From: Bewry, Nadine
To: "Jim Heimbach"
Cc: Henoud Solange
Subject: GRN 000758 (bacterial mixture): FDA"s follow-up comments - please respond by 5/11/2018
Date: Monday, April 30, 2018 1:52:00 PM
Attachments: image001.png
Bertelli 2015 Bifidobacterium longum bacteremia.pdf

Dear Dr. Heimbach,

Thank you for providing a response to our questions, including the Certificates of Analysis for each strain and for the combination.

The review team has three follow-up comments below:

1. In addition to specifications for microbes, the notice includes other specifications (i.e. heavy metals). Please provide the batch data for the other specifications in the notice.
2. We are aware of a case report on bacteremia in preterm infants with one species of the organisms (see attached document). Please discuss how the information in the case report does not represent a safety risk in the intended population (i.e. term infants).
3. The organisms that are the subject of GRN 000758 are intended for use in infant formula; however, they are also used in other foods. Please make a clear statement on whether the consumption of these organisms in foods other than infant formula would be substitutional and not result in increased exposure to the organisms as the consumption of infant formula decreases with age.

Please provide the notifier's response by COB Friday, May 11, 2018.

Feel free to contact me if you have questions.

Best regards,

Nadine Bewry, PhD, MPH
Consumer Safety Officer | Toxicology Reviewer

From: Jim Heimbach [mailto:jh@jheimbach.com]
Sent: Tuesday, April 24, 2018 2:45 PM
To: Bewry, Nadine <Nadine.Bewry@fda.hhs.gov>
Cc: Henoud Solange <shenoud@lallemand.com>
Subject: RE: GRN 000758 (bacterial mixture): FDA's comments - please respond by 4/27/2018

Dear Dr. Bewry—

Here are our responses to the three questions posed by FDA in your email of April 17.

- **The notice states that the subjects of the notice are intended for use in infant formula for healthy term infants. Please clarify whether the intended use applies to exempt or non-exempt infant formulas.**

We assumed that it was implicit that the target is non-exempt infant formula, but we should have stated this explicitly. The probiotics are indeed intended for addition to non-exempt infant formula.

- **The notice provides specifications of the subjects of the notice. Please provide the batch data to confirm these specifications.**

Certificates of Analysis are attached for each strain and for the combination.

- **The notice cites a study by Borriello et al. (2003) on the risk of bacteremia from probiotic lactobacilli and bifidobacteria. Please discuss whether or not this poses a safety concern for infants.**

We do not believe that the work of Borriello et al. (2003) poses a concern. While Borriello et al. indicate that cases of infection due to lactobacilli and bifidobacteria are not unknown, they also indicate that such adverse events are "extremely rare." Indeed, the thrust of the article is, first, that there is no such thing as zero risk (a mantra well recognized and often propounded by FDA itself), and, second, that they are sufficiently rare that the safety standard of "reasonable certainty of no harm" is accommodated. Indeed, the closing phrase of the article is that "consumption of such products presents a negligible [my emphasis] risk to consumers, including immunocompromised hosts."

Borriello et al. (2003) argue that, even though the *a priori* probability of harm from *Lactobacillus* or *Bifidobacteria* strains is quite small, that nevertheless the risk should be further reduced by addressing potential concerns such as acquired (and thus potentially transferable) antibiotic resistance or the presence of genes encoding virulence or decarboxylation, as well as by appropriately designed human studies. All of these approaches were used in demonstrating the safety of the bacterial strains addressed in GRN 000758.

With the data available, we and the Expert Panel are confident that the generally available information on the strains, both individually and in combination, satisfies both Borriello et al.'s recommendations and the GRAS safety standard of reasonable certainty of no harm.

Regards,
Jim

James T. Heimbach, Ph.D., F.A.C.N.
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Cell (+1) 202-320-3063

From: Bewry, Nadine [mailto:Nadine.Bewry@fda.hhs.gov]

Sent: Tuesday, April 17, 2018 6:19 PM
To: Jim Heimbach
Subject: GRN 000758 (bacterial mixture): FDA's comments - please respond by 4/27/2018

Dear Dr. Heimbach,

In reviewing GRN 000758, our review team would like the notifier to address our comments below:

- The notice states that the subjects of the notice are intended for use in infant formula for healthy term infants. Please clarify whether the intended use applies to exempt or non-exempt infant formulas.
- The notice provides specifications of the subjects of the notice. Please provide the batch data to confirm these specifications.
- The notice cites a study by Borriello et al. (2003) on the risk of bacteremia from probiotic lactobacilli and bifidobacterial. Please discuss whether or not this poses a safety concern for infants.

To facilitate the timely review of the notice, please email the notifier's response by COB Friday, April 27, 2018.

Please let me know if you have any questions.

