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Application to Amend the Australia New Zealand Food Standards Code to Use 3-Fucosyllactose Produced using Gene Technology as a Nutritive Substance in Infant Formula Products

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Glycom A/S is ultimately controlled by DSM-Firmenich AG, registered in Kaiseraugst, Switzerland.

Executive Summary

Glycom A/S[1] (Glycom herein), is seeking to amend the Australia New Zealand Food Standards Code (the Code) for the use of 3-fucosyllactose (3-FL) produced by microbial fermentation as a nutritive substance in infant formula products. 3-FL is among the 10 most abundant human milk oligosaccharides (HMOs) in breastmilk. It is a simple structural isomer of 2'-FL, also belonging to the fucosylated HMO structural class. However, unlike 2'-FL, 3-FL occurs in the breastmilk of all women irrespective of their Secretor status, and unlike most other HMOs, the concentration of 3-FL increases throughout lactation.

The purpose of the addition of manufactured 3-FL to infant formula products is to more closely reflect the natural composition of breastmilk and associated benefits. This is consistent with provisions set forth in the *Codex Standard for Infant Formula and Formulas for Special Medical Purposes Intended for Infants*, the *Codex Standard for Follow-Up Formula for Older Infants*, and the Australia and New Zealand Ministerial *Policy Guideline on Infant Formula Products*.

3-FL is intended to be added to infant formula products alone or in combination with other manufactured HMOs already permitted for use at a maximum use level of 2.0 g/L (equivalent to 80 mg/100 KJ). This maximum use level is within the mean concentrations of 3-FL in mature human milk and has already been evaluated and determined to be safe by the United Kingdom's Advisory Committee on Novel Foods and Processes.

Glycom's manufactured 3-FL is chemically and structurally identical to 3-FL that is naturally occuring in human breastmilk. The 3-FL ingredient is produced from the same *Escherichia coli* (*E. coli*) K-12-derived platform strain as Glycom's other HMOs already authorised for use in Australia and New Zealand (schedule 26), including:

Application A1155	• 2'-Fucosyllactose (2'-FL) • Lacto-N-neotetraose (LNnT)
Application A1265	• A combination of 2'-fucosyllactose and difucosyllactose (2'-FL/DFL) • Lacto-N-tetraose (LNT) • 6'-sialyllactose sodium salt (6'-SL) • 3'-sialyllactose sodium salt (3'-SL)

The 3-FL production strain contains the gene for α-1,3-fucosyl-transferase necessary for the biosynthesis of 3-FL. The donor gene from *Helicobacter pylori* is derived from *de novo* DNA synthesis based on defined DNA sequences obtained from bioinformatic databases, and the identity and function of the enzyme is well-characterised. The production organism will not

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enter Australia or New Zealand as 3-FL will be manufactured in Denmark under contained use of the genetically modified microorganism.

Glycom manufactures 3-FL in compliance with current Good Manufacturing Practice (cGMP) and principles of Hazard Analysis Critical Control Point (HACCP). The manufacturing process can be broadly divided into 2 stages. The first stage (upstream processing) consists of a controlled fermentation process where the production organism with adapted cellular metabolism of 3-FL is incubated with lactose (the substrate) and a carbon energy source (glucose, glycerol, or sucrose). During fermentation, 3-FL is secreted extracellularly from the fermentation organism into the culture medium. The second stage (downstream processing) consists of the removal of the production organism and the purification of 3-FL. The resulting 3-FL ingredient is specified as having a purity ≥ 90.0 w/w %. The remaining ingredient composition primarily consists of lactose (the substrate) and other related and fully characterised carbohydrates produced during the fermentation process, most of which are naturally occurring components of human milk. Food grade specifications established by Glycom include these fermentation by-products and other relevant trace elements, as well as microbiological parameters to ensure the purity and quality of the final product. Batch analyses demonstrate that the manufacturing process consistently produces 3-FL that is compliant with the established specifications.

3-FL does not undergo any significant digestion in the upper gastrointestinal tract, similar to other HMOs. 3-FL is fermented in the colon by the intestinal microbiota or is excreted unchanged in the faeces. A small proportion of ingested HMOs may be absorbed intact and excreted in the urine. Glycom's 3-FL has been tested in a comprehensive series of toxicological studies, including a bacterial reverse mutation assay, an *in vitro* mammalian cell micronucleus test in human lymphocytes, and an adapted sub-chronic (90-day) oral toxicity study in neonatal rats. These studies, which have been conducted in compliance with the Organization for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP) and relevant OECD Test Guidelines, demonstrate that the manufactured 3-FL does not pose any toxicological concern.

Three randomised controlled clinical studies have been conducted in healthy term infants receiving formula supplemented with 3-FL in combination with other HMOs. Experimental formulas containing 3-FL supported age-appropriate growth and were safe and well-tolerated. Additionally, two of the three clinical trials evaluated benefit-related outcomes. Experimental formulas containing 3-FL shifted the composition of the gut microbiome closer to that of breastfed infants by increasing the abundance of beneficial *Bifidobacteria* and decreasing pathogenic bacteria. Pre-clinical data reinforce the bifidogenic effect of 3-FL and defence against infection. Pre-clinical and clinical data also suggest that 3-FL supports intestinal barrier function and establishment of gut maturity.

Glycom's 3-FL manufactured by microbial fermentation is already authorised for use in infant formula products in other jurisdictions with comparable regulatory processes to Australia and

New Zealand. Notably, Glycom's 3-FL has obtained novel food approval in the European Union (EU) and the United Kingdom (UK), and has been notified as Generally Recognized as Safe (GRAS) in the United States of America (USA). 3-FL in combination with up to 5 other HMOs has already been commercialised in infant formula products in several markets, from which post-market surveillance data indicate no untoward effects.

Intakes of 3-FL under the proposed conditions of use were estimated using model diets for infants 3- and 9-months of age, similar to the FSANZ approach for Applications A1155 and A1265. As the maximum proposed use level of 3-FL is within the mean concentration of 3-FL in human breastmilk, the anticipated dietary intake of 3-FL from infant formula products is similar to that by breastfed infants.

Overall, the available scientific evidence, together with the history of safe consumption of 3-FL from human milk, support the safe use of Glycom's 3-FL in infant formula products. Furthermore, pre-clinical and clinical data support beneficial health effects of 3-FL supplementation in formula-fed infants, particularly in the development of a gut microbiome closer to that of breastfed infants. It is anticipated that the approval of Glycom's 3-FL as a nutritive substance for addition to infant formula products in Australia and New Zealand will benefit consumers and industry alike through the improvement of infant formula products that more closely reflect the composition of human breastmilk.