DBGNR Meeting Requests

Information for Logging into FARM/Appian

Requestor: Tania Porsgaard Bayer, Arla

Contact Information: +4589381562

tania.porsgaard.bayer@arlafoods.com

Date of Request: June 3, 2019 (meeting to be held June 17, 2019)

Subject: Discussion on intended use of osteopontin in IF

Date Request Received by DBGNR: June 3, 2019

Date Prepared by DBGNR: June 3, 2019

Prepared by: Rachel Morissette

If agent, name of company or individual this is on behalf of:

Memorandum of Meeting

Type	Teleconference
Dates & Times	November 9, 2017, 11:00 a.m. – 12:00 p.m. November 20, 2017, 11:00 a.m. – 11:30 a.m.
Location	FDA, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, 4300 River Road, College Park, MD 20740

Subject: GRN 000716 (Bovine whey-derived osteopontin (bOPN)) for use as a source of protein in milk-based, non-exempt infant formulas for term infants and in powdered beverages at levels up to 138 mg/L as consumed.

Summary: This memorandum summarizes the discussion points of OFAS' teleconference meetings with Burdock Group Consultants (agent) on November 9, 2017 and with Burdock Group Consultants and Arla Foods Ingredients Group PIS (AFI, notifier) on November 20, 2017 regarding GRN000716. OFAS has outstanding regarding the evidence for general recognition that bOPN is safe for use in infant formulas. The overarching question is whether the data provided by AFI are adequate to demonstrate general recognition of safety (reasonable certainty of no harm) by scientists with the appropriate expertise to evaluate the significance of bOPN activity at the intended consumption level by infants. OFAS considers this question to be important given the rapid development of the infant immune system, the poorly characterized modes of action for bOPN, the potential involvement of human OPN (hOPN) in infant immune maturation, lack of clarity regarding substantial equivalence of biological activities between bOPN and hOPN, and the large variation of the levels of hOPN in human milk.

On October 3, 2017, OFAS sent questions to AFI (see FDA Questions and Comments). On October 20, OFAS received AFI's responses. The amendment included information on the intended use level and resulting exposure to bOPN in infants. The amendment also included information on the bioequivalence of hOPN and bOPN. After reviewing AFI's responses, OFAS continues to question the general recognition of the safety of the intended use of bOPN in infant formulas.

On November 9, 2017 OFAS held a teleconference meeting with AFI's agents, Drs. Burdock and Matulka, to discuss the review team's outstanding questions regarding the GRAS status of the intended use of bOPN.

U.S. Food & Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740

Participants: November 9, 2017 Meeting

Notifier: Arla Foods Ingredients Group PIS (AFI)'| Agent: Burdock Group Consultants *(phone)*

George A. Burdock, Ph.D.	Owner, Burdock Group Consultants
Ray A. Matulka, Ph.D.	Director of Toxicology, Burdock Group Consultants

FDA/CFSAN/ OFAS/DBGNR (HFS-255)

Nadine Bewry, Ph.D., MPH	Consumer Safety Officer (CSO)
Jeremiah Fasano, Ph.D.	Acting Supervisory CSO
Romina Shah, Ph.D.	Chemist
Michael DiNovi, Ph.D. (*phone*)	Supervisory Chemist
Kotaro Kaneko, Ph.D.	Toxicologist
Ronald Chanderbhan, Ph.D.	Supervisory Toxicologist

FDA/CFSAN/ ONFL/ IFMS (HFS-850) (*phone*)

Linda Tonucci, Ph.D.	CSO
Suzanne Wolcoff, PhD.	Senior Dietitian-Nutritionist
Carrie Assar, Ph.D.	Lead Nutritionist

OFAS discussed three main lines of evidence contained in the notice and in the notifier's response to one of OFAS' questions, including the absence of evidence of toxicity in toxicological and clinical studies, the similarity of bOPN and hOPN, and existing infant exposure to both bOPN and hOPN.

OFAS noted that:

- OPN has multiple modes of action, including immunomodulatory and pro-inflammatory effects. None of the published safety studies discussed in GRN 000716 evaluated potential adverse effects of bOPN at the intended use level related to these modes of action.
- The available evidence indicates that hOPN and bOPN are not substantially bioequivalent in humans from a physiological perspective.
- The intended use level of bOPN in infant formula is higher than the basal level found in milk or milk-based formula.
    - Based on the literature, the levels of bOPN in cow's milk and cow's milk-derived infant formulas are 18 µg/ml and 5.3-13.0 µg/ml, respectively. However, levels of bOPN from intended use is ~138 µg/ml.
    - There is no evidence provided in GRN 000716 or in the October 20, 2017 amendment to GRN 000716 that infants have been safely exposed to higher levels of bOPN from the intended use.

OFAS considers it important that AFI provide evidence that the existing data and information are adequate to demonstrate general recognition of safety (reasonable certainty of no harm) by scientists with the appropriate expertise to evaluate the significance of bOPN activity at the intended use level in infants. OFAS further noted that AFI's GRAS Panel appears to lack

expertise in neonatal immunology, which is relevant to the intended population and the known modes of action of bOPN. OFAS explained that the importance of including such expertise would be to develop insight into the views of scientists in this area about the significance of the intended use of bOPN, including some basis for concluding that these views are broadly shared. OFAS informed AFI that simply adding a neonatal immunologist to their current GRAS panel would not be sufficient to provide evidence of general recognition. The introduction of an additional individual without reanalysis and interpretation of existing data or reference to current thinking in their field would not be sufficient to resolve our questions about general recognition. Furthermore, OFAS noted that other regulatory authorities, including EFSA, JECFA, FSANZ, and Health Canada, have not approved the use of bOPN in infant formula, indicating a lack of general recognition of bOPN's safety in infant formulas. Given these outstanding questions regarding general recognition, OFAS advised AFI to request that OFAS cease to evaluate GRN 000716.

On November 15, 2017, Dr. Matulka requested a second teleconference meeting with OFAS because AFI stated that they would like to address OFAS' questions regarding the notice rather than request that OFAS cease to evaluate the notice. The purpose of the meeting was: (1) to share the steps that AFI will take to address our questions, and (2) to gain clarification on some of the discussion points from the November 9, 2017 teleconference meeting.

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Anders Steen Jorgensen	Head, Business Unit Pediatrics, Arla Foods
Anne Staudt Kvistgaard	Senior Manager, Documentation Pediatrics, Arla Foods

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OFAS' discussion points included some of those already covered during the November 9, 2017 teleconference meeting, as well as the following discussion points:

- OFAS considers that it would not be possible for AFI to address the unresolved questions regarding general recognition of the safety of the intended use of bOPN in the short term simply by locating or conducting additional studies.
- OFAS emphasized the office's view that the unresolved questions rest on the issue of whether scientists trained to evaluate immune function and development in infants would accept the existing evidence as adequate to show reasonable certainty of no harm.
- OFAS noted that there are several potential strategies to develop evidence for general recognition of the safety of the intended use of bOPN, which would involve recruiting additional expertise and re-engaging with OFAS on the issues we identified.
- OFAS noted that any future consideration of the GRAS status of AFI's intended use of bOPN by the office would include consulting FDA staff with appropriate training and expertise relevant to neonatal immune development.

