



November 15, 2007

Delia R. Bethell, Ph.D.  
Vice President for Clinical Development  
Ventria Bioscience  
4110 N. Freeway Blvd.  
Sacramento, CA 95834

Re: GRAS Notice No. GRN 000235

Dear Dr. Bethell:

The Food and Drug Administration (FDA) has received the notice, dated September 27, 2007, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS)). FDA received this notice on October 2, 2007, filed it on October 19, 2007, and designated it as GRN No. 000235.

The subject of the notice is lactoferrin (human) purified from rice. The notice informs FDA of the view of Ventria Bioscience that lactoferrin (human) purified from rice is GRAS, through scientific procedures, for use as an ingredient in oral rehydration solutions at levels not to exceed 1 milligram of lactoferrin per milliliter of solution.

In accordance with proposed 21 CFR 170.36(f), a copy of the information in the notice that conforms to the information described in proposed 21 CFR 170.36(c)(1) is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at <http://www.cfsan.fda.gov/~lrd/foodadd.html>). If you have any questions about the notice, contact me at 301-436-1173 or [jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov).

Sincerely yours,

Jeremiah Fasano  
Division of Biotechnology and  
GRAS Notice Review  
Center for Food Safety  
and Applied Nutrition

### Revision History

Hard copy cc: **GRN 000235** (1 copy)  
Filename: GRN 235 Acknowledgement Letter  
R/D:HFS-255:JMFasano:11/20/07  
F/T:HFS-255:JMFasano:11/20/07



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Division of Biotechnology and  
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Filename: GRN 235 Acknowledgement Letter  
R/D:HFS-255:JMFasano:11/20/07  
F/T:HFS-255:JMFasano:11/20/07

October 7, 2004

Dr. Joanne Rhoads  
Division of Scientific Investigation  
7520 Standish Place  
Rockville, MD 20855

Dear Dr. Rhoads,

Below please find the requested information about the human studies sponsored by Ventria Bioscience using recombinant human lactoferrin derived from rice and recombinant human lysozyme derived from rice, two food ingredients that we are investigating for possible use as a dietary supplement and/or a medical food.

There are two studies, one is complete and one is on going. I have provided descriptions of the studies and information on the investigators, IRB and ethics committees for each study. The first study was designed to investigate the use of recombinant human holo-lactoferrin derived from rice for the dietary supplementation of iron levels in women through addition to foods or drinks.

The second study, which is ongoing, is designed to investigate the use of these food ingredients for the dietary management of diarrhea in children. If the study is successful, the product would be marketed as a medical food for use under physician supervision.

Ventria has submitted a Premarket Biotech Notification, BNF No. 082 to the Center for Food Safety and Nutrition Division of the FDA on the rice grain that produces the recombinant human lactoferrin.

If there are any additional questions or information required, please do not hesitate to contact me. Ventria is committed to an open dialog in this matter.

Sincerely,

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

## Study 1

The purpose of this study was to determine whether holo-recombinant human lactoferrin derived from rice could be used for the supplementation of iron levels. The study is completed. Eight women enrolled in the study. The exposure level was 4.8 grams of lactoferrin per day for 6 weeks. Four subjects completed the study. There were no major adverse events; one complaint of headache immediately after taking the capsules at some times. Full clinical chemistry panels were run at the beginning and end of the study and there were no significant changes in any parameters. The four individuals did not complete the study for the following reasons:

1. Screen failure
2. Non compliance
3. Screen failure
4. Decided capsules were too big and withdrew

Principle Investigator: Kathryn Rigonan, M.D.  
11100 Warner Ave., Suite 154  
Fountain Valley, CA 92708  
(714) 754-0100  
(714) 754-6806 (fax)

Study Coordinators: Southland Clinical Research Center  
11100 Warner Ave., Suite 352  
Fountain Valley, CA 92708  
(714) 430-1455  
(714) 430-1456 (fax)  
Saniata L. Batac, M.D., Clinical Research Coordinator  
[scrcenter@yahoo.com](mailto:scrcenter@yahoo.com)

IRB: Independent Review Consulting, Inc.  
100 Tamal Plaza, Suite 158  
Corte Madera, CA 94925  
(415) 485-0717  
(415) 485-0328 (fax)  
[ejheath@irb-irc.com](mailto:ejheath@irb-irc.com)  
Approval number: 04013-01

## Study 2

The purpose of this study is to determine whether the use of the human breast milk proteins recombinant human apo-lactoferrin derived from rice and recombinant human lysozyme derived from rice will support the dietary management of diarrhea in children with acute watery diarrhea and is being conducted at the Oral Rehydration Unit of the Instituto de Salud del Niño, (Children's Hospital) in Lima, Peru and Trujillo, Peru. Exposure level is 1 gram of recombinant human lactoferrin derived from rice and 200 mg of recombinant human lysozyme derived from rice per liter of ORS. These are the levels of native human lactoferrin and native human lysozyme in mature breast milk.

