GENERALLY RECOGNIZED AS SAFE (GRAS) NOTIFICATION FOR LACTOFERRIN (HUMAN) FROM RICE FOR USE AS AN INGREDIENT IN PEDIATRIC MEDICAL FOODS AND ORAL REHYDRATION SOLUTIONS

Resubmission of Amended GRN 000162

Prepared by

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Contains No Confidential Business Information
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September 27, 2007

Robert L. Martin, Ph.D.
U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
CFSAN/OO/OFAS/DBGNR
HFS-255
Harvey W. Wiley Federal Building
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Re-submission of GRAS Exemption Claim for Lactoferrin (human) from rice (GRN 0000162) for limited use as an ingredient in pediatric medical foods and oral rehydration solutions.

Dear Dr. Martin,

Ventria is resubmitting the GRAS Exemption Claim for Lactoferrin, GRN 000162, with the intended use amended to be limited to use in pediatric medical foods and oral rehydration solutions that are intended to provide additional nutritional support during episodes of diarrhea. We hereby incorporate by reference the information in GRN 162 to the extent that it relates to the use in the pediatric population.

We are resubmitting this amended GRAS Exemption Claim based on discussions with the review team at DBGRN on the presence of lactoferrin in breast milk and the use of lactoferrin in medical foods for children. This notice establishes that lactoferrin (human) from rice is GRAS as an ingredient for addition to pediatric medical foods and oral rehydration solutions, intended for intake as nutritional support during episodes of diarrhea, at levels up to 1.0 mg/mL. Lactoferrin is an important component of breast milk and the proposed levels are comparable to levels found in breast milk.

In accordance with the criteria set forth in the GRAS notification proposed regulation 21 CFR 170.36(c) (62 Federal Register 18937 (April 17, 1997)), Ventria is resubmitting the following information as part of its GRAS exemption claim.

Enclosed please find an original, two copies and one electronic copy on disk of this notification for review. If you have any questions, please contact me at the phone number and address below.

Sincerely,

Delia R. Bethell, Ph.D.
Vice President for Clinical Development

Enclosures
cc: Scott Deeter, President & CEO
GRAS Exemption Claim for Lactoferrin (human) from Rice

Name and Address of Notifier:
Ventria Bioscience
4110 N. Freeway Blvd.
Sacramento, CA 95834

Contact: Delia Bethell, Ph.D.
Vice President for Clinical Development
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Common or Usual Name of GRAS Substance:
Recombinant Human Lactoferrin from Rice is the common or trade name for the iron-binding glycoprotein isolated from transgenic rice. The published literature may also refer to lactoferrin as red milk protein (Masson and Heremans 1971), lactosiderophilin (Montreuil and Mullet 1960), ekkinosiderophilin (Schade 1977), or lactotransferrin (Legrand, Mazurier et al. 1991).

Conditions of Use:
Ventria intends to make lactoferrin (human) from rice available for addition to pediatric medical foods and oral rehydration solutions, ORS, which are designed to provide additional nutritional support during episodes of diarrhea. The inclusion level in such products is 1.0 mg/mL rhLF, which is consistent with the level of lactoferrin found naturally in human milk.

Basis for GRAS Determination:
Ventria Bioscience has determined that lactoferrin (human) from rice is a GRAS ingredient on the basis of scientific procedures. This document establishes the safety and the consensus by qualified experts that lactoferrin (human) from rice is a GRAS ingredient.

Availability of Data:
The data and information that serve as the basis for this GRAS notification will be sent to the FDA upon request or are available for the FDA’s review and copying at reasonable times at the offices Ventria Bioscience, 4110 N. Freeway Blvd., Sacramento, CA 95834.

GRAS Exemption Claim:
The use of lactoferrin (human) from rice in pediatric medical foods and oral rehydration solutions intended for use as nutritional support during episodes of diarrhea at a maximum use level of 1.0 mg/mL, is exempt from premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because Ventria Bioscience has determined that such uses are GRAS.
ADDITIONAL INFORMATION

A. IDENTIFY OF THE NOTIFIED SUBSTANCE

1. COMMON OR USUAL NAME

Human Lactoferrin; Lactoferrin (Human); Recombinant Human Lactoferrin from Rice Lactoferrin (Human) from Rice. Published literature also refers to red milk protein (Masson and Heremans 1968), Lactosiderophilin (Montreuil and Mullet 1960), Ekkrinosiderophilin (Schade 1977) and Lactotransferrin (Legrand, Mazurier et al. 1991).

2. PRODUCT DESCRIPTION

Ventria Bioscience’s recombinant human lactoferrin is expressed in rice and substantially equivalent to the lactoferrin protein present in breast milk at concentrations of 1-10 mg/mL. Incorporated by reference is the product description information provided in GRAS Notice GRN 000162.

3. METHOD OF MANUFACTURE

Incorporated by reference is the manufacturing information provided in GRAS Notice 0000162.

4. CHARACTERISTIC PROPERTIES

Incorporated by reference is the product properties information provided in GRAS Notice 0000162.

5. ANY CONTENT OF POTENTIAL HUMAN TOXICANTS

None.

6. SPECIFICATIONS FOR RECOMBINANT HUMAN LACTOFERRIN PRODUCTS

Incorporated by reference is the product specification data and information provided in GRAS Notice 0000162.
B. LACTOFERRIN PROVIDES NUTRITIONAL SUPPORT DURING DIARRHEA

Ventria Bioscience intends to make lactoferrin (human) from rice available for addition to pediatric medical foods and oral rehydration solutions, ORS. The target population for these products is children with chronic or acute diarrhea and dehydration. The intended use levels are consistent with the level of lactoferrin found naturally in human milk and the exposure of breast fed infants, 1 mg/mL.

1. LACTOFERRIN IS A BENEFICIAL COMPONENT OF BREAST MILK

One of the most compelling arguments in support of breast-feeding is that breast milk contains factors that have important benefits for infant health including protection of the infant against both systemic and gastrointestinal infections, establishment of a healthy gastrointestinal system, promotion of growth and development and improvement in absorption of key nutrients.