In conclusion, OFAS still has outstanding questions regarding the evidence for general recognition that bOPN is safe for use in infant formulas. OFAS recommends that AFI request that we cease to evaluate GRN 000716.

Attachment:

GRN 716 2017-10-03 Email_FDA Questions and Comments

Nadine N. Bewry -S

Digitally signed by Nadine N. Bewry -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014360008, cn=Nadine N. Bewry -S
Date: 2017.12.20 14:54:05 -05'00'

Nadine Bewry, Ph.D., MPH

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Date: 2017.12.20 14:51:14 -05'00'

Nadine Bewry, Ph.D., MPH

R/D:HFS-255:NNBewry: 11/20/2017
Edit/Comments/Init: HFS-255: RShah:12/5/2017
Edit/Comments/Init: HFS-255: KKaneko:12/4/2017, 12/7/2017
Edit/Comments/Init: HFS-255: JFasano:12/4/2017, 12/7/2017
Edit/Commens:HFS-255: SWestBarnette:12/19/17, 12/20/17
Init:HFS-255: SWestBarnette:12/20/17
F/T: HFS-255:NNBewry: 12/20/2017

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Date: 2018.01.25 13:51:45 -05'00'

Nadine Bewry, Ph.D., MPH

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

Date: April 10, 2018

From: Jeremiah Fasano, HFS-255

To: GRN 000716 File

Subject: Discussion of General Recognition for Use of Osteopontin in Infant Formula

Attendees

Jeremiah Fasano	CFSAN/OFAS/DBGNR
Kotaro Kaneko	CFSAN/OFAS/DBGNR
Rachel Morissette (WebEx)	CFSAN/OFAS/DBGNR
Nadine Bewry (WebEx)	CFSAN/OFAS/DBGNR
Ronald Rabin	CBER/OVRR/DBPAP
Joohee Lee	CBER/OVRR/DVRPA
Anubha Tripathi	CBER/OVRR/DVRPA
Jay Slater (WebEx)	CBER/OVRR/DBPAP
Andrea Lotze (WebEx)	CFSAN/ONFL/IFMFS
Carrie Assar (WebEx)	CFSAN/ONFL/IFMFS
Gillian Robert-Baldo (WebEx)	CFSAN/ONFL/IFMFS
Leila Beker (WebEx)	CFSAN/ONFL/IFMFS
Megan Kulas (WebEx)	CFSAN/ONFL/IFMFS
Suzanne Wolcoff (WebEx)	CFSAN/ONFL/IFMFS
Cheryl Issa (WebEx)	CFSAN/ONFL/IFMFS

Members of CFSAN's Office of Food Additive Safety and Office of Nutrition and Food Labeling met with members of CBER's Office of Vaccines Research and Review to discuss the use of bovine osteopontin (bOPN) as an ingredient in infant formula, as well as the broader issue of bioactive milk ingredients used in formula. The CBER delegation included members with expertise in immunology. The intent of the discussion was to share the evidence for the safety of the intended use of bOPN presented by Arla Foods, as well as other information on bOPN available to CFSAN, in order to assess CBER staff's views on two related questions:

- Are questions raised by CFSAN reviewers about the potential long-term consequences of bOPN exposure in infants at the intended use level reasonable, given what we know about both postnatal immunology and the properties of OPN?
- Is there a broad consensus among clinical immunologists about the kind of data and information that is appropriate and adequate to establish reasonable certainty of no harm (the standard for food ingredient safety) for this intended use, given the questions raised by CFSAN?

After a brief discussion about the statutory framework of how food additives and GRAS substances are regulated, CFSAN staff described the intended use of bOPN as well as the explicit rationale (to increase resemblance to human milk by increasing OPN levels) and the implicit rationale (to enhance or modulate

immune function and development in infants). CFSAN staff also described their questions about the consequences of increased bOPN exposure in this population and the role of general recognition in a GRAS conclusion. CFSAN and CBER staff then discussed the current scientific understanding of OPN modes of action, the basis for (or the lack thereof) the presumption that incremental changes to infant formula to increase resemblance to human milk are unambiguously beneficial and involve no increased risk, and the challenges involved in identifying a universally appropriate use level for a bioactive milk protein in infant formula based on a sampled arithmetic mean.

CBER staff expressed concerns about the intended use of bOPN in infant formula. They concurred with CFSAN's view that incremental changes in the direction of human milk could introduce unintended risks, and that application of an arithmetic mean value to all individuals consuming formula might not be appropriate. They cited insulin, a polypeptide with profound effects on physiological function and extensive pharmaceutical applications, as an example of both issues. In response to CFSAN's overall questions, CBER staff indicated that our questions were reasonable, and that, in their view, there was no consensus currently in the immunology community about what data would be appropriate and adequate to resolve them.

CFSAN staff explained that the notifier for the bOPN GRAS notice had been advised to first request that FDA cease to evaluate their notice and then to develop a strategy to generate compelling evidence of general recognition for their safety data on bOPN, given the questions CFSAN staff had raised to them about the long-term consequences of increased bOPN exposure in the infant population. CBER staff strongly recommended that CFSAN consider ways to explore the broad questions associated with the use of bioactive ingredients in infant formula in a public setting, such as a workshop or public meeting.

CFSAN staff concluded the meeting by thanking CBER staff for their time, attention, and advice, and offering to circulate a meeting memorandum outlining the discussion.

Jeremiah M. Fasano -S

Digitally signed by Jeremiah M. Fasano -S
Date: 2019.03.22 00:20:30 -04'00'

Jeremiah Fasano

Drafted:HFS-255:JMFasano:04/18/2018
Comments:HFS-255:RMorissette:04/18/2018
Comments:HFS-255:KKaneko:04/18/2018
Edit:HFS-255:JMFasano:05/03/2018
Init:HFM-422:RRabin:05/03/2018
Init:HFM-422:JSlater:05/07/2018
Init:HFS-850:CAssar:05/09/2018
Edit/Comments:HFS-255:NNBewry:05/07/2018
F/T:HFS-255:JMFasano:03/09/2018

DBGNR Meeting Requests

Information for Logging into FARM/Appian

Requestor: Cathryn Sacra, EAS Consulting Group, LLC

Contact Information: csacra@easconsultinggroup.com

571-447-5500 (main); 571-447-5505 (direct)

Date of Request: November 5, 2018

Subject: Intended use of bovine lactoferrin

Date Request Received by DBGNR: November 5, 2018

Date Prepared by DBGNR: November 30, 2018

Prepared by: Shayla West-Barnette

If agent, name of company or individual this is on behalf of:

Glanbia Nutritionals

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Memorandum of Meeting

Subject: Internal meeting with a CFSAN immunologist

Date: March 22, 2019 – 2:00 PM

Location: University Station Building, Room 2031
Center for Food Safety and Applied Nutrition (CFSAN)
College Park, Maryland

Participants:

Office of Food Additive Safety (OFAS)/Division of Biotechnology and GRAS Notice Review (HFS-255)

Kotaro Kaneko, Ph.D. Toxicologist
Supratim Choudhuri, Ph.D. Toxicologist

Office of Compliance

Stefano Luccioli, MD Senior Medical Officer/Food Allergen Program Coordinator

Dr. Kaneko asked Dr. Luccioli to meet with DBGNR representatives to discuss questions and concerns raised during GRAS review of bioactive/immunomodulatory ingredients for use in infant formula. Dr. Jeremiah Fasano from DBGNR could not attend due to scheduling conflicts.

