that the arsenic specification shown was higher than seen in past notices and also suggested specifying limits for lead and *Cronobacter sakazakii*. In support of the intended use level, which FDA noted is up to 10-fold greater than use levels addressed in prior GRAS notices (e.g. GRNs 000465 and 000669[1]), Glanbia stated that human lactoferrin is present in human breast milk and colostrum at up to 7 g/L. Additionally, Glanbia stated that bLf is approved for use worldwide at levels up to 1 g/L. Glanbia presented the estimated exposures from its intended uses of bLf for infant and toddler populations and stated that the intended uses are self-limiting due to the maximum protein level and quality, as determined by the amino acid profile, permitted under 21 CFR 107.100. Additionally, Glanbia stated that infants may be exposed to bLf from consumption of cow's milk-based infant formulas already marketed in the U.S. containing up to 0.6 g/L bLf.[2] DBGNR noted that as science evolves, we may have new questions about whether data previously used to establish safety continues to be generally accepted as sufficient by qualified experts.

To support a safety conclusion for the intended uses of bLf, Glanbia discussed acute and sub-chronic toxicity studies in rats, as well as human clinical trials involving infants and toddlers. Additionally, Glanbia discussed bLf in terms of allergenicity and the required labeling under FALCPA.

After hearing the safety data and other information presented by Glanbia, DBGNR noted that we would have questions on the following points in response to a GRAS notice based on that data, including, but not limited to, the following:

- Given that bLf has been reported to exhibit a variety of physiological activities in humans, including immunomodulation, we would ask about the basis for concluding that the intended use level of bLf would not alter the developmental trajectory of the immature infant immune system in potentially adverse ways. Traditional toxicological study endpoints do not provide meaningful information on this point. Evidence of general acceptance in the scientific community on the lack of adverse consequences from the intended use of bLf, particularly among experts qualified to assess postnatal development of the human infant immune system, would be extremely helpful in addressing this question.

---

[1] Cow's milk-derived lactoferrin was the subject of GRNs 000465 (use level 130 mg/L) and 000669 (use level 130-140 mg/L). We evaluated these notices and responded in letters dated February 18, 2014, and March 9, 2017, stating that we had no questions at that time regarding Morinaga Milk Industry Co., Ltd. and Synlait Milk, Ltd.'s GRAS conclusions, respectively.

[2] FDA has not evaluated a GRAS conclusion through the GRAS Notification Program for the intended use of bLf in infant formula at a use level higher than 140 mg/L.

- Given the intended population, intended use level, and properties of bLf, we would ask questions about the evidence that the scientific data relied on by Glanbia is generally available and generally accepted at the present time by experts with the appropriate expertise. The significance and utility of published scientific literature and of GRAS panels in providing evidence of general recognition was discussed. FDA noted that a GRAS panel is only one strategy that can be employed as evidence of general acceptance. However, if used, a GRAS panel is only effective in generating such evidence when the appropriate expert disciplines are represented on the panel. In this case, representative expertise in infant immunology and immunomodulatory proteins would be important if the panel's conclusion were being used to support the contention that bLf used at 1 g/L is recognized by qualified expert communities as safe for its intended use.

- Considering the focus of our questions, we would consider evidence for the intended use of bLf based on the previous conclusions of authoritative bodies as supportive given that such bodies did not consider and dismiss the issues we had raised above. This is also true of current uses of bLf in infant formula above 130 mg/L.

- To the extent that Glanbia's GRAS conclusion incorporates a comparison of lactoferrin levels in bovine and human milk, we would have questions about the basis for concluding that these proteins are comparable in biological activity in humans, and the significance of any known differences in this activity.

- While bLf in infant formula at lower use levels has been the subject of several GRAS conclusions for which FDA had no questions at the time, we emphasized that science evolves over time. Therefore, the data and information used to support a conclusion that an intended use is safe and accepted by qualified experts may also evolve over time. We would have some questions about bLf's immunomodulatory activities and the basis for concluding it was consistent with GRAS status in infant formula in response to a new notice regardless of use level, although the extent of our questions would differ depending on the specific use level.

In addition to the points discussed above, DBGNR attendees provided the following recommendations:

- Specify the category of infant formula and the intended infant population (e.g. non-exempt infant formula for term infants, milk or soy-based).

- Glanbia stated that the final product is specified to contain up to 5% "other proteins." In the notice, provide a discussion on the identity of the other proteins present in the final product.

- When presenting studies done in a pre-term infant population in the notice, provide a discussion bridging this information to full-term infant populations.

- Glanbia could submit a FOIA request for the amendments to GRAS notices they intend to incorporate into the current notice so that the full-breath of the review process for those notices is available for reference.

Ms. Sacra sent a follow-up email on October 10, 2018 with an attached memorandum of meeting that she and the Glanbia participants wrote to share their understanding of the outcome of this pre-submission meeting. Based on the contents of this memo, DBGNR will recommend a follow-up meeting to clarify the points discussed and options for moving forward.

Rachel Morissette -S

Digitally signed by Rachel Morissette -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014346356, cn=Rachel Morissette -S
Date: 2018.10.23 08:15:10 -04'00'

_____

Rachel Morissette, Ph.D.

ATTACHED:

1. Meeting Request (email dated August 13, 2018)
2. Email dated September 18, 2018
3. Email dated October 10, 2018
4. Powerpoint Presentation
5. Draft GRAS notice dossier

R/D:HFS-255:RMorissette:9/25/18, 10/2/18, 10/18/18, 10/23/18
Edit/Comment/Init:HFS-255:JFasano:10/1/18, 10/2/18, 10/17/18
Edit/Comment/Init:HFS-255:JMihalov:9/26/2018
Edit/Comment/Init:HFS-255:KKaneko:9/25/18
Discussion:HFS-255:RMorissette,JFasano,PGaynor,SCarlson:10/17/18
Edit/Comment:HFS-255:PGaynor:10/17/18, 10/22/18
F/T:HFS-255:RMorissette:10/23/18

From:	Cathryn Sacra
To:	Morissette, Rachel
Cc:	Robert Martin
Subject:	RE: GRAS Pre-submission Meeting Request
Date:	Monday, August 13, 2018 2:58:04 PM
Attachments:	image002.png Pre-Submission Letter8-13-18.pdf

Dear Dr. Morissette,

I am attaching a letter requesting a pre-mission meeting. Please let me know if any of the dates we propose will work for you and your team.

Best regards,
Cathryn

Cathryn W. Sacra
Director of Labeling and Cosmetic Services
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From: Cathryn Sacra
Sent: Friday, August 03, 2018 12:47 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Robert Martin <rmartin@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Dear Dr. Morissette,

Thank you. Once I have some new dates from our team for your consideration, I will reach out to you with our meeting request.

Best regards
Cathryn

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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, August 03, 2018 11:29 AM
To: Cathryn Sacra <csacra@easconsultinggroup.com>
Subject: FW: GRAS Pre-submission Meeting Request

Dear Ms. Sacra,

Please feel free to contact me when you are ready to move ahead with a pre-submission meeting for this GRAS notice.

Best regards,

Rachel Morissette, Ph.D.
Consumer Safety Officer

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: West-Barnette, Shayla
Sent: Friday, August 03, 2018 10:55 AM
To: Cathryn Sacra <csacra@easconsultinggroup.com>; Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Robert Martin <rmartin@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Hello Ms. Sacra,

Thank you for your message.