Mature human milk contains 3% to 5% fat, 0.8% to 0.9% protein, 6.9% to 7.2% carbohydrate, and 0.2% mineral constituents. The principal proteins of human milk are found in the whey fraction of the milk and include lactoferrin (Jensen 1995). Lactoferrin, which is the main whey protein in mature milk, can kill bacteria and viruses, as well as fungi, both as the complete molecule and by certain fragments in degraded form. Breast milk is also anti-inflammatory. There are few pro-inflammatory components such as IgG and IgM antibodies and complement in breast milk. Instead breast milk hinders chemotaxis and blocks production of the pro-inflammatory cytokines IL-1, TNF-α and IL-6 via human lactoferrin (Hanson et al, 2002).

Animal-derived lactoferrin, such as bovine lactoferrin, with similarity to breast milk lactoferrin have been added to infant formula (Japan). However, researchers have shown that the animal-derived proteins pose allergenic risk and that the benefits of these proteins are species specific. Bovine lactoferrin may not only be an allergen for cow’s milk allergic infants, but it also does not bind the human lactoferrin receptor, limiting its potential benefit in humans (Suzuki, Lonnerdal 2001).

a. Benefits of breast milk in reduction of diarrhea

Breast feeding is strongly promoted throughout the world; it is the gold standard in infant nutrition. Where it was once considered particularly superior in less affluent populations, it is now considered beneficial in all populations. Epidemiological studies in both the United States, as well as less developed countries, have established the benefits of human milk in the healthy development of infants.

As part of the Davis Area Research on Lactation, Infant Nutrition, and Growth (DARLING) study a cohort of matched breast fed or formula fed infants were followed for the first 2 years of life. The protective effects of breast feeding against infection, in a relatively affluent population, were monitored as one aspect of the study. In the first year of life the incidence
of diarrheal illness in breast fed infants was half that in formula fed infants (Dewey et al, 1995). In another study, (Cunningham, 1979) a cohort of 724 live births were followed and divided into three groups, breast fed (> 4 ½ months), limited breast feeding (6 weeks) and artificially fed (weaned shortly after hospital discharge). When looking at the total significant illnesses in the groups, defined as otitis media, respiratory illness, diarrhea, and hospital admissions, during the first year the frequency of these illnesses increased 2-fold with artificial feeding; during the first 4 months the difference was 4-fold; and during the first 2 months the difference was 16-fold.

In 2004 Chen and Rogan published an analysis of the rates of morbidity, especially from infectious disease, for breast fed infants, based on the US National Maternal and Infant Health Survey (NMIHS). Their results showed that children who were breastfed had lower risk of post neonatal death (0.79 times the risk) compared with children who were never breastfed. They concluded that promoting breast feeding has the potential to save or delay ~720 postneonatal deaths in the United States each year.

Compared with formula fed infants, breast fed infants experience less acute and chronic otitis media, bronchiolitis, diarrhea, meningitis and necrotizing enterocolitis. In a study of lower respiratory infection, otitis media and gastrointestinal infection in the first year of life there were 2,033 excess office visits, 212 excess days of hospitalization and 609 excess prescriptions per 1,000 never-breastfed infants compared to infants exclusively breast fed for 3 months. Health care costs were between $331 and $475 higher for each formula fed infant during the first year of life (Ball and Wright 1999).

b. Lactoferrin levels measured in breast milk

Lactoferrin is a natural constituent of the human body, found in exocrine secretions including saliva and milk, and in neutrophils and plasma. Human milk and neutrophils lactoferrins are identical except for their glycosylation; milk glycans contain fucose, while neutrophils glycans do not (Taylor, Brock et al. 2004). Children have a constant exposure to lactoferrin through exocrine secretions and infants have additional exposure through the ingestion of breast milk.

Infants who are breast-fed consume human lactoferrin, a natural constituent of human milk. A search of the scientific literature on the concentration of lactoferrin in human milk was conducted. This literature search resulted in a range of reported lactoferrin levels seen during the stages of lactation. Lactoferrin levels in human milk and colostrum have been reported from as high as 10 g/L to as low as 0.8 g/L.

A number of studies have looked at nutritional status of the mother and overall protein content in breast milk and indicated there is no significant relationship between the mother’s nutrition status and breast milk protein content (Lonnerdal, Forsum et al. 1976). However, in a study that compared milk proteins from privileged and non-privileged Ethiopian mothers with well nourished Swedish mothers, there was no difference in the protein content, but
there was an increase in the lactoferrin levels in both groups of Ethiopian mothers (Lonnerdal, Forsum et al. 1976).

The most extensive studies measuring human lactoferrin levels with respect to number of samples tested and validation of the methodology were by the Montagne group (Montagne, Cuilliere et al. 1999; Montagne, Cuilliere et al. 2001). They developed a microparticle-enhanced nephelometric immunoassay of lactoferrin and evaluated the assay with respect to intra and inter assay precision and analytical recovery of spiked purified lactoferrin. They measured not only human milk, but also serum and other secretion fluids using this methodology. Results were reported for 360 human milk samples collected from lactating volunteers over twelve weeks. The measurements were reported for lactoferrin concentration and lactoferrin as percent of milk protein. The data reported a gradual decline in lactoferrin and lactoferrin as percent of protein from colostrums to early mature milk, then a gradual increase in both measurements as the milk continued to mature.

### Table 1. Lactoferrin Levels by Microparticle-Enhanced Nephelometric Immunoassay

<table>
<thead>
<tr>
<th></th>
<th>Colostrum 1 – 5 d (n = 142)</th>
<th>Transitional 6 – 14 d (n = 106)</th>
<th>Mature 15 – 28 d (n = 34)</th>
<th>Mature 29 – 56 d (n = 50)</th>
<th>Mature 57 – 84 d (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF (g/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.8</td>
<td>3.1</td>
<td>2.0</td>
<td>2.2</td>
<td>3.3</td>
</tr>
<tr>
<td>SD</td>
<td>4.3</td>
<td>1.3</td>
<td>0.6</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>% Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26.7</td>
<td>21.6</td>
<td>19.3</td>
<td>21.7</td>
<td>30.0</td>
</tr>
<tr>
<td>SD</td>
<td>10.8</td>
<td>7.1</td>
<td>5.1</td>
<td>9.2</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Studies in the literature were deemed acceptable for use in this safety assessment if (1) there was sufficient information provided to ascertain that the samples were adequately stored prior to analysis; and (2) the study population was either from the US or a Western European nation with roughly comparable nutrition and diet. The mean, range and standard deviation, if available, of lactoferrin values from studies meeting these criteria are presented in Table 2, converted where necessary to g/L. In all of the studies included, lactoferrin milk data was reported as mean levels. Although there are variations in lactoferrin levels reported during lactation, one area of consensus is that there is a fairly constant level of lactoferrin of about 1 g/L in mature milk up to two years postpartum (Goldman, Goldblum et al. 1983; Hamosh 1998).
Table 2. Concentration of Lactoferrin in Human Milk