Dr. Kaneko briefly introduced the background information on osteopontin for use in infant formula, the subject of GRN000716, as well as on a presubmission request for bovine lactoferrin for infant formula at use levels higher than previous GRN notices for bovine lactoferrin. Drs. Kaneko and Choudhuri then briefly described the concerns by DBGNR raised during the review, which included information pertinent to establishing not only the safety standard of "reasonable certainty of no harm" but also the "general recognition" of that safety. Dr. Kaneko also briefly described the meeting highlights with CBER colleagues in the Office of Vaccines Research and Review, who agreed with our concerns on the use of osteopontin in infant formula.

Dr. Luccioli stated that he was in agreement with the concerns raised by the DBGNR reviewers. He acknowledged that GRAS evaluation for these types of immunomodulatory ingredients for use in infant formula may require reevaluation of the current safety paradigm for risk assessment. He also stated that determining safe use levels for these types of ingredients in infant formula from data on breast milk is problematic because, due to many competing immune factors in the milk. Levels of osteopontin in breast milk may not predict its immunomodulatory status. When asked whether he is aware of any clinically accepted methodologies to evaluate safety of immunomodulatory ingredients in infants, he responded that he was not aware of such methodologies.

The meeting ended with Drs. Kaneko and Choudhuri thanking Dr. Luccioli for taking the time to discuss this topic, as Dr. Luccioli is not only an expert as a clinical immunologist but also has the appropriate background to assess food safety having worked in OFAS for many years.

Kotaro J. Kaneko, Ph.D.
Toxicologist

R/D:HFS-255:KJKaneko:04/30/2019
Comments/edits: HFS-255:SChoudhuri:05/21/2019
Comments/edits: HFS-605:SLuccioli:05/21/2019
Comments/edits: HFS-255:RChanderbhan: 06/25/2019
F/T:HFS-255:KJKaneko: 06/25/2019

MEMORANDUM OF MEETING (GPS00010)

Date: June 17, 2019

Time: 9:00 a.m. – 10:30 a.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 (via WebEx):

Tania Porsgaard Bayer	Arla Foods
Kal Ramaujam	Arla Foods
Anders Steen Joergensen	Arla Foods
Anne Staudt Kvistgaard	Arla Foods
Lotte Neergaard Jacobsen	Arla Foods
Ashley Roberts	Intertek
James W. McGrath	Building Block Nutritionals
Gene Scavola	Building Block Nutritionals

CFSAN/OFAS/DFI:

Rachel Morissette, Ph.D.	HFS-255
Susan Carlson, Ph.D.	HFS-255
Supratim Choudhuri, Ph.D.	HFS-255
Kotaro Kaneko, Ph.D.	HFS-255
Jeremy Mihalov, M.S.	HFS-255
Jannavi Srinivasan, Ph.D.	HFS-255
Paulette Gaynor, Ph.D. (via WebEx)	HFS-255
Molly Harry, Ph.D.	HFS-265
Diana Doell, Ph.D.	HFS-265
Susan Carberry, Ph.D.	HFS-265
Scott Thurmond, Ph.D.	HFS-265

CFSAN/OFAS/DST:

Jeremiah Fasano, Ph.D.	HFS-255

CFSAN/ONFL/IFMFS:

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

CFSAN/OC:

Stefano Luccioli, M.D. (via WebEx)	HFS-200

Subject: Pre-submission meeting for the intended use of bovine whey-derived osteopontin (bOPN) in infant formula

Background:
In an email dated May 13, 2019, Ms. Tania Porsgaard Bayer of Arla Foods (Arla) requested a meeting with FDA/CFSAN to discuss their approach for addressing safety and general recognition concerns that FDA raised during the review of GRN 000716.[1] The issues raised during our review were primarily captured in a scientific memorandum, a policy memorandum, and a memorandum of meeting between DFI and the Center for Biologics Evaluation and Research (CBER) for the intended use of bOPN as an ingredient in infant formula. Arla had requested these memoranda under the Freedom of Information Act on April 5, 2019. In an email dated May 1, 2019, we reiterated our position regarding the unsettled nature of the science surrounding the biological effects of bOPN and the lack of general recognition in the scientific community regarding the safety of bOPN intended for use as an added ingredient in foods and infant formula. Additionally, we stated that we would welcome a continuing dialogue with Arla on long-term strategies to address the above-mentioned concerns, which led to today's meeting.

June 17, 2019:
During the meeting, Arla gave a presentation covering four main points: general recognition, toxicology and safety, human OPN (hOPN) in human milk, and history of consumption. In support of general recognition, Arla stated that their safety data were presented to and discussed with 19 experts in pediatrics and immunology.[2] However, the specific context of the questions, the data and information discussed, and the responses received from these experts were not provided to FDA. Thus, it was not clear whether the questions and concerns raised during FDA's review of GRN000716 were fully described, appropriately framed in the context of the Federal Food, Drug, & Cosmetic Act food ingredient safety standard, and adequately addressed in these discussions. Arla also stated that they intend to submit a Novel Food application to the European Food Safety Authority for the use of bOPN in infant formula at 138 mg/L.

In support of toxicology and safety, Arla discussed pre-clinical *in vitro* and animal safety studies, as well as clinical studies, with a new focus on immune markers to address concerns raised during our review of GRN 000716. Arla noted a recently published study by Lönnderdal et. al. showing that formula fed infants have high circulating levels of endogenous hOPN that they believe may be of immunological benefit in infants.[3] Arla requested guidance regarding the types of studies they should pursue to address our safety questions and what we consider to be a "long-term" study.

To compare hOPN and bOPN, Arla discussed the structural homology and post-translational modifications found between the species and stated that functional and

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[1] Bovine whey-derived osteopontin was the subject of GRN 000716. At Arla's request we ceased our evaluation of this notice and responded in a letter dated February 1, 2018.
[2] A list of conferences and publications was provided in an email to FDA dated June 3, 2019.
[3] Jiang and Lönnerdal (2019) Pediatric Research 85(4), 502-505.

structural differences between the two proteins are found more in extracellular secretions and in organs, rather than in milk. Arla referenced an FDA guidance document relevant to drug biosimilarity to support that molecules are considered similar if minor structural differences do not result in adverse functional differences.[4] We noted that the potential relevance of guidance on drug efficacy assessment for protein-based biosimilars emphasized the novelty and challenging nature of the issues under discussion in a food safety context.