Best regards,

Nadine Bewry, PhD, MPH
Consumer Safety Officer | Toxicology Reviewer

Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
FDA U.S. FOOD & DRUG ADMINISTRATION

Four pages have been removed in accordance with copyright laws. The removed reference citation is:

Bertelli, “Bifidobacterium longum bacteremia in preterm infants receiving probiotics”, Clin Infect Dis. 2015 Mar 15;60(6):924-7. doi: 10.1093/cid/ciu946. Epub 2014 Dec 3. https://academic.oup.com/cid/article-abstract/60/6/924/497369

From:	Jim Heimbach
To:	West-Barnette, Shayla
Subject:	GRN 758
Date:	Wednesday, August 01, 2018 3:18:58 PM

Dear Dr. West-Barnette—

There are no allergens in the fermentation medium used in the production of *Lactobacillus helveticus* Rosell®-52 (R0052), *Bifidobacterium longum* ssp. *infantis* Rosell®-33 (R0033), and *Bifidobacterium bifidum* Rosell®-71 (R0071) and no allergens in the final product.

Regards,
Jim

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CERTIFICATE OF ANALYSIS

Product : **Bifidobacterium infantis R0033**

Lot : **93343**

Date of beginning analysis: 19/06/17

Manufacturing date: 06/17

Microbiological control :

Tests	Specifications	Results	Methods
Physical aspect	**Fine to granular, ivory to beige powder**	Complies	Visual observation
Bif. infantis	**NA**	170.10e9/g	Bacteriological enumeration on house method
Yeasts and molds	**< 1000 cfu / g**	Complies	Enumeration on Sabouraud or PDA culture medium + chloramphenicol, after incubation at 20-25°C for 5 to 7 days
Coliforms	**< 10 cfu / g**	Complies	ISO 4831
Escherichia coli	**< 10 cfu / g**	Complies	ISO 7251
Staphylococcus aureus	**< 10 cfu / g**	Complies	ISO 6888-1
Enterobacter sakazakii (cronobacter spp) *	**30 x Absent/10g**	Complies	ISO 22964
Salmonella spp *	**60 x Absent/25g**	Complies	ISO 6579

*21CFR (code of Federal Regulations) - Part 106 Infant Formula Requirements - Section 106.55 (Controls to prevent adulteration from microorganisms)

Saint-Simon, April 24, 2018

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CERTIFICATE OF ANALYSIS

Product : **Bifidobacterium bifidum R0071**

Lot : **95967**

Date of beginning analysis: 26/09/17

Manufacturing date: 09/17

Microbiological control :

Tests	Specifications	Results	Methods
Physical aspect	**Fine to granular, ivory to beige powder**	Complies	Visual observation
Bif. bifidum	**NA**	250.10e9/g	Bacteriological enumeration on house method
Yeasts and molds	**< 1000 cfu / g**	Complies	Enumeration on Sabouraud or PDA culture medium + chloramphenicol, after incubation at 20-25°C to 5 to 7 days
Coliforms	**< 10 cfu / g**	Complies	ISO 4831
Escherichia coli	**< 10 cfu / g**	Complies	ISO 7251
Staphylococcus aureus	**< 10 cfu / g**	Complies	ISO 6888-1
Enterobacter sakazakii (cronobacter spp) *	**30 x Absent/10g**	Complies	ISO 22964
Salmonella spp *	**60 x Absent/25g**	Complies	ISO 6579

*21CFR (code of Federal Regulations) - Part 106 Infant Formula Requirements - Section 106.55 (Controls to prevent adulteration from microorganisms)

Saint-Simon, April 24, 2018

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CERTIFICATE OF ANALYSIS

Product : **Lactobacillus helveticus R0052 ND**

Lot : **62/17 S3**

Date of beginning analysis: 31/10/17

Manufacturing date: 10/17

Microbiological control :

Tests	Specifications	Results	Methods
Physical aspect	**Fine to granular, ivory to beige powder**	Complies	Visual observation
Lb helveticus	**NA**	410.10e9/g	Bacteriological enumeration on house method
Yeasts and molds	**< 1000 cfu / g**	Complies	Enumeration on Sabouraud or PDA culture medium + chloramphenicol, after incubation at 20-25°C to 5 to 7 days
Coliforms	**< 10 cfu / g**	Complies	ISO 4831
Escherichia coli	**< 10 cfu / g**	Complies	ISO 7251
Staphylococcus aureus	**< 10 cfu / g**	Complies	ISO 6888-1
Enterobacter sakazakii (cronobacter spp) *	**30 x Absent/10g**	Complies	ISO 22964
Salmonella spp *	**60 x Absent/25g**	Complies	ISO 6579

*21CFR (code of Federal Regulations) - Part 106 Infant Formula Requirements - Section 106.55 (Controls to prevent adulteration from microorganisms)

Saint-Simon, April 24, 2018

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CERTIFICATE OF ANALYSIS

Product : **PROBIOKID**

Lot : **6532347**

Date of beginning analysis: 06/11/17

Manufacturing date: 11/17

Microbiological control :

Tests	Specifications	Results	Methods
Yeasts and molds	**< 1000 cfu / g**	Complies	ISO 7954
Coliforms	**< 10 cfu / g**	Complies	ISO 4831
Escherichia coli	**< 1 cfu / g**	Complies	ISO 7251
Staphylococcus aureus	**< 10 cfu / g**	Complies	ISO 6888-1
Enterobacter sakazakii (cronobacter spp) *	**30 x Absent/10g**	Complies	ISO 22964
Salmonella spp *	**60 x Absent/25g**	Complies	ISO 6579

*21CFR (code of Federal Regulations) - Part 106 Infant Formula Requirements - Section 106.55 (Controls to prevent adulteration from microorganisms)

Saint-Simon, April 24, 2018

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