I am asking Dr. Rachel Morissette to set up your meeting (she is copied on this message). She will reach out to you shortly.

Regards,

Shayla West-Barnette, Ph.D.
Supervisory Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Shayla.WestBarnette@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

From: Cathryn Sacra [mailto:csacra@easconsultinggroup.com]
Sent: Friday, August 03, 2018 10:40 AM
To: West-Barnette, Shayla <Shayla.WestBarnette@fda.hhs.gov>
Cc: Robert Martin <rmartin@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Dear Dr. West-Barnette,

I had sent an email in July requesting a pre-submission meeting with FDA with some proposed dates in August. We are still working on the last stages of the draft dossier and would like to withdraw the request for the proposed dates. We will send a new request for a pre-submission meeting when we have finalized the draft dossier.

Thank you,
Cathryn Sacra

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From: Cathryn Sacra
Sent: Thursday, July 12, 2018 9:32 AM
To: Shayla.WestBarnette@fda.hhs.gov
Subject: GRAS Pre-submission Meeting Request

Dear Dr. West-Barnette,

With the attached letter, I am requesting a pre-submission meeting with you and your colleagues to discuss a GRAS Notice for the use of bovine lactoferrin in term infant formula. Please let me know if any of our proposed dates are acceptable to you.

Best regards,
Cathryn Sacra

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EAS CONSULTING GROUP

Specializing in FDA Regulatory Matters

August 13, 2018

Shayla West-Barnette, Ph.D.
Supervisory Consumer Safety Officer
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition, FDA
5001 Campus Drive
College Park, MD 20740
240-402-1262 (direct)
Shayla.WestBarnette@fda.hhs.gov

Dear Dr. West-Barnette:

On behalf of Glanbia Nutritionals, we are requesting a pre-submission meeting with you and your colleagues to discuss a GRAS Notice for the use of bovine lactoferrin (Bioferrin®) in term infant formula and toddler foods. This request is in accordance with FDA's guidance on pre-submission meetings intended to solicit FDA's input on the draft GRAS document where FDA's scientists, Glanbia Nutritionals, and EAS can discuss the draft document to obtain agreement on the sufficiency of the document before formally submitting the GRAS Notice to FDA.

The dates that we are proposing for this meeting are: August 27, August 28 and August 29. After the meeting date has been agreed upon, we will send you copies of the draft GRAS Notice for your use in preparation of our meeting.

Bioferrin® is substantially equivalent to the bovine lactoferrin that was the basis of GRAS Notices 465 and 669 for the same uses. We have relied heavily on the data and information in those documents to support this GRAS determination.

Attending the meeting, in person,will the individuals listed below>

Glanbia
Noreen Hobayan, Director, Regulatory Affairs
Ankur Jhanwar, Senior Manager, Technical Services
Brent Peterson, Senior Director, Research and Development
Joe Milligan, Plant Manager, Richfield
Angela Walter, Senior Product Manager, Product Management

Second Science, Inc.

Jeanne Hoskins

EAS Consulting Group, LLC

Cathryn Sacra, Director Labeling and Cosmetics
Robin Guy, Independent Expert Consultant
Robert Martin, Independent Advisor, Food Additive Safety

Should you have questions regarding this request, please feel free to contact me. Thank you for your cooperation and prompt attention to this request.

Sincerely,

Cathryn W. Sacra
Director, Labeling and Cosmetics

From:	Cathryn Sacra
To:	Morissette, Rachel
Cc:	Robert Martin; Robin Guy
Subject:	FW: GRAS Pre-submission Meeting Request
Date:	Tuesday, September 18, 2018 1:07:47 PM
Attachments:	image001.png image007.png image013.png image019.png image025.png image031.png image037.png image043.png
Importance:	High

Rachel,

The two main points that we would like FDA to consider are:

1. Compare the specifications in table II-14 and infrared spectra in figures II-3a - II-3f listed on pages 34-38 that show Bioferrin is identical to the bLfs that have been approved by FDA.
2. That use levels up to 100 mg/L is safe for use in infant formula as established by the opinions of other international regulatory bodies and FDA's reviews of other bLf GRNs and is supported by the draft GRAS dossier.

Thank you

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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Tuesday, September 18, 2018 8:10 AM
To: Cathryn Sacra <csacra@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Thank you. Are there specific sections of the dossier that you would like to us to take a look at? We will not be able to review the entire dossier at this time, but if there are specific questions that you have we can try to address them at the meeting.

Best,

Rachel

From: Cathryn Sacra <csacra@easconsultinggroup.com>

Sent: Monday, September 17, 2018 3:55 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: GRAS Pre-submission Meeting Request

Dear Rachel,

I am attaching the dossier that is the subject of the pre-submission meeting on Wednesday. I will follow with the slide deck.

Best regards,
Cathryn

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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Monday, September 17, 2018 1:15 PM
To: Cathryn Sacra <csacra@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

You're welcome!

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Cathryn Sacra <csacra@easconsultinggroup.com>
Sent: Monday, September 17, 2018 1:14 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: GRAS Pre-submission Meeting Request

Thank you!

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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Monday, September 17, 2018 1:12 PM
To: Cathryn Sacra <csacra@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Ok, thanks. The official address of our campus is 5001 Campus Drive, College Park MD. However, there's two buildings on campus, and we are located in the smaller of the two. You might tell the Uber driver to put in 4300 River Rd. as the address, because our building (University Station) is actually on River Rd, not Campus Drive. The security entrance for the parking lots is located closer to our building and is on River Rd, so I would suggest having the driver let you off at the security station and then letting the guards direct you to the correct entrance of the building. Make sure they know you're looking for University Station and not the Wiley building. Unfortunately in the past, the guards have directed some visitors to the larger Wiley building by mistake and then they had to walk all the way back. My desk number is 240-402-1212 if you have any issues.

Best,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Cathryn Sacra <csacra@easconsultinggroup.com>
Sent: Monday, September 17, 2018 1:03 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: GRAS Pre-submission Meeting Request

Thank you. At the moment, we are planning on Uber, but if that changes, I will send the information. As Dr. Martin will not be able to attend, do you have any additional information on the address? I confess I was counting on Bob to get us there as he knows the location so well and I have not been to your offices.

Thank you

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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Monday, September 17, 2018 1:00 PM
To: Cathryn Sacra <csacra@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Hi Cathryn,

Thanks for the update. Just a reminder to send the make, model, and license numbers of any vehicles that will be parking on site at least an hour before the start of the meeting so we can get that info to the security office.

Thanks,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
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rachel.morissette@fda.hhs.gov

From: Cathryn Sacra <csacra@easconsultinggroup.com>
Sent: Monday, September 17, 2018 12:49 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: FW: GRAS Pre-submission Meeting Request

Dear Rachel,

I have updated our attendee list for our meeting on Wed, September 19 at 11:00. Dr. Martin is unable to attend the meeting because of a death in his family. I will be sending a copy of the dossier and our slide deck later this afternoon.