<table>
<thead>
<tr>
<th>Lactation Stage</th>
<th>N</th>
<th>Range (g/L)</th>
<th>Mean (g/L)</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 14 d term</td>
<td>215</td>
<td>5.5 – 3.0</td>
<td>4.0</td>
<td>Microparticle-enhanced nephelometric immunoassay</td>
<td>(Montagne, Cuilliere et al. 1999)</td>
</tr>
<tr>
<td>1-14 d preterm delivery</td>
<td>153</td>
<td>6.5 – 2.7</td>
<td>4.3</td>
<td>Microparticle-enhanced nephelometric immunoassay</td>
<td>(Montagne, Cuilliere et al. 2001)</td>
</tr>
<tr>
<td>Colostrums (1-5d)</td>
<td>142</td>
<td>5.8 ± 4.3</td>
<td></td>
<td>Microparticle-enhanced nephelometric immunoassay</td>
<td>(Montagne, Cuilliere et al. 1999)</td>
</tr>
<tr>
<td>6 – 14 d</td>
<td>106</td>
<td>3.1 ± 1.3</td>
<td></td>
<td>Microparticle-enhanced nephelometric immunoassay</td>
<td>(Montagne, Cuilliere et al. 2001)</td>
</tr>
<tr>
<td>15 – 28 d</td>
<td>34</td>
<td>2.0 ± 0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 – 56 d</td>
<td>50</td>
<td>2.2 ± 1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57 – 84 d</td>
<td>28</td>
<td>3.3 ± 0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colostrum (2d)</td>
<td>10</td>
<td>5.3 ± 1.9</td>
<td></td>
<td>Electroimmunodiffusion</td>
<td>(Goldman, Garza et al. 1982)</td>
</tr>
<tr>
<td>1 m</td>
<td>11</td>
<td>1.9 ± 0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 m</td>
<td>7</td>
<td>0.8 ± 0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 m</td>
<td>11</td>
<td>1.4 ± 0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 m</td>
<td>4</td>
<td>0.9 ± 0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 m</td>
<td>5</td>
<td>1.0 ± 0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 140 d term</td>
<td>8</td>
<td>9.8 – 1.4</td>
<td>†</td>
<td>SDS-PAGE</td>
<td>(Velona, Abbiati et al. 1999)</td>
</tr>
<tr>
<td>0-140 d preterm</td>
<td>8</td>
<td>4.3 – 1.8</td>
<td>†</td>
<td></td>
<td>Means not given</td>
</tr>
</tbody>
</table>

The overall average of the mean values presented in Table 2 is 2.8 g/L ± 1.7 SD and the median is 2.2 g/L. All of the studies cited provided only means and sometimes standard deviations and ranges, no median values were available from any of the individual studies. Because of differences in methodologies and lactation stages studied, no attempt was made to derive an overall distribution of the values. The values for milk and colostrums in Table 2 are reasonably consistent across different analytical methods, even considering that more recent methods have offered improved sensitivities.

Based on the literature summarized above we have used 2.8 g/L in estimating the average intake of naturally-occurring lactoferrin by term infants who are breast-fed. However, it is important to note that the level of lactoferrin reported in the cited studies of human milk and colostrum has been reported to be as high as 9.8 g/L.

c. Exposure to naturally occurring lactoferrin in breast milk

Natural exposure to lactoferrin through the consumption of human milk was estimated for term infants. The daily consumption of human milk was determined from intake studies conducted with results reported in scientific journals. The naturally occurring level of lactoferrin in human milk was also estimated following a thorough review of the scientific
literature. These data allowed for the calculation of the typical (mean) exposure to naturally occurring lactoferrin among term infants.

The American Academy of Pediatrics (AAP) currently recommends that healthy term infants be exclusively breast-fed from 0 to 6 months. Breastfeeding should be continued for the first year or longer if mutually desired by the mother and the infant. After 6 months, foods rich in iron should compliment breastfeeding ((AAP) 2005).

US data indicate that breastfeeding has increased in the US in the 1990s through 2003 following a slight decrease in the 1980s. Published data from the “Ross Mothers Survey” show that in 2003, the percent of women breastfeeding their infants in the hospital was 66.0% (national average), up 10.1% from 1993. At 6 months of age, the percent of women still breastfeeding their infants was 32.8% (Ross 2003). This data is based on a nationally representative sample of new mothers.

A review of the current scientific literature yielded several reliable sources for data on intake of human milk among term infants. Data from several studies are combined in Table 3. A recent article reviewed the current literature and intake studies from 1975 through 2000 and derived population distributions of intake (Arcus-Arth, Krowech et al. 2005). Two datasets were constructed based on 1) those studies that had data consistent with AAP advice (AAP dataset) and 2) a 0-12 month exclusively breast fed dataset using the 0-6 month data in the AAP dataset combined with data from infants exclusively breast-fed from 6-12 months. The results from AAP Method 1 and AAP Method 2, as shown in Table 3, agreed closely with an average intake of 100.7 and 101.6 mL/kg/day.

As part of the DARLING study, authors compared energy intake and growth between breast-fed and formula-fed infants at 3, 6, 9, and 12 months (Heinig, Nommsen et al. 1993). In this study, infants in the breast-fed group received breast milk as the sole source of milk through the first 12 months. Infants in the formula-fed group were either not breast-fed or were completely weaned by 3 months of age. At 3 months of age, 100% of the infants’ energy intake was from non-human milk. At 6, 9, and 12 months, the percent of energy intake from milk was reported and therefore the intake of milk at these time points could be calculated as well. The peak intake was at three months, 128 mL/kg/day, declining to 51 mL/kg/day at 12 months (Table 3).

