

Call for Submissions – Proposal P1028:

We, Morinaga Milk Industry Co., Ltd. are writing this letter in order to give some opinions regarding Proposal P1028. We insist that we do not need to conduct a separate pre-market assessment as a novel food prior to use if there are similar or identical safety acknowledgements such as GRAS as an example and there are also multiple studies indicating benefits for children and infants, and the following proposed change will not need to include. Details are stated as follows.

Ref: 5.4 L(+) lactic acid producing microorganisms (page 42)

FSANZ assessed the risk to the health and safety of infants — healthy, as well as preterm, low birth weight and immunocompromised — from the addition to infant formula products of any L(+) lactic acid producing microorganisms (FSANZ 2021b). FSANZ concluded that the use of non-toxigenic L(+) lactic acid producing bacteria in the production of fermented infant formula, where no viable bacteria are present in the final product, does not present a risk to public health and safety. On this basis and taking into consideration information provided by stakeholders (noted in section 6 of SD1) FSANZ's preferred option is to retain the existing permission, however clarify that L(+) lactic acid producing microorganisms may only be added for acidification purposes. FSANZ also proposes to clarify the permission that only non-pathogenic or non-toxigenic microorganisms may be used.

FSANZ also notes that microorganisms added to infant formula products for a probiotic purpose require pre-market assessment as a novel food prior to use.

The use of L(+) lactic acid producing microorganisms for acidification in SMPPi should only be used if supported by generally accepted scientific data.

1. Usage history and Safety proof of Bifidobacterium strains

Bifidobacteria are a natural component of the normal human gut microflora. Especially, our Bifidobacterium strains stated as follows were proved its safety and widely used in infant formula all over the world. We can say that they are not categorized as Novel food.

a. *Bifidobacterium longum* BB536

- Its safety for infant formula use was approved by some global strict standards. Such as USA GRAS (GRN877) and Chinese New food ingredient.
- *Bifidobacterium longum* BB536 was first commercially available in Japan in 1977. At present, several products containing *B. longum* BB536 are available in various countries. The availability of *B. longum* BB536 in Europe began in 1986 with the production of Morinaga Bifidus Yogurt in France, followed by Sweden in 1989. In 1994, *B. longum* BB536 was sold as a frozen starter to dairy companies in Germany, Russia, Poland and other EU countries.
- In Australia, Bubs organic, LLC. has been using BB536 in their infant formula. In addition, BB536 has been used in Australian NICU and proved its safety (Rao et al., 2021).

b. *Bifidobacterium breve* M-16V

- Its safety for infant formula use was approved by some global strict standards. Such as USA GRAS (GRN454, 455) and Chinese New food ingredient.
- *B. breve* M-16V was introduced into the Japanese market in 1976 in a dietary supplement. In 1982, Morinaga added *B. breve* M-16V to a growing-up powdered formula for the first time and has since added it to several other products in various countries.

- M-16V has been used in Australian NICU and proved its safety (Rao et al., 2021).

c. *Bifidobacterium infantis* M-63

- Its safety for infant formula use was approved by USA GRAS (GRN1003).
- *B. infantis* M-63-containing ingredients for use in infant formulas in international markets since 2006. M-63 is also widely used in infant formula, and follow-on formula in various countries, such as Spain, France, Indonesia, China and so on.
- M-63 has been used in Australian NICU and proved its safety (Rao et al., 2021).

2. Examples of International regulation regarding probiotics usage for infant formula

There are already some positive list system for probiotics which can be used in infant formula in the world. Since these registration requirement are quite severe, we believe that these lists can be helpful in order to skip or shorten the pre-assessment process by FSANZ. Because some probiotics ingredients are already used in infant formula launched in Australia, these lists are also helpful to avoid the confusion in market.

- FDA GRAS in USA

According to USA FDA, substances used in infant formula must be generally recognized as safe (GRAS) and those that are used in accordance with the FDA's food additive regulations (FFDCA 201(s) and 409). We can refer the probiotics list which are obtained GRAS status in FDA website, and our *Bifidobacterium*, *Bifidobacterium longum* BB536, *Bifidobacterium breve* M-16V, *Bifidobacterium infantis* M-63, have already obtained FDA GRAS status.

- New Food Ingredient in China

In China, there are probiotics positive lists showing the approved ingredients to add in final products targeted <3 years age. As there are only less than 15 strains in this list, we believe that this list shows the well-proved safety. Our *Bifidobacterium longum* BB536 and *Bifidobacterium breve* M-16V are listed in.

3. Examples of studies regarding probiotics usage for infant formula

Lists of research papers on the three strains described in 1-a, b, and c are attached. In each list, the following numbers of papers in the list correspond to articles related to infants or children.

- In the study list of BB536: 12, 19, 28, 52, 69, 102, 106, 110, 136, 139, 142, 147, 152, 160, 173, 221, 232, 233
- In the study list of M-16V : 40, 66, 114, 121, 122, 47, 49, 64, 110, 57
- In the study list of M-63 : 6, 27, 28, 29, 30, 12, 18, 17

These results provide evidence for the benefits of these strains in children and infants. In other words, it is not necessary to conduct a separate pre-market assessment again.

References;

GRN 454 (2013). *Bifidobacterium breve* M-16V. Morinaga Milk Industry Co., Ltd.

<https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=grasnotices&id=454>.

GRN 455 (2013). *Bifidobacterium breve* M-16V. Danone Trading B.V.

<https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=grasnotices&id=455>.

GRN 877 (2019). *Bifidobacterium longum* BB536. Morinaga Milk Industry Co., Ltd.

<https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=877>.

GRN 1003 (2022). *Bifidobacterium infantis* M-63. Morinaga Milk Industry Co., Ltd.

<https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=1003>.

National Health Commission of the People's Republic of China (2022)

<http://www.nhc.gov.cn/sps/s7892/202205/fc11e1c1a90d4b99b87e313cce938697.shtml>

Rao, S., Esvaran, M., Chen, L. et al. Probiotic supplementation in neonates with congenital gastrointestinal surgical conditions: a pilot randomised controlled trial. *Pediatr Res* (2022).

<https://doi.org/10.1038/s41390-021-01884-x>

Guidance for Industry: Frequently Asked Questions about FDA's Regulation of Infant Formula

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-frequently-asked-questions-about-fdas-regulation-infant-formula>