Glanbia:

Peter Budde, Senior Director, Product Management

Angela Walter, Senior Product Manager, Product Management

Noreen Hobayan, Director, Regulatory Affairs

Ankur Jhanwar, Senior Manager, Technical Services (Foreign National – from India)

Brent Peterson, Senior Director, Research and Development

Joe Milligan, Plant Manager, Richfield

EAS Consulting Group:

Robin Guy, Expert Consultant
Cathryn Sacra, Director, Labeling and Cosmetics

Best regards,
Cathryn

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From: Cathryn Sacra
Sent: Thursday, August 23, 2018 3:18 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: GRAS Pre-submission Meeting Request

Dear Rachel,

Thank you for confirming the date. We look forward to the meeting. We will have a slide presentation and will forward them to you when they are completed. Please let me know if I can

forward them as an attachment in an email. The attendees are listed below and will be participating in person. There is one foreign national attending. Please let me know what additional information you will need from him.

Glanbia:

Peter Budde, Senior Director, Product Management

Angela Walter, Senior Product Manager, Product Management

Noreen Hobayan, Director, Regulatory Affairs

Ankur Jhanwar, Senior Manager, Technical Services (Foreign National – from India)

Brent Peterson, Senior Director, Research and Development

Joe Milligan, Plant Manager, Richfield

EAS Consulting Group:

Robin Guy, Expert Consultant
Cathryn Sacra, Director, Labeling and Cosmetics

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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Monday, August 20, 2018 2:09 PM
To: Cathryn Sacra <csacra@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Dear Cathryn,

Thank you for your email. I scheduled your meeting for Wednesday Sept. 19, 2018 from 11 am -12 pm EST. I just have a few questions for you below.

1. How many people will be attending the meeting? Please provide their names and affiliations.

2. Will you or others be attending in person or will you require a WebEx remote meeting access?

3. Will any non-U.S. citizens be attending the meeting in person?

4. Will you be showing PowerPoint slides or require any other computer or technical accommodations? If you are giving a presentation and would like to send the slides ahead of time, I can circulate them to the review team. Please note that any materials provided to FDA prior to the meeting may be releasable under the Freedom of Information Act. Therefore, please do not provide any confidential or trade secret information in the materials you provide to us.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Cathryn Sacra [mailto:csacra@easconsultinggroup.com]
Sent: Monday, August 20, 2018 1:42 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: GRAS Pre-submission Meeting Request

Dear Rachel,

I apologize for the delay in responding as I was waiting for several people to respond on available dates.

We would like to request a meeting on September 18, 19th or 20th.

Best regards,
Cathryn

Cathryn W. Sacra
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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Monday, August 20, 2018 9:16 AM
To: Cathryn Sacra <csacra@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Dear Cathryn,

I'm following up on my email from last Monday. Are you still interested in scheduling a pre-submission meeting?

Best regards,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Morissette, Rachel
Sent: Monday, August 13, 2018 3:03 PM
To: 'Cathryn Sacra' <csacra@easconsultinggroup.com>
Subject: RE: GRAS Pre-submission Meeting Request

Dear Cathryn,

Thank you for your request. Unfortunately, we will not be able to accommodate the dates that you requested in your letter. Please provide three potential alternate dates and times starting in September or October that might also work, and I will try to accommodate your schedule as best as possible.

Best regards,

Rachel

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Consumer Safety Officer

Center for Food Safety and Applied Nutrition
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U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From:	Cathryn Sacra
To:	Morissette, Rachel
Subject:	RE: pre-sub meeting memo on bovine lactoferrin
Date:	Wednesday, October 10, 2018 5:13:26 PM
Attachments:	image007.png Glanbia - Memorandum of Meeting with CFSAN FINAL 10-10-2018.docx.pdf

Rachel,

Thank you for the update. In the meantime, we have put together a Memorandum of Meeting with our understanding of the issues that were raised in the meeting, which I have attached. Please let me know if you or the team have any comments or questions.

Best regards,
Cathryn

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csacra@easconsultinggroup.com
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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Thursday, October 04, 2018 9:15 AM
To: Cathryn Sacra <csacra@easconsultinggroup.com>
Subject: pre-sub meeting memo on bovine lactoferrin

Hi Cathryn,

I just wanted to let you know that I haven't forgotten about sending you the meeting memo. We're waiting on a staff member to weigh in on the memo before I can finalize and send it to you. Hopefully within the next week or so I should have it to you.

Best,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

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FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum of Meeting

On Wednesday, September 19, 2018, representatives from Glanbia Nutritionals and EAS Consulting Group met with officials from CFSAN to discuss a draft GRAS notice for the use of bovine lactoferrin (bLf) in infant formula and toddler foods. The meeting took place at the CFSAN Office of Food Additive Safety, College Park, MD from 11:00 a.m. – 12 noon. The individuals attending the meeting are listed below.

Visitors

Glanbia Nutritionals

Angela Walter, Senior Product Manager, Lactoferrin
Noreen Hobayan, Director of Quality Assurance, Specialties
Peter Budde, Senior Director Product Management, Lactoferrin
Brent Peterson, Senior Director, Ingredient/Bioactives R&D
Ankur Jhanwar, Senior Technical Services Manager

EAS Consulting Group

Cathryn Sacra, Director of Labeling and Cosmetic Services
Robin Guy, MS, DABT, RQAP-GLP

CFSAN Attendees

NOTE: A sign-in sheet was maintained. Regrettably, we did not get a copy of the sign-in sheet. Based on the introductions, we understood that the CFSAN representatives were from OFAS and the Infant Formula Group.

After introductions of the meeting attendees, Ms. Hobayan thanked the CFSAN representatives for arranging this meeting to allow Glanbia Nutritionals (Glanbia) and EAS to discuss their draft GRAS Notice for its use in infant formula and toddler foods and to seek advice and input from CFSAN as Glanbia planned to go forward on this project. This was followed by a brief introduction of Glanbia by Ms. Hobayan. Glanbia's bLf (Bioferrin) was then discussed by Glanbia and EAS representatives to include: its formula, regulatory status, chemistry, exposure, and safety information.

The meeting revolved around a PowerPoint presentation prepared by Glanbia and EAS that had been submitted to CFSAN in advance of the meeting. In advance of the meeting, Glanbia and EAS had indicated to CFSAN that there were two questions that they hoped to resolve and confirm at the meeting:

1. Bioferrin is substantially equivalent to the bovine Lf's that were previously reviewed by FDA for use in IF. Comparison of the specifications in table II-14 and infrared spectra in figures II-3a - II-3f listed on pages 34-38 of the draft GRN establish that Bioferrin is identical to the bLfs that have been approved by FDA.

2. That use levels up to 1000 mg/L is safe for use in infant formula as established by the opinions of other international regulatory bodies and FDA's reviews of other bLf GRNs and is supported by the draft GRAS dossier.