Additionally, The Harriet Lane Handbook provides standard estimates of daily energy recommendations for 0-1 yr olds (Robertson and Shilkofski 2005). Based on the standard energy content of human milk (0.67 kcal/mL) (Robertson and Shilkofski 2005), the daily volume of human milk intake can be calculated from energy intake estimates as shown in Table 3 using the following standard formula:

\[
\text{[Energy intake (kcal/kg bw/day)] \times [\% energy intake from milk]} \times \frac{0.67 \text{ kcal/mL milk}}{} = \text{mL milk/kg bw/day}
\]

A summary of human milk intake estimates from all these reports for term infants is provided in Table 3.
Intake of lactoferrin by term infants through the consumption of human milk was estimated by multiplying the average concentration of lactoferrin in human milk (2.8 g/L) with human milk intakes. Using this mean is justified based on the data illustrated in Table 2 above.

The estimated human milk intakes of lactoferrin by term infants are presented in Table 3. Mean human milk lactoferrin intake ranges from 0.14 g/kg/day to 0.50 g/kg/day. This estimate of intake is in agreement with two studies on ingestion of immunologic components of human milk which reported lactoferrin ingestion from about 1.3 to 0.75 g/day in the first four months and from about 0.275 to 0.125 g/kg/day (McClelland, McGrath et al. 1978; Butte, Goldblum et al. 1984). It is important to note that lactoferrin levels in human milk have been reported as high as 3.3 g/L at 3 months (Montagne, Cuilliere et al. 2001), the point of greatest intake (Heinig, Nommsen et al. 1993) and therefore background intake could potentially be as high as ~0.42 g/kg/day (0.128 L/kg/day x 1.3 g LF/L milk).

### Table 3. Lactoferrin Intake from Human Milk in Term Infants

<table>
<thead>
<tr>
<th>Infant Age</th>
<th>Mean Intake</th>
<th>Human milk (mL/kg/day)</th>
<th>Human Milk LF intake&lt;sup&gt;1,2&lt;/sup&gt; (g/kg bw/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 months AAP Method 1&lt;sup&gt;3,6&lt;/sup&gt;</td>
<td>100.7</td>
<td>0.282</td>
<td></td>
</tr>
<tr>
<td>0-12 months AAP Method 2&lt;sup&gt;4,6&lt;/sup&gt;</td>
<td>101.6</td>
<td>0.284</td>
<td></td>
</tr>
<tr>
<td>0-12 months EBF&lt;sup&gt;6&lt;/sup&gt;</td>
<td>113</td>
<td>0.316</td>
<td></td>
</tr>
<tr>
<td>3 months&lt;sup&gt;7&lt;/sup&gt;</td>
<td>128</td>
<td>0.358</td>
<td></td>
</tr>
<tr>
<td>6 months&lt;sup&gt;7&lt;/sup&gt;</td>
<td>102</td>
<td>0.286</td>
<td></td>
</tr>
<tr>
<td>9 months&lt;sup&gt;7&lt;/sup&gt;</td>
<td>80</td>
<td>0.224</td>
<td></td>
</tr>
<tr>
<td>12 months&lt;sup&gt;7&lt;/sup&gt;</td>
<td>51</td>
<td>0.143</td>
<td></td>
</tr>
<tr>
<td>0-12 months&lt;sup&gt;5,8&lt;/sup&gt;</td>
<td>120-180</td>
<td>0.336 - 0.504</td>
<td></td>
</tr>
</tbody>
</table>

AAP = The American Academy of Pediatrics  
EBF = Exclusive breast-feeding  
1 2.8 g LF/L milk  
2 Energy density of human milk = 0.67 kcal/mL.  
3 Method 1 = The average population daily intake at each age is described by a regression line, assuming normality.  
4 Method 2 = Probabilistic model with distribution of intake based on empirical mean, SD, and assumption of normality.  
5 Assuming that 100% of energy requirements are met by milk consumption.  
6 (Arcus-Arth, Krowech et al. 2005)  
7 (Heinig, Nommsen et al. 1993)  
8 (Robertson and Shilkofski 2005)
2. **LACTOFERRIN SUPPORTS THE GROWTH OF BENEFICIAL BACTERIA IN THE INTESTINE**

The composition of the bacteria that comprise the gastrointestinal microflora have important ramifications for human health. Bifidobacteria are considered to be one of the most important genera of beneficial bacteria (Gibson, Beatty et al. 1995). The genus Bifidobacterium consists of at least 25 distinct species, of which 10 colonize the human large intestine. In infants, bifidobacteria are one of the first bacterial groups to establish themselves in the intestinal tract and, within one week, become the predominant group (Poupard, Husain et al. 1973).

Bifidobacteria may provide a defense against pathogenic bacteria. It is thought that the predominance of bifidobacteria produces the lower morbidity and mortality seen among breast-fed infants (Yoshioka, Iseki et al. 1983; Roberts 1986; Ogawa, Ben et al. 1992). Human milk provides growth factors that encourage the proliferation of a protective enteric flora. One of the factors in human milk that is thought to promote the levels of bifidobacteria as well as inhibit the growth of selected pathogens in the colon is lactoferrin (Goldman, Chheda et al. 1998).

In vitro and in vivo studies have been done to demonstrate the ability of lactoferrin to promote the growth of bifidobacterium and lactobacillus. Petschow and Talbott demonstrated in vitro that both human lactoferrin and bovine lactoferrin could support the growth of bifidobacterium spp. and that the growth promotion activity was independent of iron saturation and did not require the binding of lactoferrin to the bifidobacteria cells (Petschow, Talbott et al. 1999).

Recently a group identified peptides from human milk that selectively stimulated the growth of bifidobacteria (Liepke, Adermann et al. 2002). Several bifidogenic peptides were purified chromatographically from pepsin-treated human milk and identified as proteolytically generated fragments from lactoferrin. Further hydrolysis of the identified peptides with the gastrointestinal proteases pepsin, trypsin and chymotrypsin did not lead to the loss of bifidogenic activity, indicating their potential function in vivo. Sequential comparison revealed a similar structural motif within the identified peptides. A correspondingly designed small peptide, lactoferrin-derived peptide-I, was found to stimulate the growth of bifidobacteria as effectively as the native peptides.