Finally, Arla discussed the history of consumption of hOPN. Arla showed data from human milk samples from a total of 629 women in four countries that showed a mean concentration of 167.4 mg/L hOPN; however, the concentrations varied widely across samples and throughout the lactation period. Arla stated that there have been no adverse events reported so far in China, Korea, and the European Union where bOPN has been marketed as an ingredient in infant formula. Additionally, Arla stated that a U.S. clinical trial using bOPN-enriched infant formula reported no safety concerns.

Arla ended the presentation by asking for guidance on strategies to achieve general recognition of safety for bOPN, further studies they may undertake to support a safety conclusion, and clarification on what we consider "long-term" studies.

FDA provided comments emphasizing the following points:

- While general recognition is an important component of GRAS, the bigger issue is the unsettled nature of the science surrounding the safe use of bOPN in infant formula. Issues surrounding general recognition cannot be addressed until the safety of bOPN is demonstrated. A more basic scientific understanding of bOPN's biological effects in the body is needed.
- Arla has acknowledged that the science surrounding bioactive ingredients is evolving and their safety cannot be determined by traditional toxicological endpoints. Arla demonstrated this by exploring other means of studying immunomodulatory effects and their impact on the developing infant immune system.
- Arla stressed the perceived beneficial effects of bOPN. However, the expectation is that either this ingredient has no biological effect on the infant gut and immune system, or it has such effects that must be evaluated for potential adversity without mitigation by anticipated benefits. The food safety paradigm, unlike drugs and biologics, does not involve the kind of risk/benefit analysis presented in Arla's slides. We cautioned Arla about the challenges involved in pursuing intended food uses driven by anticipated benefits, especially in infant formula.
- To address the safety concerns surrounding bOPN, a long-term, on-going, and robust debate is needed among different scientific and medical disciplines. Likely more basic research will be required to answer these questions. Depending on the outcome of that debate and research, there is no guarantee that a consensus of

[4] Guidance to Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, from the Center for Drug Evaluation and Research and CBER, April 2015.

opinion on the safety of bOPN will be reached. We agreed to provide guidance on the types of disciplines and suggest potential experts in the relevant disciplines as a starting point for that debate. We would also identify the types of scientific forums most suited to discuss the safety of the use of bOPN in infant formula and food. Assembling of this broader platform of expertise could help serve Arla's and FDA's considerations for what constitutes an appropriate long-term study.

We concluded the meeting by agreeing to provide Arla a list of needed expertise in relevant scientific and medical disciplines as a starting point for the needed broader discussion on the safety of bOPN in infant formula within 3-4 weeks of this meeting. Additionally, we agreed to share a copy of this memorandum of meeting with Arla.

Rachel Morissette -S

Digitally signed by Rachel Morissette -S
Date: 2019.07.11 13:57:42 -04'00'

Rachel Morissette, Ph.D.

ATTACHED:

1. Updated attendee list (email dated June 17, 2019)
2. List of questions for FDA (email dated June 17, 2019)
3. Agenda and list of conferences (email dated June 3, 2019)
4. Meeting Request (email dated May 13, 2019)
5. Email from FDA to Arla (dated May 1, 2019)
6. Powerpoint presentation

R/D:HFS-255:RMorissette:7/1/19, 7/2/19, 7/3/19, 7/5/19
Edit/Comment/Init:HFS-255:KKaneko:7/2/19
Edit/Comment/Init:HFS-255:SChoudhuri:7/1/19
Edit/Comment/Init:HFS-255:JFasano:7/2/19
Edit/Comment/Init:HFS-255:JMihalov:7/3/19
Edit/Comment/Init:HFS-255:JSrinivasan:7/3/19
Edit/Comment/Init:HFS-265:SCarberry:7/3/19
Edit/Comment/Init:HFS-265:MHarry:7/3/19
Edit/Comment/Init:HFS-265:MHonigfort:7/5/19
Edit/Comment/Init:HFS-255:SCarlson:7/5/19
F/T:HFS-255:RMorissette:7/11/19

From:	Tania Porsgaard Bayer
To:	Morissette, Rachel
Subject:	SV: Arla"s request for a meeting to discuss osteopontin
Date:	Monday, June 17, 2019 8:37:03 AM
Attachments:	image007.png image015.png image021.png

Hi Rachel

Besides the attendance listed below there will be 2 additional attendances:

- Lotte Neergaard Jacobsen, Arla Foods Ingredients, Scientist
- Gene Scavola, Building Block Nutrition

I hope this is okay

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
+4589381562

Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 17. juni 2019 14:05
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: RE: Arla's request for a meeting to discuss osteopontin

Hi Tania,

Can you please confirm the attendance list below? Sometimes it's difficult to catch everyone's names over the phone.

- Tania Porsgaard Bayer, Arla Foods Ingredients, Director of Global Regulatory
- Kal Ramaujam, Arla Foods Ingredients, Senior Scientific Advisor
- Anders Steen Joergensen, Arla Foods Ingredients, Director BU pediatric
- Anne Staudt Kvistgaard, Arla Foods Ingredients, Senior Manager Science and sales development
- Ashley Roberts from Intertek, Senior Vice President – Food & Nutrition
- James W McGrath, Building Block Nutrition

Thanks,

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

From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Monday, June 17, 2019 2:07 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: SV: Arla's request for a meeting to discuss osteopontin

Dear Rachel

Just for the overview I've gathered all our questions in one document that I have attached in this email. All the questions are in the previously send presentation, and are all questions we would like to discuss with FDA or get some guidance from FDA.

I look forward to speaking to you and your team tomorrow.

Best regards, Tania

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

Arla Foods Ingredients Group P/S

Phone: +4589381562
VAT no.: 33372116

tania.porsgaard.bayer@arlafoods.com
http://www.arlafoodsingredients.com

please inform us by returning this e-mail without producing, distributing or retaining copies hereof.

Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 3. juni 2019 20:26
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: RE: Arla's request for a meeting to discuss osteopontin

Ok, thank you!

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

From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Monday, June 03, 2019 2:18 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: SV: Arla's request for a meeting to discuss osteopontin

Dear Rachel

Thank you very much for your fast reply for arranging a meeting.
I'll send you a presentation next week that I would like to go through at the meeting

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
+4589381562

Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 3. juni 2019 19:08
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: RE: Arla's request for a meeting to discuss osteopontin

Hi Tania,

I have scheduled your teleconference for Monday June 17, 2019 from 9:00-10:30 am EST. If you have other materials that you would like me to circulate to the review team, or if you have presentation slides you'd like to show, please let me know prior to the meeting. I will forward a calendar invite with WebEx information to you shortly. Please let me know if you do not receive it by the end of the day. If you have any further questions at this time, please let me know.

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

From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Monday, June 03, 2019 11:13 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: VS: Arla's request for a meeting to discuss osteopontin

Hi Rachel

Any meeting before 11th July will be okay for us, we will prioritize the meeting and are just happy that you can set aside time for meeting with us over phone. If possible, we would like a meeting before lunch (your time), since we are based in Europe and are 7 hours in front of you timewise.