There was good discussion related to the product. The CFSAN representatives essentially agreed that Bioferrin is equivalent to the bLfs that FDA had previously evaluated. Among the questions/issues raised by an OFAS toxicologist were:

- The FDA Toxicologist stated that the Agency has changed the way that they consider GRAS since GRN 669 for bioactive molecules. The Toxicologist stated that they want to make sure that there is a reasonable certainty of no harm, especially since this is for infants who inherently have an underdeveloped immune system. We note that Bioferrin in this GRN is intended for use in term infants who are presumed to be healthy at birth. Clarification is needed as to exactly what the toxicologist was referring to here.
- Most of the studies conducted have specific normal toxicological endpoints, especially with the studies conducted in adult rats. He implied that he didn't know how these types of studies would be appropriate with regard to infant endpoints. He stated that he had not read the dossier; however, since the clinical trials were set up to address specific endpoints, we need to address how this relates to the infant, and how does this effect the preterm and VLBW infants. Again, as noted above, this is confusing as the GRN use is intended for term infants and not VLBW infants or premature infants, etc.
- He stated that even if EFSA found this use to be okay, we don't know if they did the correct evaluations.
- He wants the GRAS document to address:

    The functionality of the protein
    Intended population
    Studies not looking at more subtle safety endpoints such as immunological effects.

As this was not clear to us, it was suggested that we contact the toxicologist and request any pertinent references that may have led to his concerns in this area.

The meeting ended at 12 noon. The visitors thanked the CFSAN representatives for their input.

Cathryn W. Sacra
Director, Labeling and Cosmetics
EAS Consulting Group

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GLANBIA NUTRITIONALS LACTOFERRIN

BIOFERRIN®

Agenda

- **Introduce Participants**
  - Glanbia
  - EAS
  - FDA

- **Introduction to Glanbia Nutritionals**

- **General Introduction and Overview**

Agenda (continued)

- **Dossier Highlights**
  - Bioferrin® Background Information
  - Dietary Exposure
  - Self Limiting Levels of Use
  - Regulatory Assessments
  - Current Uses
  - Safety Related Information

- **Summary and Conclusions**

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Participants

- **Glanbia Nutritionals**
  - Angela Walter
  - Noreen Hobayan
  - Brent Peterson
  - Ankur Jhanwar
  - Peter Budde
- **EAS Consulting**
  - Edward Steele
  - Robert Martin
  - Robin Guy

FDA/CFSAN/OFAS

Glanbia Nutritionals develops dairy protein, plant nutrition, flavor, premix, and bioactive solutions for the food, beverage, supplement and animal nutrition industries.

We are part of a global organization

- Glanbia Plc is a global nutrition company.
- We are grounded in science and nature.
- We are dedicated to delivering better nutrition for every step of life's journey

Glanbia's vision is to be one of the world's top performing nutrition companies, trusted to enrich lives every day.

General Introduction

- **The name of the substance under consideration is bovine lactoferrin (bLf) also referred to as lactotransferrin. The tradename for Glanbia's bLf is Bioferrin®.**

- **The purpose of this notice is to substantiate the GRAS determination for Glanbia's bovine lactoferrin (bLf) at intended use levels up to 1 g/L (1000 mg/L) in infant or toddler formula.**

- **The statutory basis for this GRAS determination is scientific procedures in accordance with 21 CFR 107.30 (a) and (b).**

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Bioferrin ®

Glanbia's bLf is approved for use by several regulatory bodies for use in food, including infant formula (IF), among them being FSAI, and EFSA and it meets the regulatory standard for use in China.

Currently, Glanbia markets its brand of bovine lactoferrin, Bioferrin®, in over 130 countries for a variety of uses including IF.

Glanbia convened an expert panel who has concluded Bioferrin is GRAS and intends to notify FDA that we will market Bioferrin® for IF use in the U.S.

[redacted]

Overview

- Lactoferrin is present at levels ranging from 1-3 g/L in human breast milk to 6-7 g/L in colostrum (Montagne et al., 2001).
- Bovine lactoferrin is approved in the EU at maximum use level in infant formula at 1g/L (Annex II of 2012/725/EU) after EFSA safety assessment (17 July 2012).
- Per the Food Safety Authority of Ireland, Glanbia's Bioferrin® is substantially equivalent to bLf authorized to Morinaga (2012/725/EU), the latter of which is GRAS in US (GRN 465) .
- Currently in US, bLf is GRAS at less than the approved EU level (GRAS Notices GRN 465 [Morinaga 2014]) - at 130 mg/L); and GRN 669 (Synlait 2017) - at 130-140 mg/L infant formula.
- There is history of use of lactoferrin in US infant formula at levels exceeding the current US GRAS levels e.g., Mead Johnson's ENSPIRE infant formula in US has lactoferrin at 600 mg/L.
- This GRAS notice is for Glanbia's bLf at intended use levels up to 1 g/L (1000 mg/L) in infant or toddler formula.
- This GRAS notice gives examples of growth and safety and other clinical data in infants up to 1g/L in infant formula.

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Background Information

- **Bioferrin is bovine lactoferrin (bLf) which occurs naturally in cows' milk.**
- **Bovine lactoferrin, manufactured by various processes and manufacturers, has previously been determined to be GRAS for specific uses including infant formula.**

GRN NO.	SUBSTANCE	CLOSURE DATE	APPLICANT	PURPOSE / USE
669	Bovine milk-derived lactoferrin	Mar 9, 2017	Synlait Milk Ltd New Zealand	For use as an ingredient 130-140 mg/L infant formula (ready-to-feed (RTF) or prepared for consumption from powder or liquid concentrate and in follow-on formula at a level of 150 mg/L RTF or prepared for consumption from powder.
465	Cow's milk-derived lactoferrin	Feb 18, 2014	Morinaga Milk Industry Co. Ltd	For use as an ingredient at a level of 130 mg/L of formula (ready-to-feed or prepared for consumption from powder or liquid concentrate)
464	Cow's milk-derived lactoferrin	Feb 18, 2014	Morinaga Milk Industry Co. Ltd	For use as an ingredient in cow's milk-based products [yogurts (100 milligrams (mg) per 100 grams (g)), powdered milk (400 mg/100 g), and milk-based frozen desserts (200 mg/100 g)] and in chewing gum (30 mg/g)
77	Milk-derived lactoferrin	Aug 14, 2001	DMV International	Sports and functional foods at 100mg / serving

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Identity

- **bLf is an iron-binding glycoprotein of approximately 77 kDa and consists of a single polypeptide chain of 689 amino acids.**

- **It is isolated from cow's milk whey via ion exchange and subsequent ultra-filtration steps. Finally it is dried by spraying and large particles are sieved out.**

Physical-chemical properties of bovine lactoferrin

Property	Typical Value	Method
Moisture	less than 4.5 %	**AOAC 927.05 17th Ed.**
Ash	less than 1.5 %	**AOAC 945.46 Gravimetric**
Arsenic	less than 2 mg/kg	**EPA 7010 GFAA**
Iron	less than 350 mg/kg	**Glanbia Method**
Protein of which is bLf other proteins	>93 % >95 % < 5 %	**SMEDP 17th Ed., Chapter 15 Ion Exchange – Glanbia Method**
pH (2 % solution, 20 °C)	5.2 to 7.2	**pH Meter**
Solubility (2 % solution, 20 °C)	complete	**Glanbia Method**

Identity

- **Bovine lactoferrin is well characterized. Chemical Abstracts Service Registry Number (CAS Reg. No.) 146897-68-9 is a 689 amino acid glycoprotein, with five potential glycosylation sites (Mead and Tweedie, 1990; Pierce et al., 1991).**
- **It contains N-glycosidically-linked glycans possessing N-acetylneuraminic acid, galactose, mannose, fructose, N-acetylglucosamine, and N-acetylgalactosamine (Coddeville et al., 1992). The generally accepted physical and chemical properties of bLf are outlined in Table 2 (GRN 669, page 000026)).**