3. **LACTOFERRIN HAS A ROLE IN MAINTAINING THE BALANCE OF THE INFLAMMATORY RESPONSE**

Human milk can actively stimulate the immune system of breast-fed infants (Hanson et al. 2002). Lactoferrin may have a positive role in protection of the intestinal mucosa through helping to maintain the balance of the inflammatory response. Human milk seems to be mainly anti-inflammatory. There are few pro-inflammatory components such as IgG and IgM antibodies and complement in breast milk. Instead breast milk hinders chemotaxis and blocks production of the pro-inflammatory cytokines IL-1, TNF-α and IL-6 via human lactoferrin (Hanson et al, 2002).
Studies in animals with oral administration of lactoferrin have demonstrated a protective effect against development of colitis via modulation of the immune system (Togawa, Nagase et al. 2002; Togawa, Nagase et al. 2002). When lactoferrin was given to control animals, there was no difference in cytokine levels between lactoferrin controls and saline controls. However, when animals received an inflammatory agent and lactoferrin, the pro-inflammatory cytokines were inhibited and the anti-inflammatory cytokines were increased. Lactoferrin has also protected gut mucosa against the effects of bacterial lipopolysaccharide in mice through binding of the LPS (Kruzel, Harari et al. 2000). These protective mechanisms may result in less damage and more rapid repair of gut mucosal tissue injury, leading to more rapid restoration of normal permeability and growth and recovery from the damage associated with diarrhea.

C. SELF-LIMITING USE OF PEDIATRIC MEDICAL FOODS AND ORAL REHYDRATION SOLUTIONS AS NUTRITIONAL SUPPORT FOR DIARRHEA

Acute gastroenteritis, particularly of viral origin, is usually self-limited, lasting less than a week. The greatest risk in children is dehydration.

Acute gastroenteritis is well documented as a prime cause of morbidity and mortality in developing countries; however, it is also a major cause of morbidity and an important clinical illness in children in the United States. Approximately 70% of children will become ill from diarrhea and 10% of the hospitalizations in children under the age of five will be due to acute diarrhea (Tucker, Haddix et al. 1998). It is estimated that 16.5 million children have between 21 and 37 million episodes of pediatric diarrhea annually (Glass, Lew et al. 1991). The incidence rate in children under the age of 5 is 1.3 to 2.3 episodes per year; children in day care have higher rates (Burkhart 1999). Acute diarrhea accounts for over 1.5 million outpatient visits, 200,000 hospitalizations and between 325 and 425 deaths annually (King, Glass et al. 2003).

In the mid 1960s the scientific discovery of the coupled transport of sodium and glucose provided the basis for the development of Oral Rehydration Therapy (ORT) as an alternative to IV therapy for dehydration due to diarrhea. ORT has now been safely and successfully used throughout the world for more than 40 years (AAP 1996). Although the glucose-electrolyte ORT is very effective in rehydrating, it has no effect on stool volume or the duration of diarrhea. One approach to address this limitation is the replacement of the glucose with starch and simple proteins to provide more co-transport of molecules with little osmotic change (Carpenter, Greenough et al. 1988; Gore, Fontaine et al. 1992). This allows additional fluid and electrolyte uptake and some reduction of stool losses.

The best studied cereal-based ORT contains rice at 50 g/L instead of glucose. The rice-based oral rehydration solution can reduce stool volume by 30% in children with toxicogenic diarrhea and by 20% in non-toxicogenic diarrhea (Gore, Fontaine et al. 1992).
Oral rehydration therapy includes rehydration and maintenance of fluids using pediatric medical foods and oral rehydration solutions (ORS), as well as age-appropriate nutrition during maintenance. ORT has been the major contributor to the decrease in mortality in children under the age of 5. In the United States, pediatric medical foods and ORS are used in the enteral nutritional management of patients and are regulated as Medical Food (MF) per Orphan Drug Act Amendments of 1988 [21 USC 360ee (b)(3)]. A medical food is administered under the supervision of a physician.

The use of oral rehydration therapy occurs in two phases. In the first stage, rehydration, pediatric medical foods and ORS are used to replace existing fluid deficiency in the child due to loss from diarrhea and possibly vomiting. This phase generally lasts from 4 to 6 hours. The second phase is the maintenance phase. This phase includes replacement of ongoing fluid loss and age-appropriate nutrition (King, Glass et al. 2003). In the case of severe dehydration and the presence of shock or near-shock, intravenous therapy is indicated. This can be followed by oral rehydration maintenance. In the case of persistent diarrhea (> 14 days in duration) with mild or moderate dehydration, ORS solution is considered the most effective response; with persistent diarrhea accompanied by signs of severe dehydration hospitalization is recommended (WHO 2000). Thus the duration of medical food and ORS intake is expected to average 3 days following onset of diarrhea. The average number of diarrheal episodes per year is 1.3 to 2.3.

D. EDI OF rhLF FROM THE USE INTENDED BY VENTRIA

Ventria intends the following uses for recombinant human lactoferrin enrichment. The target population is medical foods and ORS (under supervision of a physician) for children up to 5 years of age. The estimated intake of these products during the critical four hour rehydration period would range from 40 to 1200 mg (see Table 4). The products would contain 1.0 mg/mL rhLF.

Upon the onset of a diarrheal episode, both WHO and AAP recommend that the intake of breast milk and other foods and liquids cease or be significantly reduced and that oral rehydration therapy be instituted to prevent the risk of dehydration. The World Health Organization (WHO) has issued guidance for administration of ORS in the first 4 hours to children with some dehydration [http://www.who.int/child-adolescenthealth/publications/referral_care/chap4/chap41.htm]. Using these recommended dosages, an oral rehydration solution containing 1 mg/mL rhLF (the proposed enrichment level) would correspond to the lactoferrin intakes during the rehydration phase presented in Table 4. The estimated intake per kilogram body weight averages 0.08 to 0.12 g/kg bw.
Table 4. Estimated rhLF Intake During The Rehydration Phase From ORS Enriched At 1 mg/mL