Principle Investigator: Nelly M. Zavaleta

Instituto de Investigación Nutricional  
Av. La Molina 685 – La Molina – Lima 12  
Peru  
51 1 3496146 ex 223  
51 1 3496025 (fax)  
[nzavalet@iin.sld.pe](mailto:nzavalet@iin.sld.pe)

Co-Investigators:

Dr. Dante Figueroa  
Director General  
Instituto de Salud del Niño  
Av. Brasil 600  
Breña – Lima 5  
Peru

Dr. Bo Lonnerdal  
Department of Nutrition  
University of California Davis  
One Shields Avenue  
Davis, CA 95616  
(530) 752-8347  
(530) 752-3564  
[bllonerdal@ucdavis.edu](mailto:bllonerdal@ucdavis.edu)

IRB/Ethics:

Instituto Nacional de Salud  
Dr. Luis Fernando Lianos Zavalaga  
No. 148-2003-J-OPD/INS

Instituto de Salud  
Dr. Carlos del Augila Villar  
Ministerio de Salud  
Instituto de Salud del Niño  
No. 0066-DIDT-ISBN-2003

Instituto de Investigacion Nutricional  
Hilary Creed-Kanashiro  
President, Committee Ethics  
No. 189-2003/CEI-IIN

University of California, Davis  
Office of Human Research Protection  
Ambulatory Care Center, Suite 3870  
UCDMC  
(916) 734-6864  
Frank Hirtz, Acting Chair  
No. 200311050-2

**Fasano, Jeremiah**

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**From:** Scott Deeter [sdeeter@ventria.com]  
**Sent:** Monday, March 03, 2008 4:33 PM  
**To:** Fasano, Jeremiah  
**Subject:** Previous FDA Correspondence  
**Attachments:** Final DSI letter 10-7.pdf

Dear Jeremiah:

In response to your inquiry about who we have communicated with at FDA regarding the studies Ventria has sponsored and the FDA review of these studies, I have the following information:

- 1) We were contacted on October 6<sup>th</sup>, 2004 by Lloyd Johnson (301) 827-5459 of the Division of Scientific Investigations. He said he would like information on the human studies we were conducting or intended to conduct. At the time, he mentioned that another Company had filed an IND application for a different recombinant human lactoferrin for therapeutic use. He asked that we inform the FDA of our studies. He suggested that we send a letter to Dr. Joanne Rhoads at FDA/Division of Scientific Investigations describing our studies. He said he would keep Ruthanne Giusti informed as well. He communicated that they wanted to make sure our studies were appropriate for our designation as foods.
- 2) On October 7<sup>th</sup>, 2004 we sent the attached letter to Dr. Rhoads.
- 3) On October 22<sup>nd</sup>, 2004 Lloyd Johnson called to say that he had circulated our letter and wanted to confirm that the letter included all studies. We informed him that this was the case. He said Ruthanne Giusti reviewed the situation and mentioned that the studies we had completed and intended were appropriate for foods and the Ventria product was not considered a drug as long as there are not drug claims in the marketing of the product. Ventria was asked to keep FDA/CDER informed of studies completed in the future.

Following October 22<sup>nd</sup>, 2004 Dr. Delia Bethell (Ventria's VP) informed Ruthanne Giusti and Lloyd Johnson of human studies sponsored by Ventria for use of recombinant human lactoferrin derived from rice.

If you have further questions regarding this matter, please let me know.

Sincerely,

Scott Deeter  
President & CEO  
Ventria Bioscience  
(970) 420-9598  
[www.Ventria.com](http://www.Ventria.com)

*Your Life. Our Passion.*

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## MEMORANDUM OF MEETING

March 7, 2008

11:00 a.m. – 12:00 p.m.

Parklawn Building

**Attendees:** FDA: Andrew von Eschenbach, Stephen Mason, Dotty Foellmer, Bill McConagha, Michael Landa, Laura Tarantino, Kristy Moran, Shawnee Jacobs

Ventria Bioscience:

Scott Deeter, President and CEO of Ventria Bioscience

William Rutter, Ph.D., Chairman of Synergenics, Member, National Academy of Sciences, Founder of Chiron and previous Board Member of Novartis

Thomas Urban, Jr, Chairman of Ventria Bioscience and former Chairman and CEO of Pioneer Hi-Bred International; Board Member Carnegie Institute

Stephen Taylor, Ph.D. Professor of Food Science and Technology, University of Nebraska, Lincoln and Chairman of Ventria's "generally recognized as safe" GRAS panels for GRN 235 and GRN 191

**Subject:** Meeting with Ventria Bioscience to discuss their GRAS applications for recombinant human lactoferrin and lysozyme (GRN 235 and GRN 191).