Based on the different documents from the FOIA request, I've extracted 4 main points that FDA have addressed as concerns before the agency can confirm that GRN 000716 "reasonable certainty of no harm", all 4 points is what we would like to have on the agenda, below is my suggestion for an agenda for our meeting.

Agenda:
Arla wishes to discuss with the FDA how best to address the concerns raised by FDA, the points raised by FDA that we would like to address is:

1. **General recognition**
   - The safety data we have on hOPN have been presented for a total on 19.000 experts within pediatric and immunology on 12 different conferences, we believe this show a broad consensus among clinical immunologists about the data and information presented establish reasonable certainty of no harm for the use of bOPN in infants. (list of conferences attached)
2. **Toxicological and safety**

- We would like to present our strategy for showing 'absence for adverse effects', and inform about the similar concerns addressed in Europe by EFSA, and how we are working with EFSA to address the concern

3. **hOPN in human milk**
   - Since the 29 milk samples, FDA are referring to in the scientific memo, we have plenty of new human milk OPN-level information that we would like to present to FDA
     Bruun et al. 2018 - +800 milk samples from Korea, China, Japan and DK
     Jiang & Lönnerdal 2019 – milk samples from USA
4. **History of consumption**
   - We would like to show data that hOPN has been consumed by infants for many years. Furthermore, we can show that the homology between hOPN and bOPN is very high and the functional domains are conserved. In order to show history of consumption.

Arla looks forward to having dialogue with the agency on these matters in the hope of obtaining guidance on the strategy as develop.

List of participants from our side would be (might vary depending on the date of the meeting):

- Tania Porsgaard Bayer, Arla Foods Ingredients, Director of Global Regulatory
- Kal Ramaujam, Arla Foods Ingredients, Senior Scientific Advisor
- Anders Steen Joergensen, Arla Foods Ingredients, Director BU pediatric
- Anne Staudt Kvistgaard, Arla Foods Ingredients, Senior Manager Science and sales development
- Ashley Roberts from Intertek, Senior Vice President – Food & Nutrition
- James W McGrath, Building Block Nutrition

Please let me know if you have any questions. I look forward to hearing from you

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

Arla Foods Ingredients Group P/S

Phone: +4589381562
VAT no.: 33372116

tania.porsgaard.bayer@arlafoods.com
http://www.arlafoodsingredients.com

Questions to FDA- Pre-submission meeting- Bovine Osteopontin 17th June 2019

General Recognition:

- Bovine OPN safety and efficacy has been presented in many conferences and the list of publication that is directly relevant is also listed.

Question 1:

1) Furthermore, we plan to assemble a round table panel with leading pediatric, immunology and OPN structural experts to discuss short and long-term safety of OPN. Would FDA scientists be available to participate?

Safety and Toxicology:

- Published studies and available information at the time of our Lacprodan OPN-10 dossier compiled led to the safety of the dosage (138 mg/L) requested. As pointed out by FDA, immune end points were not studied in the pre-clinical safety protocol. The clinical study looked at immune markers, vaccine response and infection rates and did not see any safety concerns when compared to the breast fed infants. New information on the analysis of plasma samples from clinical study (not presented in the dossier or discussed with FDA previously) shows high levels of endogenous hOPN even in formula fed infants that might play a role in immune programming and contributing to long term health outcomes in all infants. Compared to hOPN, the bOPN measured even in supplemented infants was 20 fold less and is lower than any of the plasma levels observed and presented in the dossier (Table 17, Page 69).Also, high levels of endogenous OPN in plasma will create complexity in designing exogenous bovine OPN feeding studies to look at long term outcomes as the specific immune role of bOPN will be difficult to prove. Given this we need following guidance from FDA.

Questions 2-7:

2) The FDA has raised the concern of the "…long-term consequences of perturbing the developing infant immune system…". In the design of studies to answer this concern, what is the agencies definition of "long Term"?

3) Given information presented on high levels of endogenous hOPN early in infancy, is there a reason to consider additional animal safety studies ?

4) Does the agency agree that the proposed mini pig model with dosing and immune assessment study will provide toxicological answers to the potential long term effects of Osteopontin (OPN)? (follow up to the question above)

5) Does additional measurement of hOPN in USA infants add value to existing knowledge and evaluation of our application?

6) Given the current safety information, publications and general recognition presented, is there any level beyond the 13 mg/ L (innate) that FDA is comfortable approving?

7) Given substantially higher levels of hOPN compared to bOPN, does the agency agree that any long term effects would be attributed to hOPN

hOPN and bOPN structural similarity:

Experts acknowledged that differences in post translational modifications are noted within lactation period and between breast milk and other secretions. Since there is substantial similarity in amino acid sequence and active binding domains, post translational modifications may have minimal functional consequences (if any). Based on available literature information, bOPN plays a beneficial role in model systems studied.

Questions 8-9:

8) Does the FDA agree that the minor differences noted in homology may not be functionally consequential?

9) Given this complexity, is there any binding studies the FDA would recommend to alleviate its concerns?

Miscellaneous Questions 10-11:

10) How helpful is the BBN OPN clinical safety study to safety of OPN?

11) Would the agency like to see the full results of the BBN safety clinical in support of the OPN GRAS approval?

Year	Conference/event	Presenter	Format	Title
2009	Milk Genomics,	Sharon Donovan	Oral presentation	*OPN gene expression*
2011	ESPGHAN, Sorrento	Esben Skipper Sørensen	Oral presentation	*Osteopontin – a bioactive milk protein with implications in infant nutrition?*
2011	ESPGHAN, Sorrento	Sharon Donovan	Oral presentation	*Transcriptional responses of the neonatal Rhesus intestine to Osteopontin*
2011	ESPGHAN, Sorrento	Bing Wang	Oral presentation	*Osteopontin – a bioactive milk protein with implications in infant nutrition?*
2014	Early Nutrition, Power of Programming, Munich	Bo Lönnerdal	Oral presentation	*Growth, nutrition and early programming of immune function in breast-fed infants and infants fed formula with added osteopontin (OPN)*
2014	Experimental Biology, San Diego	Sharon Donovan	Oral presentation	*Osteopontin supplementation of formula shifts the peripheral blood mononuclear cell transcriptome to be more similar to breastfed infants*
2014	Experimental Biology, San Diego	Bo Lönnerdal	Poster	*Growth, nutrition and immune function of breast-fed infants and infants fed formula with added osteopontin*
2014	Experimental Biology, San Diego	Sharon Donovan	Poster	*Dietary bovine osteopontin increases vaccine response, T-cell phenotype and cytokine secretion in piglets*
2017	Nestlé 90th Symposium	Sharon Donovan	Webcast	*Proteins in human milk – composition and biological effects*
2018	Ordesa Symposium, Madrid	Lotte Neergaard Jacobsen	Oral presentation	*Osteopontin – cornerstone in immunology*
2018	ESPGHAN, Geneve	Signe Bruun	Oral presentation	*Osteopontin levels in human milk vary across countries and within lactation period: Data from a multicenter study*
2019	Event Catedra Ordesa, VI International Scientific Symposium, Palma de Mallorca	Lotte Neergaard Jacobsen	Oral presentation	*Osteopontin in human milk and infant nutrition*