<table>
<thead>
<tr>
<th>Weight</th>
<th>Age</th>
<th>Amount of ORS in first 4 hours</th>
<th>rhLF intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 kg</td>
<td>&lt;4 months</td>
<td>200 - 400 mL</td>
<td>0.2 - 0.4 g</td>
</tr>
<tr>
<td>5 - &lt;8 kg</td>
<td>4 - &lt;12 months</td>
<td>400 - 600 mL</td>
<td>0.4 – 0.6 g</td>
</tr>
<tr>
<td>8 - &lt;11 kg</td>
<td>12 months to &lt;2 years</td>
<td>600 - 800 mL</td>
<td>0.6 – 0.8 g</td>
</tr>
<tr>
<td>11 - &lt;16 kg</td>
<td>2 - &lt;5 years</td>
<td>800 - 1200 mL</td>
<td>0.8 – 1.2 g</td>
</tr>
</tbody>
</table>

During the maintenance phase, fluid is replaced as lost. Normal replacement, once the child is rehydrated, is 60 – 120 mL for each diarrhea stool or vomiting episode in children < 10 kg body weight and 120 – 240 mL per episode in children > 10 kg body weight (King, Glass et al. 2003).

Table 5. Estimated rhLF Intake During The Maintenance Phase From ORS Enriched At 1 mg/mL

<table>
<thead>
<tr>
<th>Weight</th>
<th>Amount of ORS per episode</th>
<th>rhLF intake per episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 kg</td>
<td>60 – 120 mL</td>
<td>0.06 – 0.12 g</td>
</tr>
<tr>
<td>&gt; 10 kg</td>
<td>120 – 240 mL</td>
<td>0.12 – 0.24 g</td>
</tr>
</tbody>
</table>

The recommendations of the American Academy of Pediatrics are similar. They suggest intervention based on level of dehydration (AAP 1996).

- No dehydration, 10mL/kg for each stool.
- Mild dehydration, 50 mL/kg for 4 hours followed by 10 mL/kg for each stool.
- Moderate dehydration, 100 mL/kg for 4 hours followed by 10 mL/kg for each stool.
- Severe dehydration, IV therapy followed by ORT when the patient is stabilized.

Using the data from Tables 4 and 5 and the recommended dosing from the AAP, we prepared two tables to compare lactoferrin intake from breast milk or pediatric medical foods and ORS during daily and weekly use. The assumptions used to construct Tables 6 and 7 are in the footnotes. An average weight was calculated for each age group and the intake from breast feeding per day and per 7 days was calculated. Using practice standards from AAP, the amount of lactoferrin intake during the rehydration and maintenances phases was calculated and combined to estimate a weekly intake from ORT.

In a recent clinical study using ORS in children with acute diarrhea, during Phase I the average intake of ORS was 672 mL and the average weight was 10 kg for an average
possible intake of 0.67 g lactoferrin in 4 hours. This agrees very well with the 10 kg weight in Table 6.

Table 6. Comparison of EDI for Breast Milk and ORS Lactoferrin

<table>
<thead>
<tr>
<th>Age (mo)</th>
<th>Weight(^1) (kg)</th>
<th>Breast Milk LF Intake(^2) (g/day)</th>
<th>ORS Phase I Rehydration LF Intake(^3) (g/4 hrs)</th>
<th>ORS Phase II Maintenance LF Intake(^4) (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5.8</td>
<td>2.08</td>
<td>0.58</td>
<td>0.23</td>
</tr>
<tr>
<td>6</td>
<td>7.7</td>
<td>2.20</td>
<td>0.77</td>
<td>0.31</td>
</tr>
<tr>
<td>9</td>
<td>9.1</td>
<td>2.04</td>
<td>0.91</td>
<td>0.36</td>
</tr>
<tr>
<td>12</td>
<td>10.2</td>
<td>1.46</td>
<td>1.02</td>
<td>0.41</td>
</tr>
</tbody>
</table>

\(^1\)Average weight is min for females + max for males from CDC charts divided by 2
\(^2\)LF g/kg/day from Table 3 times average kg weight
\(^3\)From AAP guidelines, 100 mL/kg, for moderate dehydration from diarrhea
\(^4\)Based on 4 stools per day (diarrhea defined as 3 or more/day)

Table 7. Estimated Exposure To Recombinant Human Lactoferrin During Acute Diarrhea

<table>
<thead>
<tr>
<th>Age (mo)</th>
<th>Weight(^1) (kg)</th>
<th>Breast Milk LF Intake (g/wk)</th>
<th>ORS LF Intake (g/d) 25(^{th})</th>
<th>ORS LF Intake (g/3d) Avg</th>
<th>ORS LF Intake (g/wk) 90(^{th})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5.8</td>
<td>14.53</td>
<td>0.81</td>
<td>1.27</td>
<td>2.20</td>
</tr>
<tr>
<td>6</td>
<td>7.7</td>
<td>15.42</td>
<td>1.08</td>
<td>1.70</td>
<td>2.93</td>
</tr>
<tr>
<td>9</td>
<td>9.1</td>
<td>14.27</td>
<td>1.27</td>
<td>1.99</td>
<td>3.46</td>
</tr>
<tr>
<td>12</td>
<td>10.2</td>
<td>10.21</td>
<td>1.43</td>
<td>2.25</td>
<td>3.88</td>
</tr>
</tbody>
</table>

\(^1\)Average weight is min for females + max for males from CDC charts divided by 2

Estimated exposure during an episode of diarrhea is based on typical clinical practice and acceptance of the treated child. The 25\(^{th}\) percentile exposure represents the child that is treated for dehydration for one day, then provided complimentary feeding and other liquids. The average exposure is based on a three day episode diarrhea and the 90\(^{th}\) percentile is based on a week of diarrhea. Based on estimated and actual data from a study, the lactoferrin intake during a week of ORT is less than the lactoferrin intake during a week of breast feeding.
E. SAFETY OF ORAL RECOMBINANT HUMAN LACTOFERRIN

1. ANIMAL STUDIES

Ventria Bioscience’s recombinant human lactoferrin has been fed to animals and humans with no reports of adverse events or indication of IgE allergic reactions. The rhesus monkey animal model is often chosen to test the safety of products prior to human trials. In collaboration with a team at UC Davis, infant rhesus monkeys were fed with a modified infant formula containing 1.0 mg/mL rhLF and 0.1 mg/mL of rhLZ (recombinant human lysozyme) from day one after birth to four months. Animals were fed a whey-based formula containing recombinant human lactoferrin from an extract of the rice flour. The formula also included recombinant human lysozyme. There were no adverse effects were observed at a dosage ranging from 0.5 to 0.8 g/kg body weight for rhLF and 0.05 to 0.08 g/kg body weight for rhLZ.