### Highlights:

- Ventria introduced themselves and presented information regarding their recombinant human lactoferrin and lysozyme products, Lactiva and Lysomin.
- Ventria gave a chronology of events and interactions with FDA/CFSAN relevant to the FDA regulatory process and their GRAS Notices.
- Ventria presented their perspective that section 912 of the Food and Drug Administration Amendment Act of 2007 does not apply to their intended uses of their products.
- The visitors and FDA discussed the agency's proposed plans to engage the wider scientific community for further consideration of complex scientific issues.

### Action Items:

- FDA will follow-up with Ventria to facilitate reaching a decision regarding their applications.

Shawnee Jacobs  
Jr. Policy Analyst  
FDA Executive Secretariat





## Fasano, Jeremiah

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**From:** Slater, Jay  
**Sent:** Wednesday, May 14, 2008 1:48 PM  
**To:** Fasano, Jeremiah; Tarantino, Laura M  
**Cc:** Rosenberg, Amy; Rabin, Ronald  
**Subject:** rhLF and rhLZ allergy summary

[From Rabin, edited by Slater:]

The sponsor proposes use of recombinant human lactoferrin (rhLF) and/or lysozyme (rhLZ), expressed in transgenic rice, in an oral rehydration formula for infants with diarrhea. These two recombinant proteins are not perfectly identical to their endogenous counterparts, as there may be differences in glycosylation or other post-translational modification that in turn may generate novel epitopes for T cell recognition and activation. While infectious diarrhea may be due to active secretion of solutes (and the water that follows) or an impairment in absorption of solutes (and water), the mucosal injury associated with infection and inflammation is frequently if not always accompanied by increased permeability of large molecules from the intestinal tract into the blood stream. Since infants may experience 3-6 diarrheal episodes per year for the first two years of life, inclusion of rhLF and rhLZ in oral rehydration fluids has the potential for repeated intermittent systemic exposure to neoantigens. This is precisely the scenario that is known to induce allergic responses to exogenous proteins. Furthermore, after T cell responses to neoantigens, there is potential for the process of "antigenic spread" to other parts of the recombinants that are identical to their endogenous counterparts. If an allergic response is precipitated by the neoantigens, it is possible that the infants may become allergic to endogenous LF and LZ. Antigenic spread is also associated with induction of autoimmunity that when directed, for example, against pancreatic islet beta cells, can cause type I diabetes mellitus. Therefore, it is our opinion that these two recombinants should not be considered GRAS, as they have the potential of inducing in infants allergic responses to the recombinants themselves and their endogenous counterparts, and may also induce autoimmunity.

Jay E. Slater, MD  
Deputy Director, DBPAP  
Chief (Acting), Laboratory of Immunobiochemistry  
301.496.4575  
301.480.4103 (fax)

June 3, 2008

**Robert Merker, Ph.D. (HFS-255)**  
Consumer Safety Officer  
Division of Biotechnology and GRAS Notice Review  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
Room 3044  
University Station  
4300 River Road  
College Park, Maryland 20740

**Re: Ongoing Concerns About Recombinant Human Lactoferrin from Transgenic Rice (GRN No. 000235 Submitted by Ventria Biosciences)**

Dear Dr. Merker:

This letter is to address the claim of Ventria Biosciences ("Ventria") in GRN No. 000235, submitted to FDA's Center for Food Safety and Applied Nutrition (CFSAN), that recombinant human lactoferrin (rhLF) from transgenic rice is generally recognized as safe (GRAS) for use in oral rehydration solutions and pediatric "medical" foods. GRN No. 000235 is a re-submission of GRN No. 000162, which was substantially narrowed in scope to include only the above mentioned uses. We received a copy of GRN No. 000235 under the Freedom of Information Act.

Our original scientific assessment on GRN No. 000162 was submitted to CFSAN on November 9, 2005 and a subsequent response to additional Ventria comments was submitted on September 11, 2006. As this Supplemental Scientific Assessment incorporates the November 9, 2005 Scientific Assessment on GRN 000162 submitted to CFSAN, as well as the additional submission of September 11, 2006, we ask that that assessment and all related materials submitted by Agennix to GRN 000162 be added to the file for GRN 000235 as well.