Publication list OPN:

Ren et al. 2019. Gut and immune effects of bioactive milk factors in preterm pigs exposed to prenatal inflammation. Am J Physiol Gastrointest Liver Physiol. 15 . [Epub ahead of print] (https://www.ncbi.nlm.nih.gov/pubmed/31091150)

Donovan 2019. Human milk proteins: Composition and physiological significance. Nestle Nutr Inst Workshop Ser. 90: 93-101 (https://www.ncbi.nlm.nih.gov/pubmed/30865978)

Jiang & Lönnerdal 2019. Osteopontin in human milk and infant formula affects infant plasma osteopontin concentrations. Pediatr Res. 85(4): 502-505 (https://www.ncbi.nlm.nih.gov/pubmed/30636771)

Chen et al. 2018. Osteopontin-enriched formula feeding improves the T-cell-dependent humoral immune response in infant rats. Int J Food Sci Nutr. 69(8): 969-975 (https://www.ncbi.nlm.nih.gov/pubmed/30001650)

Bruun et al. 2018. Osteopontin levels in human milk vary across countries and within lactation period: Data from a multicenter study. JPGN. 67(2): 250-256 (https://www.ncbi.nlm.nih.gov/pubmed/29668569)

Demmelmair et al. 2017. Benefits of lactoferrin, osteopontin and milk fat globule membranes for infants. Nutrients. 9(8) (https://www.ncbi.nlm.nih.gov/pubmed/28788066)

Lönnerdal 2017. Bioactive protein in human milk – potential benefits for preterm infants. Clin Perinatol. 44(1): 179-191 (https://www.ncbi.nlm.nih.gov/pubmed/28159205)

Jiang & Lönnerdal 2017. Biological roles of milk osteopontin. Curr Opin Clin Nutr Metab Care. 19(3): 214-219 (https://www.ncbi.nlm.nih.gov/pubmed/27504516)

Lönnerdal 2016. Human milk: Bioactive proteins/peptides and functional properties. Nestlé Nutr Inst Workshop Ser. 86: 97-107 (https://www.ncbi.nlm.nih.gov/pubmed/27337145)

Christensen & Sørensen 2016. Structure, function and nutritional potential of milk osteopontin. Int Dairy J. 57: 1-6 (https://www.sciencedirect.com/science/article/pii/S0958694616300437)

Lönnerdal 2016. Bioactive proteins in human milk: Health, nutrition, and implications for infant formulas. J Pediatr. 173: S4-S9 (https://www.ncbi.nlm.nih.gov/pubmed/27234410)

Lönnerdal et al. 2016. Growth, nutrition, and cytokine response of breast-fed infants and infants fed formula with added bovine osteopontin. JPGN. 62(4): 650-657 (https://www.ncbi.nlm.nih.gov/pubmed/26465791)

Donovan et al. 2014. Bovine osteopontin modifies the intestinal transcriptome of formula-fed infant rhesus monkeys to be more similar to those that were breastfed. J Nutr. 144(12): 1910-1919 (https://www.ncbi.nlm.nih.gov/pubmed/25320184)

Kvistgaard et al. 2014. Pre-clinical in vitro and in vivo safety evaluation of bovine whey derived osteopontin, Lacprodan® OPN-10. Food Chem Toxicol. 73: 59-70 (https://www.ncbi.nlm.nih.gov/pubmed/25072164)

Lönnerdal 2014. Infant formula and infant nutrition: bioactove proteins of human milk and implications for composition of infant formulas. Am J Clin Nutr. 99(3): 12S-17S (https://www.ncbi.nlm.nih.gov/pubmed/24452231)

Chatterton et al. 2013. Anti-inflammatory mechanisms of bioactive milk proteins in the intestine of the newborns. Int J Biochem Cell Biol. 45(8): 1730-1747 (https://www.ncbi.nlm.nih.gov/pubmed/23660296)

Lönnerdal 2011. Biological effects of novel bovine milk fractions. Nestlé Nutr Workshop Ser Pediatr Program. 67: 41-54 (https://www.ncbi.nlm.nih.gov/pubmed/21335989)

Schack et al. 2009. Considerable variation in the concentration of osteopontin in human milk, bovine milk, and infant formulas. J Dairy Sci. 92(11): 5378-5385 (https://www.ncbi.nlm.nih.gov/pubmed/19841198)

List of participants from our side would be (might vary depending on the date of the meeting):

- Tania Porsgaard Bayer, Arla Foods Ingredients, Director of Global Regulatory
- Kal Ramaujam, Arla Foods Ingredients, Senior Scientific Advisor
- Anders Steen Joergensen, Arla Foods Ingredients, Director BU pediatric
- Anne Staudt Kvistgaard, Arla Foods Ingredients, Senior Manager Science and sales development
- Ashley Roberts from Intertek, Senior Vice President – Food & Nutrition
- James W McGrath, Building Block Nutrition

Please let me know if you have any questions. I look forward to hearing from you

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

Arla Foods Ingredients Group P/S

Phone: +4589381562
VAT no.: 33372116

tania.porsgaard.bayer@arlafoods.com
http://www.arlafoodsingredients.com

Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 21. maj 2019 16:09
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: RE: Arla's request for a meeting to discuss osteopontin

Hi Tania,

Thank you for your response. I would be happy to set up a teleconference to discuss your strategy. As I

mentioned before, we will not be able to accommodate an in-person meeting at this time. Please suggest several possible dates and times over the next two months that could work for you and I'll try to accommodate your schedule as best as possible. Keep in mind that it may be more difficult to accommodate a summer meeting with staff travel schedules. Also, please provide a list of attendees and an agenda, along with any materials you'd like our review team to look at ahead of time. Please note that any materials you send may be releasable under the FOIA. Please let me know if you have any questions.

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

From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Monday, May 13, 2019 11:20 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: SV: Arla's request for a meeting to discuss osteopontin

Dear Rachel

Sorry for the late reply, we needed an internal evaluation of your comments below.

We would however, like to proceed with a meeting with FDA, we would prefer a physical meeting since it is often beneficial to sit face-to-face, but understand the shortage of staff and resources.

We will like to talk about a general topic on how to generate compelling evidence of general recognition, we have several ideas and proposals and would like FDA to give some advice to our suggestions. Further we are well aware of the lack in long term effects of our ingredient and would like to work with FDA and experts to create a guideline on this. We are already involved in this at EU level, where EFSA have addressed similar questions.

We hope that this meeting could lead to a more in-depth discussion of GRN 000716 where we can present our strategy the questions addressed by FDA in the scientific memo.

I look forward to hearing from you, hopefully with a date for our meeting.

Best regards, Tania

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

Arla Foods Ingredients Group P/S

Phone: +4589381562
VAT no.: 33372116

tania.porsgaard.bayer@arlafoods.com
http://www.arlafoodsingredients.com

Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 1. maj 2019 17:17
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: Arla's request for a meeting to discuss osteopontin

Dear Tania,

Thank you for your request to meet with FDA to discuss Arla's scientific and regulatory strategies for concluding that osteopontin is safe for use in infant formula. Before we move ahead with a meeting, I want to clarify a few points and make sure that Arla is in agreement with FDA's approach.