Two 28 day repeated dose oral toxicity studies were done in rats. One tested iron saturated (holo) recombinant human lactoferrin and the second tested iron desaturated (apo) recombinant human lactoferrin.

In the holo-lactoferrin study, twenty health males and twenty healthy female Wistar albino rats were randomly selected and assigned to one of four groups of five males and five females per group. All animals were dosed once daily, seven days a week by oral gavage technique. One group received vehicle (saline), three groups received recombinant human holo-lactoferrin from rice dosed at 100, 500, and 1000 mg/kg/day. No animals exhibited any adverse events or symptoms of allergic reaction during the feeding phase; the histopathology and serum chemistry indicated no evidence of allergic response. There were no treatment related, toxicologically relevant changes in clinical signs, growth, food consumption, hematology, clinical chemistry, organ weights and pathology. The no observed adverse effect level (NOAEL) was greater than 1000 mg/kg/day.

In the apo-lactoferrin study, fifteen healthy male and fifteen healthy female Wistar albino rats were randomly selected and assigned to one of three groups of five males and five females per group. All animals were dosed once daily, seven days a week by oral gavage technique. One group received vehicle (saline), two groups received recombinant human apo-lactoferrin from rice dosed at 180 and 1800 g/kg/day. No animals exhibited any adverse events or symptoms of allergic reaction during the feeding phase; the histopathology and serum chemistry indicated no evidence of allergic response. Based on the hematological, clinical chemistry and microscopic data, the no observed adverse effect level (NOAEL) of recombinant human lactoferrin is considered to be greater than 1800 g/kg/day, more than 10 times the estimated maximum exposure from the use of recombinant human lactoferrin in medical foods and ORS for nutritional support in diarrhea.

2. PEDIATRIC STUDIES

Ventria Bioscience has sponsored a study using a rice-based oral rehydration solution (ORS) with lactoferrin at 1.0 mg/mL and a second recombinant human milk protein from rice,
lysozyme, at 0.2 mg/mL (Zavaleta, Figueroa et al. 2007). The study conducted in Lima, Peru, enrolled 140 children with acute watery diarrhea in a blinded study comparing volume and duration of diarrhea in three groups. Children were admitted to the Oral Rehydration Unit at the Children’s Hospital in Lima and were randomized to receive WHO low-osmolarity ORS, a rice based ORS or a rice based ORS with lactoferrin and lysozyme. Children received the ORS based on a standard dosing protocol established by WHO related to the amount of dehydration and diarrhea. Children remained in the Oral Rehydration Unit for 48 hours, divided into the initial 4 hours for rehydration, then 44 hours of maintenance. Children in the study received from 0.09 to 1.0 g of lactoferrin in the first four hours based on level of dehydration. After 48 hours in the Oral Rehydration Unit, children went home and a healthcare worker visited the home daily to monitor volume of diarrhea, volume of ORS, and grade of diarrhea. Dosing continued until diarrhea had resolved for 48 hours or ORS intake had continued for 14 days. There were additional clinic visits on Day 7 and Day 14. There were no material related serious or non-serious adverse events. Twelve children had 16 adverse events. Most adverse events (11) were associated with common cold and bronchial congestion, one child swallowed a coin, one had periorbital cellulitis, one had skin insect bites, and two children on WHO-ORS had vomiting, one required IV therapy. There was no difference in the demographics of the three groups. A pathogen was identified in 72% of the children; E. coli being the most frequently identified pathogen. There were no significant differences in the two control groups, WHO-ORS and Rice-ORS, and they were combined and compared to the group receiving ORS with lactoferrin and lysozyme. The clinical outcomes of the study are shown in Table 8.

### Table 8. Clinical Outcome in ORS Study

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>LF/LZ-R-ORS (N=47)</th>
<th>Combined WHO&amp;R-ORS (N = 91)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ORS intake (mL)</td>
<td>1910</td>
<td>2162</td>
<td>0.18</td>
</tr>
<tr>
<td>Duration of diarrhea after randomization (days)</td>
<td>3.67</td>
<td>5.21</td>
<td>0.05</td>
</tr>
<tr>
<td>Total stool volume g/kg</td>
<td>97.2</td>
<td>102.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Percent with solid stool for 48 h</td>
<td>85.1</td>
<td>69.2</td>
<td>0.04</td>
</tr>
</tbody>
</table>
F. SUMMARY OF THE BASIS FOR THE NOTIFIER’S DETERMINATION THAT A PARTICULAR USE OF THE NOTIFIED SUBSTANCE IS EXEMPT FROM THE PREMARKET APPROVAL REQUIREMENTS OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT BECAUSE SUCH USE IS GRAS

The neonatal period is marked by high susceptibility to infection and innate immunity represents the first barrier to infections and plays a pivotal role in the induction of adaptive immunity (Kovarik and Siegrist 1998). Supported historically by studies involving thousands of infants, breast milk contains bioactive factors that protect the infant against both systemic and gastrointestinal infections. These protective factors are protein in nature and the most important are lactoferrin, lysozyme, and immunoglobulins. In an extensive review of the proteins in human milk, Bezkorovainy reported lactoferrin levels measured in whey as 1.55 and 2.10 mg/mL (Bezkorovainy 1977).

There are many beneficial effects of bifidobacteria on human health. Bifidobacteria may provide a defense against pathogenic bacteria. The predominance of the bifidobacteria in breast-fed infants is believed by many to afford some of the protection against enteral as well as systemic disorders caused by bacterial pathogens. It is thought that the predominance of bifidobacteria produces the lower morbidity and mortality seen among breast-fed infants. Lactoferrin and specifically pepsin generated peptides from lactoferrin are highly stimulating to the growth of bifidobacteria (Liepke, Adermann et al. 2002).