The Supplemental Scientific Assessment has been endorsed by all of the scientific experts who signed the November 9, 2005 assessment, in addition to a number of additional experts. Because of Ventria's current focus on the pediatric population, the Supplemental Scientific Assessment has also been endorsed by Michael P. Sherman, M.D., a pediatrician from the Department of Pediatrics at the Southern Illinois University School of Medicine. Dr. Sherman is a highly respected physician and researcher with over 30 years of experience in pediatric medicine. A copy of Dr. Sherman's CV, along with those for the other experts endorsing the Supplemental Scientific Assessment, are attached for your reference. We have also included at the end of this Supplemental Scientific Assessment a list of supplemental references that further support arguments made in response to our previous submissions on GRN No. 000162.

Before addressing our specific concerns with Ventria's re-submission, it should be noted that GRN No. 000235 bases its conclusion of safety for rhLF largely on a *presumption* of equivalence to human breast milk and native human lactoferrin. Indeed, the majority of evidence presented (18 of 25 pages) deals *only* with human breast milk or native human lactoferrin. Such a presumption of equivalence is fallacious, and the safety of human breast milk (or even of native human lactoferrin) is not relevant to evaluation of the safety of Ventria's recombinant product. Ventria is seeking GRAS approval for recombinant human lactoferrin produced in rice, not human breast milk or native human lactoferrin. As discussed in our previous submissions to CFSAN, rhLF produced in rice has structural differences from native human lactoferrin, including major changes in glycosylation that could pose significant health risks.<sup>1</sup> Any conclusion of safety must be based on data with Ventria's rhLF and not on anecdotal comparisons to either breast milk or native human lactoferrin.

In its re-submission, Ventria provides no new safety data for rice-produced rhLF, with the exception of a single pediatric clinical trial conducted in Peru involving children suffering from acute diarrhea. We have asked leading experts in the relevant fields to review this new GRAS notice, and they have prepared the attached Supplemental Scientific Assessment which we ask become a part of the file for GRN 235. In this Supplemental Scientific Assessment, these experts address some of the significant flaws with this trial, and the reasons it does not address the serious safety concerns with rhLF produced in rice raised earlier. Unaddressed safety risks include the possibility of acute allergic reactions, risks of targeting vulnerable pediatric populations and the risk of longer-term immunological complications.

In light of these points and the added specificity provided in the attached Supplemental Scientific Assessment, we continue to believe very strongly that Ventria has not met the criteria for GRAS:

1. Ventria has not provided adequate scientific data demonstrating a *reasonable certainty of no harm*.
2. Ventria has not provided *publicly available* data demonstrating the safety of its rice-based rhLF product.
3. There is no scientific consensus of general recognition of safety—to the contrary, there continues to be a clear *disagreement* among qualified experts as to whether Ventria's rhLF is GRAS.

Accordingly, we do not see any basis, given the current record and attached Supplemental Scientific Assessment, on which FDA could uphold a finding of GRAS for

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<sup>1</sup> Scientific Assessment Submitted to CFSAN, November 9, 2005, pages 4-6.

Letter to Robert Merker, Ph.D.

Page 3 of 3

Ventria's rice-based rhLF. We therefore urge FDA to deny Ventria's proposed finding of GRAS.

We very much appreciated your attention to these issues when we met with you on November 14, 2005. If you believe that a follow-up meeting would be useful, we would be pleased to arrange for relevant experts to visit with you in your Maryland offices.

Sincerely yours,

A handwritten signature in cursive script that reads "Rick Barsky".

Richard Barsky  
Chief Executive Officer  
Agennix, Inc.

Cc: Frank E. Young, M.D., Ph.D.  
Chairman, Agennix

Joseph A. Levitt, Esq.  
Partner, Hogan & Hartson, LLP  
Counsel to Agennix

## **Supplemental Scientific Assessment GRN 235: Rice-Based Recombinant Human Lactoferrin**

We, the undersigned scientific experts, have reviewed GRN 235 submitted by Ventria BioSciences for use of its rice-based recombinant human lactoferrin (rhLF) in oral rehydration solutions and pediatric “medical” foods. This review supplements an earlier assessment of Ventria’s original GRAS notice. We continue to believe that Ventria has not established a reasonable certainty of no harm from ingestion of its rhLF, that there are many unanswered safety issues, and that, if anything, targeting use of the product in infants and young children increases our safety concerns. We are, therefore, in strong and unanimous agreement that Ventria’s rhLF is *not* Generally Recognized as Safe (GRAS) for use in food products. The basis for this conclusion follows.