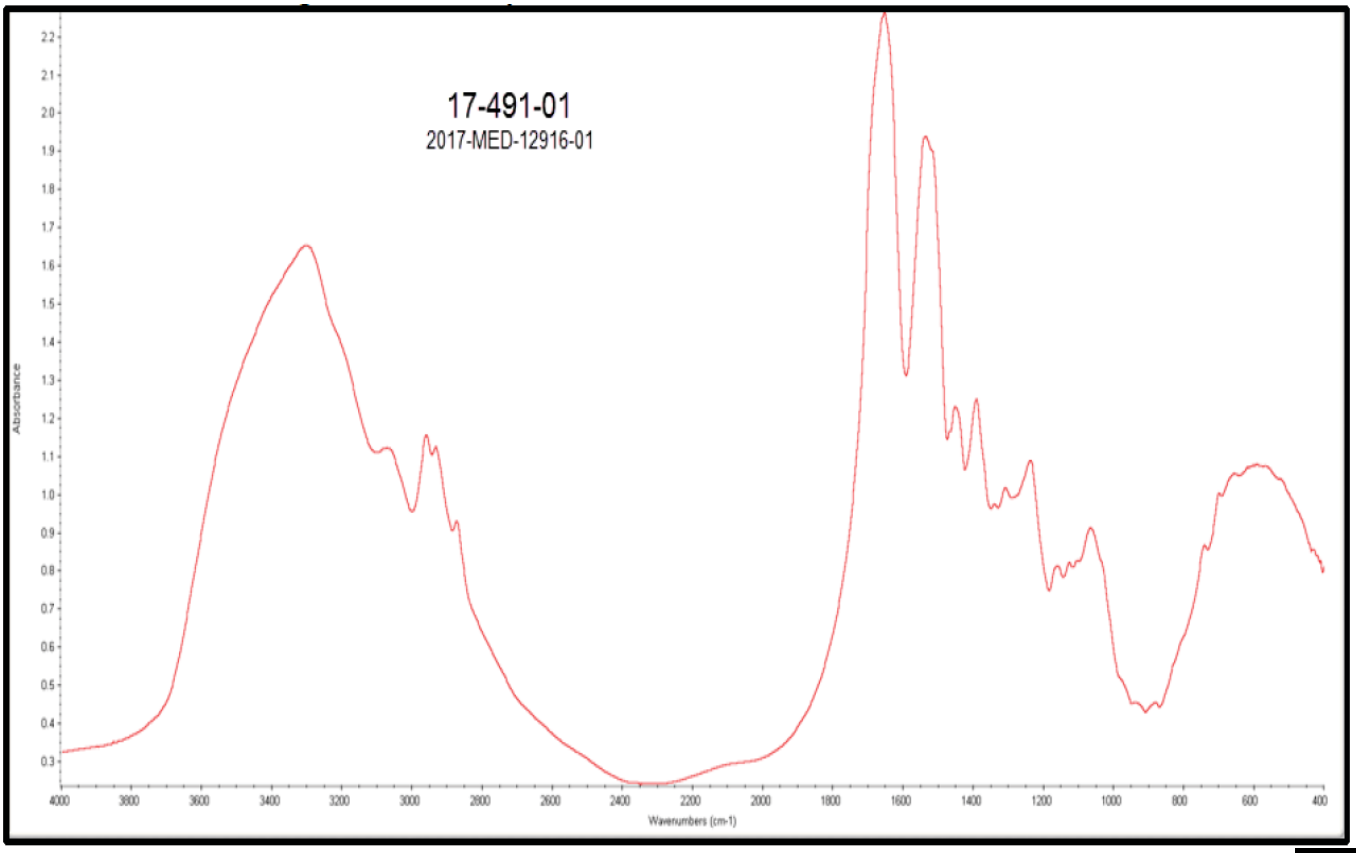
Physical and Chemical Properties of Bovine Lactoferrin

Property		Value	Reference
Molecular Mass (Da)			
	Sedimentation co-efficient (aqueous)	77,100 ± 1,500	Castellino et al. (1970)
	SDS-Page	76,400 ± 2,400	Castellino et al. (1970)
	Iron Titration	78,000	Aisen and Leibman (1972)
Isoelectric Point (pH)			
	Chromatofocusing	8.2-8.9	Shimazaki et al. (1993)
	Isoelectric focusing	9.5-10.0	Yoshida and Xiuyun (1991)
Absorption Spectra			Aisen and Leibman (1972)
	Apo-form at 280 nm	12.7	
	Holo-form at 470 nm	0.400	
Protease sensitivity		Relatively low	Brines and Brock (1983)
Iron-binding			Aisen and Leibman (1972)
	Equilibrium dialysis (K1 x 10^{-4})	3.73	
Thermal Denaturation			Paulsson et al. (1993)
	Apo-Lf denaturation (T_{max}: °C)	71 ± 0.3 and 90 ± 0.3	
	Apo-Lf enthalpy (ΔH_{cal}: J/g)	12 ± 0.4 and 2 ± 0.5	
	Holo-Lf denaturation (T_{max}: °C)	65 ± 0.3 and 93 ± 0.3	
	Holo-Lf enthalpy (ΔH_{cal}: J/g)	2 ± 1 and 37 ± 1	

[redacted]