By now you've likely had a chance to read the documents that were requested under FOIA, specifically the policy memo, CBER memo, and scientific memo regarding ostepontin and its use in infant formula. FDA's position on this ingredient is clear in these documents: the science surrounding osteopontin, and bioactive ingredients in general, is unsettled and there does not appear to be a general consensus of safety in the greater scientific community. FDA has not seen evidence that questions regarding the long-term consequences of perturbing the developing infant immune system have been asked, let alone there being any sort of consensus on the issue by the greater scientific community. Therefore, FDA is of the position that until this paradigm shift occurs in terms of considering non-traditional toxicological endpoints and possible long-term effects from using bioactive ingredients in infants, and is vetted by the broader scientific community, including experts with appropriate infant immunological expertise, or new data and information become available, FDA would still have questions regarding the basis for a GRAS conclusion for the intended use of osteopontin (and potentially other bioactive ingredients, in general) in infant formula.

With that caveat, FDA is committed to assisting industry in finding a way to generate the general recognition and expert consensus that's currently missing in the field. Therefore, FDA is willing to meet with Arla to discuss its long-term strategies for achieving this goal should Arla still want to move ahead with what will likely be a long-term and resource-intensive endeavor. I want to emphasize that our discussion will focus on Arla's ideas to facilitate a broader discussion to achieve consensus in the greater scientific community surrounding the questions FDA has put forth in its various communications to Arla, and that our discussion should not involve how to "fix" GRN 000716 or spin the existing scientific data to support a current GRAS conclusion.

I should also note that due to a severe shortage in staff and resources, we are currently not accepting in-person meeting requests; however, we can accommodate a teleconference. If Arla is amenable to this approach, then I am happy to work on setting up a meeting.

Please let me know what you think and whether we should move ahead with a teleconference.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Tuesday, April 30, 2019 4:57 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Dodson, Sharon R <Sharon.Dodson@fda.hhs.gov>
Subject: SV: FOI2019-2922 RE: requestor requires assistance with submitting a FOIA

Hi Rachel

Thank you for you fast reply.

No problem, the important thing is that we have the right records for preparation of our meeting.

Do you know when we can expect to have the pre-submission meeting that we have requested? Just for me to prepare flight tickets and arrange hotel.

Thanks.
Tania

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
+4589381562

Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 29. april 2019 17:23
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Cc: Dodson, Sharon R <Sharon.Dodson@fda.hhs.gov>
Emne: FOI2019-2922 RE: requestor requires assistance with submitting a FOIA

Hi Tania,

Yes, these are the same documents. I apologize that you haven't received your responsive records for FOI2019-2922. I fulfilled your FOIA request weeks ago.

Sharon, can you please check on the status of this FOI and whether the records were sent or not?

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Monday, April 29, 2019 11:03 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Dodson, Sharon R <Sharon.Dodson@fda.hhs.gov>
Subject: SV: requestor requires assistance with submitting a FOIA

Dear Rachel

I hope you are doing well.

A customer of ours send me the attached documents last week, that are related to GRN 716 and the

minutes of meetings that you previously referred to. I just wanted to ask you, if you know whether this is the documents we are waiting requested in the FOIA I submitted.

If this is the documents, there is no need for you to spend your time on this

I hope to hear from you soon and look forward to meeting you when we get the pre-submission meeting.

Thanks,
Tania

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

Arla Foods Ingredients Group P/S

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VAT no.: 33372116

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Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 2. april 2019 22:41
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>; Dodson, Sharon R <Sharon.Dodson@fda.hhs.gov>
Cc: Dodson, Sharon R <Sharon.Dodson@fda.hhs.gov>
Emne: requestor requires assistance with submitting a FOIA

Hi Tania,

I'm sorry you're still having problems getting this FOIA submitted. I'm ccing our office's FOIA contact, Sharon Dodson. Sharon will be able to help you find someone else to help if you're not getting anywhere with Yessenia. The policy memo is referenced in the scientific memo and various emails in the GRN 000716 record. The memo of meeting held by the Office of Food Additive Safety with participants from CBER is the second document that you should request. This memo originated from CFSAN and therefore does not require a record search by CBER.

Sharon, can you please assist Ms. Bayer with her FOIA request? If you recall, she was having technical difficulties when trying to submit the request online and kept getting error messages. I referred her to Yessenia Garcia as you suggested, but she has not been able to get a hold of her.

Thanks,

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

From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Tuesday, April 02, 2019 10:18 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: SV: Request for a Pre submission meeting GRN 000716

Dear Rachel

I didn't manage to get a hold on Yessenia Garcia, but I'll try again.

We do have the memo from the meeting we had on March 1st and also the scientific memo. What we do not have is the meeting memo you refer to, the interaction with CBER. Also, I am not sure what is the OFAS policy memo.
I am not sure whether we are missing additional documents, hence I'll try to get a hold on Yessenia Garcia and submit a FOIA.

Thank you for your support on this.

Best regards, Tania

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

Arla Foods Ingredients Group P/S

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VAT no.: 33372116

tania.porsgaard.bayer@arlafoods.com
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Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 28. marts 2019 18:01
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: RE: Request for a Pre submission meeting GRN 000716

Dear Tania,

I just wanted to follow-up with a point of clarification on this FOIA request. This is a CFSAN-only document search. The mention of “CBER” in the request may trigger the FOIA office to forward this to both CFSAN and CBER. If the FOIA office reaches out to you for clarification, you can inform them that this is a memo for a meeting that was held by CFSAN with a few CBER attendees. Therefore, it is a CFSAN meeting memo and does not require a search by CBER. Please ask them to reach out to me directly if there are any issues.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

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

U.S. FOOD & DRUG ADMINISTRATION

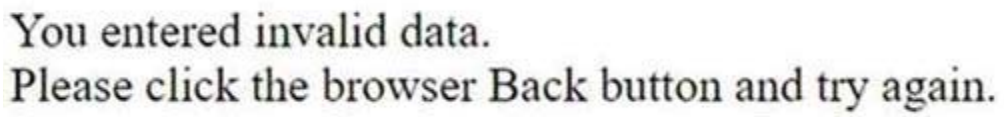
From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Tuesday, March 26, 2019 11:05 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: SV: Request for a Pre submission meeting GRN 000716

Dear Rachel

Thank you for your feedback.
Unfortunately, I'm not able to submit the FOIA, attached it the request, but when I press 'submit' I keep getting a message that I've entered invalid data and have to start over again, but I've only filled in the required data.

In the FOIA I've asked for:
I would like to get a copy of the policy memo (OFAS policy) referenced in the GRN 000716 documents.
and I would request CBER meeting memos related to osteopontin and GRN 000716.
Any additional materials and documents related to osteopontin and GRN 000716 would also be of interest. Thanks

Can you send me this based on the attached request?