### **Ventria’s Safety Data Remains Inadequate and Raises More Questions than it Answers**

Ventria’s GRAS re-submission contains the same animal safety data that was presented in GRN No. 000162. To the best of our knowledge, this data has not been published or peer reviewed. Expert commentary on the inadequacy of Ventria’s animal safety data was presented in the earlier Scientific Assessment, which was submitted to CFSAN on November 9, 2005.<sup>1</sup> Concerns expressed in that initial Scientific Assessment are hereby incorporated in this Supplemental Scientific Assessment by reference.

The only new data presented in Ventria’s re-submission comes from a Peruvian clinical trial involving 140 children suffering from diarrhea (Zavaleta 2007), about a third of whom received Ventria’s rhLF for a few days. Ventria claims that no related material adverse events were observed in this trial.<sup>2</sup> However, contrary to Ventria’s claim, this trial received substantial public criticism for a lack of proper clinical methodologies and controls after it was reported that two children suffered serious allergic reactions following administration of the study drug.<sup>3</sup> We agree with this criticism. The conduct of this clinical trial is also reported to be the subject of a government ethics investigation.<sup>4</sup> In addition, the trial administered both rhLF and recombinant human lysozyme (rhLZ) concurrently in an oral rehydration solution (Zavaleta 2007), precluding a proper safety and efficacy analysis of the individual drugs by themselves. As stated by the authors themselves “It is not certain that the effects observed were caused by the combination of lactoferrin and lysozyme, even though in vitro data support this notion. Lysozyme alone could have exerted an antibacterial effect because of its enzyme activity ...”. Further, rather than establishing the safety of Ventria’s rhLF, this clinical data increases our concerns about its safety, including concern regarding the risk of acute allergic reactions to its foreign glycosylation.

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<sup>1</sup> Scientific Assessment Submitted to CFSAN, November 9, 2005, pages 2-3.

<sup>2</sup> Ventria GRAS Re-submission, September 2007, page 19.

<sup>3</sup> “A Grain of Caution: A Critical Assessment of Pharmaceutical Rice” Center for Food Safety, April 2007, page 20.

<sup>4</sup> Leighton, P. Study on infants in Peru sparks ethics inquiry. Science and Development Network, July 18, 2006. <http://www.scidev.net/content/news/eng/study-on-infants-in-peru-sparks-ethics-inquiry.cfm>.

The conduct of this trial has been widely criticized by the media in both Peru (Diaz 2006) and the United States.<sup>5</sup> Some of the concerning issues reported include the lack of proper informed consent, the occurrence of allergic reactions and selective and potentially misleading presentation of the data.<sup>6</sup> A published analysis of Ventria's trial touches on both safety and consent issues, as follows:

“According to an account in Peru’s *La Republica* (Diaz 2006), at least one mother whose infant was enrolled in the experiment was not informed that the treatment (“suero de arroz” or “rice serum”) was experimental and involved compounds from transgenic rice. Diana Canessa Garay, who enrolled her son Fabrizio in the experiment on February 15, 2005, states that she was “deceived”. According to Garay: “After they gave him the serum, my baby became sickly, delicate. Now he is allergic to everything...” A second mother, Johana Sanchez Turreate, says that her 3-year-old son Jordano also developed allergies after receiving the “serum”. Peruvian Member of Parliament Mercedes Cabanillas has initiated an investigation of the experiment by the Public Defender’s office.”<sup>6</sup>

Although it has not been conclusively established that Ventria’s rhLF is responsible for the allergic reactions reported by these mothers, it is clear that substantial additional clinical research is needed before a reasonable researcher could conclude that it is safe for this indication. In addition, other potential safety concerns have been identified in the publication describing this trial (Zavaleta 2007). For example, the authors state that there was a higher frequency of bacterial pathogen isolation in the stool of children receiving the Lf/Lz-R-ORS. The administration of lactoferrin to patients suffering from high loads of bacterial pathogens is a great concern, as Ventria’s rhLF is reported to induce transitory antibiotic tolerance in certain pathogenic bacteria (Andres 2005). That is, simultaneous treatment with antibiotics may be less effective in patients receiving lactoferrin-containing ORS.

There also appears to be a lack of proper follow-up on the trial subjects. The researchers reportedly followed up on the infants for only 14 days (Bethell 2006) which, as noted in the initial Scientific Assessment of November 9, 2005, is far too short a period to detect many potential immunological consequences of rhLF administration.<sup>7</sup> It is also concerning that in its GRAS submission Ventria failed to disclose these reported allergic reactions as well as the follow-on concerns by the patients’ families and the Peruvian authorities regarding this trial.