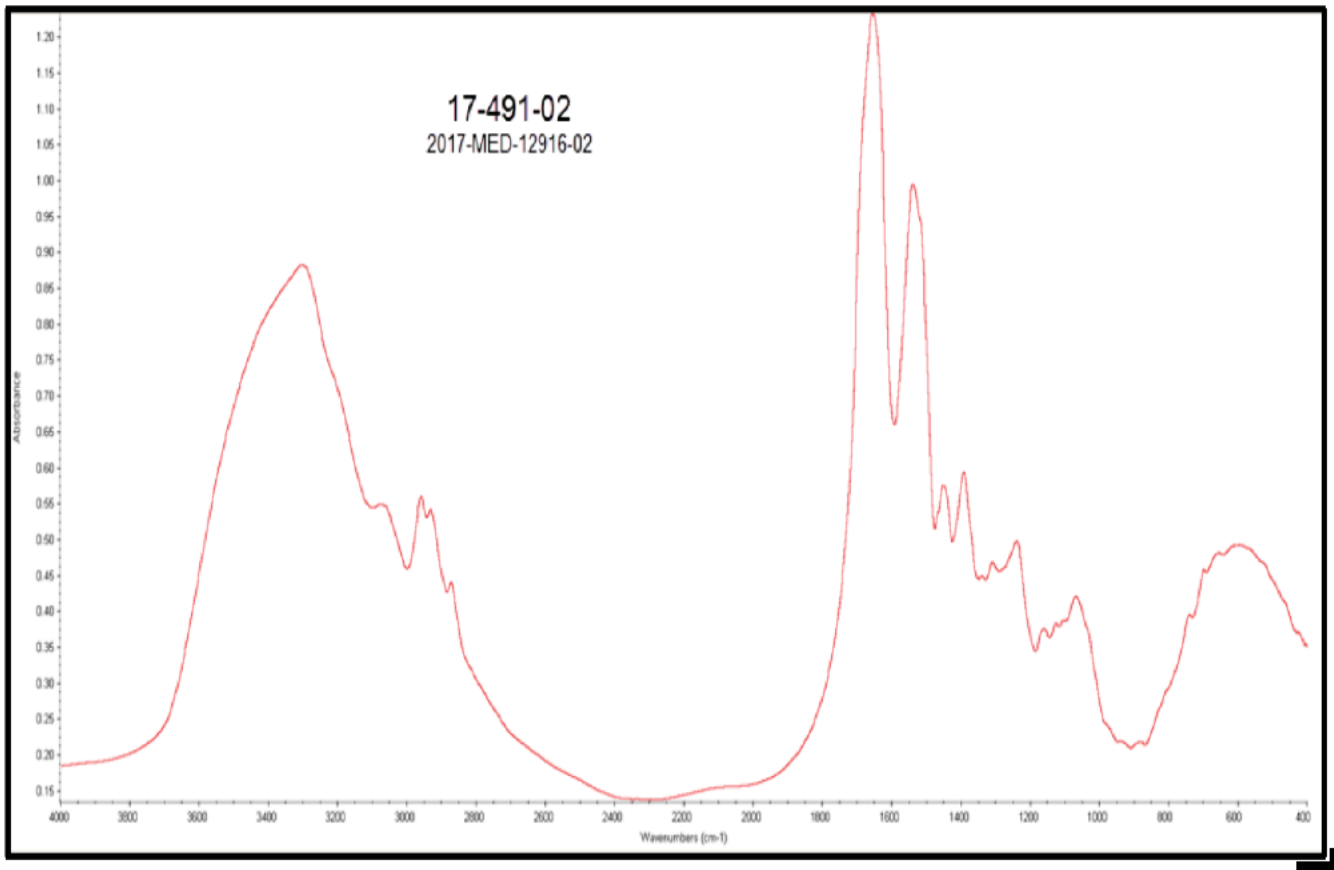
(b) (4)

Bioferrin® bLf FTIR

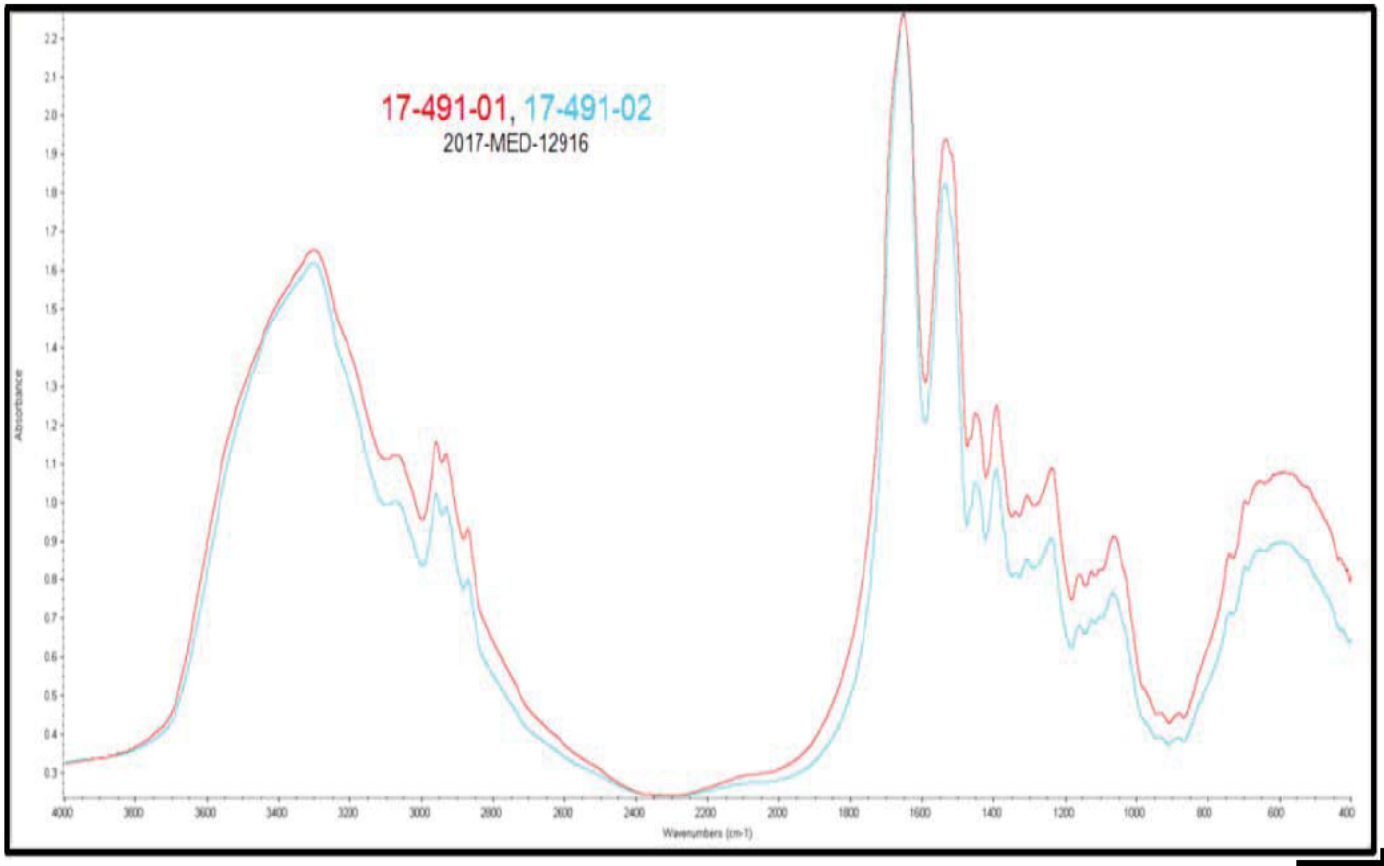


[redacted]

Morinaga bLf FTIR



Bioferrin® & Morinaga bLf FTIR Overlay



[redacted]

17-491-01 = Bioferrin® **17-491-02 = Morinaga bLf**

Dietary Exposure

- **The highest concentration of human lactoferrin (hLf) is found in milk and colostrum (5-7 g/L) (Trend et al., 2016; Rodriguez et al., 2005).**

- **Mean hLf concentration in breast milk of mothers of VLBW infants at various time points in the lactation cycle were determined (n=104 to 277): colostrum: 14.92 g/L, milk at one month of lactation: 10.34 g/L, milk at two months of lactation: 8.52 g/L (Turin et al., 2017).**

- **The purpose of this notice is to provide to the FDA the determination of GRAS of Bioferrin® bLf for use in infant formula and toddler formula in the U.S. at levels of use up to 1 g /L.**

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Bioferrin® Exposure

Estimated Daily Intake (EDI) of bLf from proposed use of 1g/L in Infant Formula and Toddler Formulas				
Age Group	bLf Intake of added bLf[4]			
	mg/day		mg/kg bw/day	
	Mean	90th Percentile	Mean	90th Percentile
0 - 6 months[1]	1023	1484	179	269
7 - 12 months[2]	963	1420	111	162
13-36 months[3]	770	1373	92	152