Milk seems to be mainly anti-inflammatory. There are few pro-inflammatory components such as IgG and IgM antibodies and complement in breast milk. Instead breast milk hinders chemotaxis and blocks production of the pro-inflammatory cytokines IL-1, TNF-α and IL-6 via human lactoferrin (Hanson et al, 2002). Studies in animals with oral administration of lactoferrin have demonstrated a protective effect against development of colitis via modulation of the immune system (Togawa, Nagase et al. 2002; Togawa, Nagase et al. 2002). This protective mechanism may result in less damage and more rapid repair of gut mucosal tissue leading to normal permeability and growth. Lactoferrin may have a positive role in protection of the intestinal mucosa during diarrhea.

Lactoferrin has general biological activities beneficial for children which would support nutritional status during diarrhea in the following manner:

- Lactoferrin is a beneficial component of human milk (Hanson, Korotkova et al. 2002).
- Lactoferrin promotes the beneficial gastrointestinal microflora by supporting beneficial bacterial growth such as bifidobacteria and inhibiting many pathogenic bacteria via sequestration of iron needed for growth (Liepke, Adermann et al. 2002);
- Lactoferrin helps balance the inflammatory response in the gastrointestinal tract (Togawa, Nagase et al. 2002; Togawa, Nagase et al. 2002);
Numerous studies have been done in infants to test the use of lactoferrin as an addition to infant formula. Inclusion levels have generally been at the 1 mg/mL, the level close to that found in breast milk. Various endpoints of iron balance (McMillan, Oski et al. 1977; Fairweather-Tait, Balmer et al. 1987; Schulz-Lell, Dorner et al. 1991; Chierici, Sawatzki et al. 1992) and gastrointestinal fecal flora (Balmer, Scott et al. 1989; Roberts, Chierici et al. 1992) have been measured in the infant formula studies. No safety or allergenicity issues have been reported in any of the trials.

Ventria Bioscience has evaluated the use of recombinant human lactoferrin produced in and extracted from rice for addition to pediatric medical foods and oral rehydration solutions not to exceed 1 mg/mL. The addition of lactoferrin to these foods is intended to improve health status of children during diarrheal episodes through the characterized functions described above.

The gene for lactoferrin was introduced into rice using the recombinant ExpressTec™ technology which targets the expression of the new protein to only the grain of the rice plant. In addition, the antibiotic resistance proteins, used in the process of selection, are not found in the vegetative form of the rice. The production of the rice itself is tightly controlled through the use of dedicated equipment and facilities separate from any used in the production of commercial rice. The manufacturing methods of extraction and purification are similar to those used in the food industry and only food-grade or higher materials are used throughout. The recombinant human lactoferrin is produced in accordance with good manufacturing practices and is free from foreign material and contamination and safe for inclusion in foods. The final preparations meet the appropriate food-grade specifications. Ventria Bioscience has published the methods and results of production, purification and characterization of recombinant human lactoferrin from rice.

Children are constantly exposed to human lactoferrin by exposure to the natural secretions of the body, such as tears, saliva, naso-gastric, bronchial and uro-genital. Lactoferrin is also a component of neutrophilic granules and serum. Lactoferrin is consumed in significant quantities though breast milk with no adverse effects. Human lactoferrin is not a toxin or an allergen. Lactoferrin from bovine milk has been designated GRAS for use in foods and is available as a dietary supplement.

Recombinant human lactoferrin is safe for use in pediatric medical foods and oral rehydration solutions for children with diarrhea (Lonnerdal 2006). There is a natural background intake of lactoferrin protein. The gene source is human lactoferrin, a non-allergenic protein. The amino acid sequence of human and recombinant human lactoferrin is equivalent. There is no difference between lactoferrin and recombinant human lactoferrin in resistance to pepsin digestion.

CONCLUSION

In conclusion, there is no indication that adverse effects would result from consumption by children of medical foods and oral rehydration solutions containing recombinant human lactoferrin from rice.
• Breast milk is the gold standard in child nutrition and studies have documented its role in improved health, including reduced diarrheal episodes.
• The addition of lactoferrin to medical foods and oral rehydration solutions for the pediatric population provides the nutritional support similar to that from breast milk.
• Lactoferrin is associated with the maintenance of beneficial bacteria in the intestine.
• Lactoferrin can support the rebalance of the inflammatory response and protection of the gut mucosa.
• The use of lactoferrin in medical foods and oral rehydration solutions is associated with acute use, diarrhea generally being a self-limiting condition of 14 days or less.
• The amino acid sequence and structure of the protein are identical to human lactoferrin, which has been studied extensively.
• There is no difference in the resistance to pepsin digestion of recombinant human lactoferrin and human lactoferrin.
• Based on histamine release, there is no evidence that the biological IgE binding by sera with pre-existing IgE antibodies to plant N-glycan CCD structures, would result in a clinically relevant reaction in pollen allergic individuals.
• There is no evidence that residual rice proteins would trigger an allergic response in pollen allergic individuals.
• For the rare individual with true rice allergy, the products will be labeled as recombinant human lactoferrin from rice.
• The clinical literature on autoantibodies to lactoferrin provides no evidence that these antibodies play a pathological role and it is highly unlikely that ingestion of recombinant human lactoferrin would have any adverse effect.
• Using the data generated for this application and other generally available and accepted scientific data, information, methods, and principles, there is reasonable certainty that recombinant human lactoferrin from rice will be safe under the intended conditions of use in medical foods and oral rehydration solutions for children.

Based on a comprehensive and critical evaluation of the data and information, published and unpublished, pertinent to safety, the specially-convened qualified Expert Panel unanimously concluded that the use of Ventria’s recombinant human lactoferrin from rice, meeting appropriate food-grade specifications and produced by current good manufacturing practice, in pediatric medical foods and ORS products for nutritional support during diarrhea, at levels up to exceed 1 mg/mL, is generally recognized as safe based on scientific procedures. Furthermore, it is the Panel’s unanimous opinion that qualified experts in the field would generally recognize that recombinant human lactoferrin from rice is safe for this use. The Expert Panel members are:

Jeremy Brock, Ph.D.
Robert Bush, M.D.
Bo Lonnerdal, Ph.D.
Lloyd Mayer, M.D.
Stephen L. Taylor, Ph.D.
Ronald van Ree, Ph.D.
REFERENCES


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