In addition to these safety issues, the validity of Ventria’s analysis of the trial results has been questioned. According to published papers (Zavaleta 2007, Zavaleta 2006), 140 Peruvian boys aged 3 – 36 months with acute diarrhea and dehydration were enrolled in the study and treated in one of three cohorts:

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<sup>5</sup> USA Today, “Uprou in Peru over genetically-engineered diarrhea treatment” July 14, 2006.

<sup>6</sup> “A Grain of Caution: A Critical Assessment of Pharmaceutical Rice” Center for Food Safety, April 2007, page 20.

<sup>7</sup> Scientific Assessment Submitted to CFSAN, November 9, 2005, page 16.

- 1) Cohort 1: Low osmolality WHO oral rehydration solution (G-ORS);
- 2) Cohort 2: ORS based on conventional rice (R-ORS); or
- 3) Cohort 3: ORS based on conventional rice to which recombinant lactoferrin and lysozyme extracted from Ventria's rice had been added (Lf/Lz-ORS).

An analysis of the data in these two reports shows several flaws:

1. As mentioned previously, co-addition of recombinant human lysozyme and recombinant human lactoferrin precludes the ability to assess the safety and efficacy of either of the two compounds. Perhaps any activity comes from lysozyme, and it is even possible that lysozyme reduces some of the potential side-effects of lactoferrin. The current study thus does not prove nor disprove anything about the safety or efficacy of lactoferrin.

2. The three study groups are clearly not similar, despite claims to the contrary. The authors report in Table 3 that the group receiving the Lf/Lz-ORS contains a much larger proportion of children with identified bacteria in their stool upon study entry (almost 80% versus below 55%). In particular, E.coli infections are more prominent in the Lf/Lz-ORS group (50% of all children, vs. 30% in the other groups). In contrast, the other two groups have a larger proportion of children with no identified pathogens in their stool. The children with bacterial load as a cause of diarrhea may be more susceptible to ORS treatment compared to those with another unidentified cause, thus creating a bias towards the group receiving Lf/Lz-ORS.

3. The authors combine the two control groups receiving R-ORS and G-ORS, claiming there are no significant differences between these two groups. This finding is surprising, since several previous studies have shown a clear benefit of adding nutritional support (such as rice) to the ORS formulation (Wall 1997; Sarker 2001; Dutta 2000; Maulen-Raduvan 2004, see also discussion in CDC 1992). A meta-analysis of 13 clinical trials (Gore 2002) shows that rice-based ORS reduced the rate of stool output in children with cholera by 32% and for those with acute non-cholera diarrhea by 18% versus children treated with standard glucose-based (WHO) ORS.

4. The Kaplan-Meyer curves for the study (Zavaleta 2007, Figure 2) show that the R-ORS group mostly follows the Lf/Lz-ORS group, except for day 1+2, and after day 6. Furthermore, combining the R-ORS and G-ORS groups, as was done to evaluate clinical outcomes (Table 4), creates a bias in the data. Since the G-ORS group is expected to do worse than the R-ORS group, combining these two groups for use as the control group artificially creates a favorable apparent comparison for Lf/Lz-ORS.

In conclusion, the data does not seem to suggest that there is a meaningful, or statistically significant, benefit from adding LF/LZ to a rice-based ORS solution, although the primary concern from the GRAS perspective is still the absence of established safety.



At a minimum, the reported issues with this Peruvian trial raise serious questions about whether either the safety or efficacy data from this trial have been adequately disclosed, and whether even the selective disclosures of the data can be relied upon without a full investigation and audit by the FDA. The reported occurrence of allergic reactions, and the fact that these reports do not appear to have been disclosed by Ventria to CFSAN when they would clearly be relevant to Ventria's GRAS notice, casts doubt about the accuracy, completeness and reliability of the GRAS notice.

Even if there had not been serious safety concerns raised by the Peruvian trial, it would not have resolved the safety concerns regarding Ventria's rhLF described by numerous leading experts. The number of patients was far too small and the treatment duration was far too short. As discussed in the initial Scientific Assessment of November 9, 2005, long term human studies are necessary to assess the risks of immunogenicity,<sup>8</sup> a concern that is even more relevant in this particularly vulnerable population. The fact that the treatment duration hypothesized in Ventria's amended GRAS notice is relatively short, does not rule out longer term exposure from other uses that Ventria has publicly described, nor even from multiple uses over several years by the children that Ventria now claims (for purposes of its amended GRAS notice) to be targeting.

### **The Possibility of Acute Allergic Reactions Was Raised Previously**

RhLF produced in rice is a biologically active immunostimulatory molecule that has potential risks which have not been thoroughly evaluated by credible human studies. These risks were outlined in the initial Scientific Assessment submitted to CFSAN dated November 9, 2005.