1. Formula fed infants (all-user) 0-6 months consumed an average of 799.1 g of formula per day (129.1 g/kg/BW/day; 6.3 kg BW) and 1220.0 g/d (203.3 g/kg/BW/d; 6.0 kg BW) for heavy users (90th percentile) as calculated using data from U.S. NHANES 2007-2008 survey and cited in GRN 669, Pages 57-58.
2. Formula fed infants (all-user) 7-12 months consumed an average of 679.7 g of formula per day (76.7 g/kg/BW/day; 8.9 kg BW) and 1021.8 g/d (114.8 g/kg/BW/d; 8.9 kg BW) for heavy users (90th percentile) as calculated using data from U.S. NHANES 2007-2008 survey and cited in GRN 669, Pages 57-58.
3. Toddlers aged between 13 to 35 months old consumed an average of 621.5 g of formula per day (62.4 g/kg/BW/day; 10 kg BW) and 915.0 g/d (100.6 g/kg/BW/d; 9.1 kg BW) for heavy users (90th percentile) as calculated using data from U.S. NHANES 2007-2008 survey and cited in GRN 669, Pages 57-58. However, for these numbers (13-36 months), intake estimates may not be statistically reliable, as the sample size was very low.
4. The concentration of bLf used in these calculations is 1 g/L in reconstituted infant or toddler formula

Self-limiting Levels of Use

- **The intended use of bLf in infant formula is driven by the intent to closely align the protein composition of the formulas to that of human milk.**
  - The amount of protein in infant formula is strictly regulated by the Infant Formula Act in the U.S. and is codified at 21 CFR 107.100.
  - Global recommended CODEX standards also restrict the level of protein in infant formula.
  - The amino acid profile of bLf is lower in histidine, isoleucine, methionine, phenylalanine, tryptophan and tyrosine to meet the protein quality requirements for infant formula and must be supplemented with other proteins.
- **The total maximum protein level permitted and the protein quality as determined by the amino acid profile, are self-limiting factors for the potential maximum level of use of bLf in formula.**

Global Regulatory Assessments

GOVERNMENTAL AUTHORITY	YEAR	LEVEL /CONDITIONS OF APPROVAL
Standardization Administration of China - Guobiao (SAC)	2017	100 mg/100g in infant formula
Singapore	2015	1 g/L ready to feed infant formula
Food Safety Authority of Ireland (FSAI)	2013	Determined that Bioferrin® was substantially equivalent to Morinaga's bLf at this level
EU	2012	1 g/L ready to feed infant formula
Japan	1986	No limit
Taiwan	2000	As practically needed in infant formula
South Korea		Food additive for infant and follow on formula

Comparison of Bovine Lactoferrin Regulatory & Company Specifications

PARAMETER	Glanbia	European Union (European Commission, 2012a, 2012b)	Peoples Republic of China	Synlait Milk Ltd.	Morinaga (GRN 465, 2014, pp. 28-29 (pdf))	Friesland Campina (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2012, p. 8)
PHYSICAL AND CHEMICAL PARAMETERS						
DESCRIPTION	(b) (4)	Virtually odorless, light pinkish powder	Pale pink to reddish brown powder	Pink to tan powder	Pink, odorless powder	
PROTEIN **OF WHICH** **BOVINE LACTOFERRIN** **OTHER PROTEINS**		> 93.0% > 95.0% < 5.0%	93.0% 90.0%	95.0% 95.0%	94.5% 96.0%	93.0% 95.0%
MOISTURE (LOSS ON DRYING)		<4.5%	<4.5%	< 4.5%	<4.2%	< 4.5%
ASH		< 1.5%	< l.5%	< 1.3%	< 1.3%	< 1.0%
ARSENIC		<2 mg/kg	< 1 mg/kg	< 0.02 mg/kg	<1 mg/kg	<1 mg/kg (total heavy metals)
IRON		< 350 mg/kg	< 350 mg/kg	< 200 mg/kg	< 350 mg/kg	100 - 160 mg/kg
IRON SATURATION		< 25%	< 25%	< 20%	< 25%	< 11%
pH (2% SOLUTION, 20°C)		5.2 to 7.2	5.2 to 7.2	5.2 to 7.2	5.2 to 7.2	5.5 - 6.5
SOLUBILITY (2% SOLUTION, 20°C)		Complete	Complete, transparent	Complete, transparent	80% transmission, Complete	80 - 100% transmission, Complete

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Comparison of Bovine Lactoferrin Regulatory & Company Specifications

PARAMETER	Glanbia	European Union (European Commission, 2012a, 2012b)	Peoples Republic of China	Synlait Milk Ltd.	Morinaga (GRN 465, 2014, pp. 28-29 (pet))	Friesland Campina (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2012, p. 8)
MICROBIOLOGICAL						
TOTAL STANDARD PLATE COUNT	(b) (4)	<1000 cfu/g	< 1000 cfu/g	< 1000 cfu/g		< 1000 cfu/g
YEASTS & MOLDS		<10 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g
COLIFORMS		<10 cfu/g	< 3 MPN/g	ND / g	Negative / 0.1 g	ND
SALMONELLA			ND / 25 g	ND / 250 g	Negative / 25 g	Negative in 10 g
STAPHYLOCOCCUS AUREUS (COAGULASE POSITIVE)		Neg in 1 g	ND / 25 g	ND / g	Negative / g	Negative in 1 g

cfu = colony forming unit; MPN = mean probable number; ND= Not Detected

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Current Uses and Levels (EU)

FOOD CATEGORY	MAXIMUM USE LEVELS OF bLf
INFANT FORMULAE AND FOLLOW ON FORMULAE (READY TO DRINK)	1 g/ L
FOODS ON DAIRY BASIS INTENDED FOR YOUNG CHILDREN (READY TO EAT/DRINK)	200 mg/100 g
PROCESSED CEREAL FOOD (SOLID)	670 mg/100 g
FOODS FOR SPECIAL MEDICAL PURPOSES	Depending on individual needs - up to 3 g/day
BEVERAGES BASED ON MILK	200 mg/100 g
POWDERED DRINK MIXES BASED ON MILK (READY TO DRINK)	330 mg/100 g
BEVERAGES BASED ON FERMENTED MILK (INCLUDING YOGHURT DRINKS)	50 mg/100 g
NON-ALCOHOLIC DRINKS	120 mg/100 g
PRODUCTS BASED ON YOGHURT	80 mg/100 g
PRODUCTS BASED ON CHEESE	2000 mg/100 g
ICE CREAM	130 mg/100 g
CAKES AND PASTRIES	1000 mg/100 g
CANDIES	750 mg/100 g
CHEWING GUM	3000 mg/100 g

Toxicological Studies

- **Both acute and sub-chronic (4-week and 13-week) oral toxicological studies in rats indicate that bLf is safe for consumption, with a no observed adverse effects level (NOAEL) of 2000 mg/kg and does not result in treatment-related adverse effects or significant changes in clinical measures.**

- **Chronic oral toxicity was evaluated in 40 and 65-week feeding studies containing bLf at 0.2% of diet and up to 5% of the diet respectively. No significant treatment related effects were reported in either study, however the studies could not be used to establish a NOAEL.**