Med venlig hilsen / Best regards

Tania Porsgaard Bayer
+4589381562

Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 26. marts 2019 12:59
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: RE: Request for a Pre submission meeting GRN 000716

Hi Tania,

Sorry for the delay. Before we move ahead with scheduling this meeting, I want to let you know that we have finalized the policy memo that was referenced in the GRN 000716 documents. We strongly encourage Arla to FOIA this document. There is also a meeting that occurred between our staff and our colleagues at the Center for Biologics Evaluation and Research (CBER). We also suggest that Arla FOIA this meeting memo. In your FOIA request you can reference the OFAS policy and CBER meeting memos related to osteopontin and GRN 000716. I will receive that FOIA request and will fill it promptly, as the documents are ready to go. Once you've had a chance to review those documents, then we can schedule a meeting. We wanted Arla to have all the information necessary in preparation for a meeting with FDA on the intended use of its bovine osteopontin product. Please let me know if you have any questions at this time.

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: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Thursday, March 14, 2019 8:02 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Ashley Roberts Intertek (ashley.roberts@intertek.com) <ashley.roberts@intertek.com>; Kal Ramanujam <Kal.Ramanujam@arlafoods.com>; Anders Steen Jørgensen <anders.steen.jorgensen@arlafoods.com>; Ida Aabrandt Ottosen <ida.aabrandt.ottosen@arlafoods.com>; Anne Staudt Kvistgaard <anne.staudt.kvistgaard@arlafoods.com>
Subject: SV: Request for a Pre submission meeting GRN 000716

Dear Rachel

Our suggestion for an agenda is:

RE: To discuss the development of a future scientific and regulatory strategy to support the future general recognition of the safety of the intended use of bOPN in infant formula.

In the last face to face meeting held on March 1st 2018, and subsequent correspondence with FDA, we have been advised to consult FDA after going through information outlined in scientific memo dated June 29th 2018. We have reviewed the scientific memo and previous discussions with FDA and also consulted scientific experts and have outlined several possible avenues. We would like to discuss with FDA how best to address the safety and general recognition concerns raised by the

agency. We would like to discuss the following topics in the pre-submission meeting and seek guidance on the relevant approaches that would help us navigate the safety concerns expressed.

As part of this process Arla wishes to outline the following within the meeting;

1. How to develop evidence to support the general recognition of the intended use of bOPN. the use of an Expert Panel, a publication program within a supplementary scientific journal, or a third approach
2. A review of current evidence to address the potential adverse consequences of exogenously provided bOPN on the developing immune system as expressed by FDA.
3. A review of the recent published studies on hOPN levels within breast milk within various regions/locations to provide support for the recommended levels of bOPN to be added to infant formula
4. Any additional topics or avenues to be pursued

Arla looks forward to having dialogue with the agency on these matters in the hope of obtaining guidance on the strategy as develop.

List of participants from our side would be (might vary depending on the date of the meeting):

- Tania Porsgaard Bayer, Arla Foods Ingredients, Director of Global Regulatory
- Kal Ramaujam, Arla Foods Ingredients, Senior Scientific Advisor
- Anders Steen Joergensen, Arla Foods Ingredients, Director BU pediatric
- Anne Staudt Kvistgaard, Arla Foods Ingredients, Senior Manager Science and sales development
- Ida Ottosen, Arla Foods Ingredients, Regulatory Specialist
- Ashley Roberts from Intertek, Senior Vice President – Food & Nutrition
- James W McGrath, Building Block Nutrition

Med venlig hilsen / Best regards

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

Arla Foods Ingredients Group P/S

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VAT no.: 33372116

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http://www.arlafoodsingredients.com

Fra: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sendt: 26. februar 2019 15:44
Til: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: RE: Request for a Pre submission meeting GRN 000716

Hi Tania,

Can you please provide an agenda with list of participants for this pre-submission meeting?

Thank you.

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, February 25, 2019 12:50 PM
To: 'Tania Porsgaard Bayer' <tania.porsgaard.bayer@arlafoods.com>
Subject: RE: Request for a Pre submission meeting GRN 000716

Hi Tania,

I just wanted to reach out and let you know that I'll be handling your pre-submission meeting request. I'll be in touch shortly to start the scheduling process.

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: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Thursday, February 21, 2019 3:14 PM
To: West-Barnette, Shayla <Shayla.WestBarnette@fda.hhs.gov>
Cc: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: SV: Request for a Pre submission meeting GRN 000716

Dear Shayla

I hope you are well, and I was sorry for the lock down of your department in January that I know have resulted in a heavy workload for you after returning. Nevertheless I wanted to ask you if you have appointed a Consumer Safety Officer that will work with us on a pre submission meeting for GRN 000716?

Med venlig hilsen / Best regards

Arla

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

Arla Foods Ingredients Group P/S

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Fra: West-Barnette, Shayla <Shayla.WestBarnette@fda.hhs.gov>
Sendt: 18. december 2018 15:26
Til: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>; Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Emne: RE: Request for a Pre submission meeting GRN 000716

Thank you, Rachel.

Ms. Bayer, I will work on routing your request to a Consumer Safety Officer who can help you.

Regards,

Shayla

From: Morissette, Rachel
Sent: Tuesday, December 18, 2018 8:51 AM
To: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Cc: West-Barnette, Shayla <Shayla.WestBarnette@fda.hhs.gov>
Subject: RE: Request for a Pre submission meeting GRN 000716

Dear Ms. Bayer,

Thank you for reaching out to me regarding your request for a pre-submission meeting. I apologize that you haven't been able to reach our staff. Nadine Bewry is no longer with the agency. However, I am ccing her former supervisor, Dr. Shayla West-Barnette (who was also the supervisor involved in GRN 000716), on this email. Dr. West-Barnette or a member of her team will reach out to you shortly. Merry Christmas to you as well.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Acting Supervisory 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

U.S. FOOD & DRUG ADMINISTRATION

From: Tania Porsgaard Bayer <tania.porsgaard.bayer@arlafoods.com>
Sent: Tuesday, December 18, 2018 7:43 AM
To: Nadine.Bewry@fda.hhs.gov
Cc: Better-Nolan, Robin * <Robin.Better-Nolan@fda.hhs.gov>
Subject: Request for a Pre submission meeting GRN 000716

Dear Rachel Morissette

I'm reaching out to you because I keep getting a 'non-delivery' message when I write to Nadine Bewry, she has been the contact person when we had any contact with FDA on our previous GRAS submission of GRN000716. I hope you can help me with my request or pass the email on the to relevant person.

Back in June 2018 we (Arla Foods Ingredients) received a scientific memorandum based for our ingredient bovine osteopontin (GRN 000716). Internally we have discussed how to best accommodate the safety concerns raised, and I hope we can get a pre-submission meeting with CFSAN and/or other relevant staff members, to discuss our approach for addressing the safety concerns raised by FDA.

Attached is my request for a meeting, I hope it will be possible to meet in the beginning of the new year.

Please let me know if you need further from be before such a meeting can be arranged.

Merry Christmas.

Med venlig hilsen / Best regards

Arla

Tania Porsgaard Bayer
Director / Head of Global Regulatory Affairs

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