In that assessment, the potential acute and long-term health risks posed by the foreign glycosylation of Ventria's rhLF were detailed. The assessment stated

“that  $\alpha(1,3)$  fucose and  $\beta(1,2)$  xylose glycans appear on virtually 100% of rice-produced rhLF, and that these are cross-reactive carbohydrate determinants (CDDs) known to produce IgE antibodies. These same epitopes have been shown to induce immunogenicity in other therapeutic proteins produced in plants (Bardor 2002). It has been demonstrated that a considerable number of healthy individuals have antibodies circulating against  $\alpha(1,3)$ -fucose and  $\beta(1,2)$ -xylose residues. Furthermore, these  $\alpha(1,3)$ -linked fucose and  $\beta(1,2)$ -linked xylose glycans occur on many parasites and microorganisms that cause disease in people, and immune responses to these unusual carbohydrates, and even the carbohydrates themselves, may be profoundly important in disease pathogenesis (Die 2006, Foetisch 2003, Malandain 2005, Nyame 2004).”<sup>9</sup>

The potential adverse events that could be triggered by these glycans include acute allergic reactions as well as a host of longer-term immunological consequences. In view of this

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<sup>8</sup> Scientific Assessment Submitted to CFSAN, November 9, 2005, page 7.

<sup>9</sup> Scientific Assessment Submitted to CFSAN, November 9, 2005, page 4.

assessment, it is of particular concern that some of the children in Ventria's clinical study are reported to have experienced acute allergic reactions. It is also of concern that insufficient follow-up monitoring was conducted to determine whether other delayed reactions or allergic sensitization may have occurred.

### **Pediatric Populations May be at Increased Risk**

Ventria's revised intended use targeting pediatric populations is also cause for increased concern. Exposure to recombinant, non-natural proteins, especially in infants where the immune system is under development, may pose an increased risk for development of allergy or autoimmune diseases later in life. The risk would even be higher if ORS containing the recombinant protein is administered during gastrointestinal infections. Children are especially prone to a variety of gastrointestinal infections, including diarrheal diseases that increase gut permeability (leaky gut syndrome) and result in stimulation of the gut-associated lymphoid tissue. Published data suggests that such infections can result in abnormal antigen delivery across the mucosal barrier of the gut that triggers multi-organ processes leading to autoimmunity (Fassano 2005, Turley 2005, Wildner 2003). Enteric viral infections in children have also been associated with type 1 diabetes and an enhanced antibody response to other dietary ingredients such as bovine insulin in infant formula (Makela 2006). In view of the data associating autoimmune responses in children to increased intestinal permeability resulting from gastrointestinal infections, it is troubling that Ventria's rhLF is specifically targeted for children and infants suffering from gastrointestinal infections and diarrhea and that the FDA may not have been properly informed of the apparent immune reactions. The initial Scientific Assessment of November 9, 2005 specifically cautioned that the novel mechanism of action of rhLF might actually exacerbate these risks:

“RhLF is a biologically active immunostimulatory drug that interacts directly with receptors in the gut responsible for regulating immune response. Through receptor binding, lactoferrin might actually serve as a vector to deliver cross-reactive plant glycans directly to activated immune cells. It would seem likely that the presence of these glycans on lactoferrin might actually *increase* the risk of an IgE response.”<sup>10</sup>

Given the reported occurrence of allergic reactions in Ventria's trial, this caution should not be overlooked. Also of concern is the occurrence of food protein-induced enterocolitis syndrome caused by rice-derived proteins (Hjsak 2006; Nowak-Wegrzyn 2003). In this syndrome, children with rice allergy can present with vomiting, diarrhea and dehydration without a diagnosis of allergy. Although the appropriate treatment in these patients is the withdrawal of rice-derived proteins from their diet, a GRAS approval for the use of rice-derived rhLF in these patients could potentially result in an additional exposure to rice-derived proteins, worsening of the allergy and potentially death.

In summary, children, especially neonates and infants with GI disorders, are a uniquely vulnerable patient population whose physiological state may make them especially

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<sup>10</sup> Scientific Assessment Submitted to CFSAN, November 9, 2005, page 6.

susceptible to many of the potential risks from unsupervised administration of rice-derived rhLF. In the absence of large, long term, credible studies proving otherwise, children suffering from intestinal conditions should not be considered safe targets for the unsupervised administration of compounds containing Ventria's rhLF.