- **No potential mutagenicity of bLf was determined based on the Ames test.**

Allergenicity

- **Cow's milk allergy (CMA) is a hypersensitivity reaction initiated by immunologic mechanisms in response to bovine proteins. In most children it is IgE-mediated.**

- **Currently there is no evidence to support a role for lactoferrin as a causative agent in CMA.**

- **The intended uses of bLf are in milk-based formula which by law require labeling for the major allergen, milk protein of which bLf is a minor fraction.**

Bovine Lactoferrin Human Studies involving Infants & Toddlers

- **A significant body of evidence supports the safety of bLf for infants.**
- **In the 36 clinical trials identified in infants (from preterm and term at birth – 12 months) and in children (>12 months) and involving approximately 4000 participants, no adverse events related to the administration of bLf have been reported.**
- **Studies consistently report that the use of bLf is well tolerated. These studies include a wide range of exposure to bLf levels from 9.75 mg/kg BW/day (Kawaguchi et al., 1986) to 200 mg/kg BW/day (Ochoa et al., 2015) in preterm and VLBW infants; 36 mg/day (Chen et al., 2016) to 2300 mg/day (Balmer et al., 1989) in term infants; and 100 mg/day (Egashira et al., 2007) to 3000 mg/day (Zuccotti et al., 2009) in children.**
- **The range in amounts of bLf safely consumed and tolerated in these studies is higher that the maximum predicted EDI's of bLf subject to this notification (mean 1023 mg/day or 179 mg/kg BW/day, 90th percentile 1484 mg/day or 269 mg/kg/BW /day, Table III-4) in term infants aged 0 - 6 months**
- **Most of the studies in preterm and/ or VLBW infants are typically targeted toward the reduction in incidence or duration of LOS, NEC or other infective conditions to which this highly vulnerable population is especially prone. The studies confirm the safe consumption and tolerance of bLf in these infants, and suggest that bLf affords a degree of protection from infection but not necessarily colonization by pathogenic species (Manzoni, 2016).**

Bovine Lactoferrin Human Studies Involving Infants & Toddlers

- **The safety and tolerance of bLf for term infants has recently been specifically addressed in the study by Johnston et al. (2015) who investigated the use of bLf in term formulas at levels of 0.6 g/L and 1.0 g/L, the later is equal to the level of bLf added to term formula that is the intended use of this notification. The study concluded that bLf, together with other functional ingredients, added to formula was safe, well tolerated and associated with normal infant growth. This is supported by a number of other studies, that have also looked at potential benefits of bLf added to term formula.**
- **Formula supplemented with bLf may decrease the burden of respiratory (King et al., 2007) and gastrointestinal (Chen et al., 2016; Ochoa et al., 2013) morbidity in term infants (Manzoni, 2016). A number of studies have considered the role of bLf as an iron source, however there is little evidence to suggest it provides a more bioavailable source than that of elemental iron sources (Lönnerdal and Hernell, 1994), although there is some evidence to suggest bLf is involved in iron transport (Chierici et al., 1992).Other studies suggest bLf may modulate fecal flora (Liu etal., 2016; Roberts et al., 1992), and thereby provide indirectly a range of other developmental and health benefits to infants.**
- **The potential of bLf to prevent or mitigate the severity of infections in toddlers and children has been investigated in a number of studies all of which have not reported any adverse treatment related effects.**
- **In especially vulnerable immunocompromised children, high daily doses of bLf were well tolerated and no adverse treatment related effects were reported.**
- **In conclusion, there are a substantial number of studies in infants and toddlers that provide convincing and consistent evidence for the safe consumption and tolerance of bLf for the intended use in infants and toddlers.**

Bovine Lactoferrin Human Studies Involving Infants & Toddlers

- Mead Johnson markets an IF product in the U.S. (ENSPIRE) that contains 0.6 g/L (600 mg/L as fed); this level is higher than those noted for infant formula in GRN 465 and 669).

- This infant formula has been commercialized in the U.S. since 2016 without incident - see levels in https://www.meadjohnson.com/pediatrics/us-en/products/about-enfamil-enspire.

- A Mead Johnson-sponsored large scale pediatric growth monitoring clinical study designed to evaluate growth and tolerance in healthy infants when fed study formulas with bLf within the range of mature human milk at 0.6 and 1 g/L demonstrated normal growth in healthy term infants through 365 days of age (Johnston et al., 2015).

- Additionally, in a double-blind placebo-controlled study of bLF in bottle-fed infants, King et al. (2007) fed term infants an infant formula containing 850 mg/L bLf for one year with “beneficial outcomes.”

Conclusions

- A significant body of evidence, including both animal and human exposure and safety data, supports the safe consumption of bLf.
  - Both acute and sub-chronic (4-week and 13-week) oral toxicological studies in rats indicate that bLf is safe for consumption, with a no observed adverse effects level (NOAEL) of 2000 mg/kg and does not result in treatment-related adverse effects or significant changes in clinical measures.
  - In the 36 clinical trials identified in infants (from preterm and term at birth – 12 months) and in children (>12 months) and involving approximately 4000 participants, no adverse events related to the administration of bLf have been reported.
- Infants are currently exposed to bLf with the consumption of cow's milk-based infant formulas.
- When consuming cow's milk-based infant formulas as the sole source of nutrition the average daily exposure of infants 0 to 6 and 7 to 12 month old, and toddlers 13 to 36 months old is approximately 137, 120, and 104 mg/day, respectively.
- With the consumption of bLf from the intended uses their average daily exposure will increase to mean daily intakes of 1023, 963, 770 mg/day (1484, 1420, and 1373 mg/day at 90% percentile), respectively.
- The proposed bLf use levels are equal to the levels approved for use in Europe and lower than the levels of lactoferrin in breast milk.

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Conclusions (continued)

- Lactoferrin is present at levels ranging from 1-3 g/L in human breast milk to 6-7 g/L in colostrum (Montagne et al., 2001).
- bLf is approved in the EU at maximum use level in infant formula at 1000 mg/L (Annex II of 2012/725/EU) after EFSA safety assessment (17 July 2012).
- Per the Food Safety Authority of Ireland, Glanbia's Bioferrin® is substantially equivalent to bLf authorized to Morinaga (2012/725/EU), the latter of which is GRAS in US (GRN 465) .
- Currently in US, bLf is GRAS at less than the approved EU level (GRAS Notices GRN 465 [Morinaga 2014]) - at 130 mg/L); and GRN 669 (Synlait 2017) - at 130-140 mg/L infant formula.
- There is history of use of lactoferrin in US infant formula at levels exceeding the current US GRAS levels e.g., Mead Johnson's ENSPIRE infant formula in US has lactoferrin at 600 mg/L.
- This GRAS notice is for Glanbia's bLf at intended use levels up to 1 g/L (1000 mg/L) in infant or toddler formula.
- This GRAS notice gives examples of growth and safety and other clinical data in infants up to 1g/L in infant formula.

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Overall Conclusion

The proposed use of bovine lactoferrrin (Bioferrin) as a food ingredient in term infant formula and toddler food, at a level of up to 1 g/L in reconstituted infant formula (equivalent to 770 mg/100 g formula solids when reconstituted at 130 g powder per liter) is safe and GRAS based on scientific procedures.

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Questions?

THANK YOU

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