### **Longer-Term Safety Risks Remain**

In addition to these acute risks, the initial Scientific Assessment of November 9, 2005 also pointed out that there may be longer term risks with the administration of rhLF including among others:

- Long-term immunogenicity risks. As discussed previously, long-term immunogenicity risks can take time to manifest and can only be evaluated with appropriately sized long-term human trials. Although these risks are significant even with the general population, they may be substantially enhanced in the population targeted by Ventria's current GRAS notice. The factors that may enhance the long-term immunogenicity risks in this patient population include: (i) potentially increased gut permeability and breakdown of normal gut-protective mechanisms in these patients; (ii) a heightened immune responsiveness in response to gut-derived infection; and (iii) a dosing schedule consisting of a bolus of the antigen administered for short periods of time followed potentially by additional exposures during future diarrheal episodes, reminiscent of an immunization schedule. Some of the immunogenicity risks include:
  - The risk of immunogenicity and the breaking of B-cell tolerance, which may take over a year to manifest;
  - The risk of inducing anti-lactoferrin antibodies, which could both cross-neutralize endogenous lactoferrin with negative biological effects and neutralize the efficacy of exogenous lactoferrin, which could compromise future treatments;
  - The risk of exacerbating autoimmune diseases that are associated with anti-lactoferrin antibodies;
- The risk of toxicity in individuals with iron overload;
- The risk of iron delivery to iron constrained pathogens;
- The risk of iron delivery to tumors, which need iron for growth;
- The risk of systemic amyloidosis caused by lactoferrin variants; and
- The risk of viral activation by lactoferrin.

These risks have not been evaluated in human populations. Ventria notes in its re-submission that children up to 5 years of age are targeted for receiving treatment with rhLF

and that the average number of episodes of diarrhea may be as high as 2.3 per year.<sup>11</sup> This could potentially expose children to as many as 11 multi-dose administrations of Ventria's rhLF in their first 5 years of life. It is our continued opinion, as experts in the fields relevant to the safety of rhLF, that the longer-term risks described above (and more fully described in previous submissions<sup>12</sup>) remain real and substantial concerns under Ventria's revised conditions of use.

## **Conclusion**

Ventria's current resubmission of September 2007 provides insufficient evidence to warrant a GRAS determination for rice-produced rhLF to be marketed as a treatment for diarrhea in pediatric populations. Serious safety issues remain.

- Ventria's trial in Peruvian children was not designed to address the serious safety concerns. The children received only a single cycle of only a few days of treatment, the number of children receiving treatment with Ventria's rhLF was small, and they did not receive adequate follow-up. Moreover, published reports of allergic reactions in the trial – even though the trial involved administration of Ventria's rhLF to only a small number of children and for only a few days of treatment – only adds to the safety concerns. The other reported issues, including those involving selective and inadequate disclosure, further undermine the credibility of the trial and of the GRAS notice.
- Children with intestinal conditions may be particularly vulnerable to adverse reactions following administration of Ventria's rhLF.
- The potential longer-term risks described in the initial Scientific Assessment of November 9, 2005 remain serious safety concerns.

It is our scientific judgment, in view of the continuing risks described above and in the initial Scientific Assessment of November 9, 2005, that Ventria's rice-based rhLF is not GRAS for its proposed uses, and that Ventria's GRAS notice should be denied.

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<sup>11</sup> See Ventria's September 2007 re-submission, page 15.

<sup>12</sup> Scientific Assessment Submitted to CFSAN, November 9, 2005, pages 9-15.

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## Addendum to Scientific Assessment of November 9, 2005: Supplemental References

The following supplemental references further support arguments made in the scientific assessment previously submitted on November 9, 2005. We are submitting these additional references for inclusion in the record.

### **Topic: Glycosylation Risks**

A recent publication showed that even expression of a plant protein (bean  $\alpha$ -amylase inhibitor) in a different plant species (peas) produced novel post-translational protein modifications (including variations in glycosylation). This resulted in altered immunogenicity, including CD4+ TH2-type inflammation in mice (**Prescott 2005**).

\* \* \* \*

Besides being antigenic and allergenic, carbohydrate moieties of glycolipids and glycoproteins in plants, animals and humans have very high biological activity and are involved in a tremendous range of biological processes including cell-cell adhesion, cell-cell signaling, immune regulation, innate immunity, and cell biological phenomena including organelle biosynthesis (**Bertozzi 2001, Engering 2002, Feizi 2000, Freeze 2005, Gu 2004, Helenius 2004, Rudd 2004, van Kooyk 2004**).

\* \* \* \*

Carbohydrate moieties have increasingly been implicated in the immunogenicity and allergenicity of recombinant proteins (**Betenbaugh 2004, Fotisch 2001, Jin 2008**)

### **Topic: Immunostimulation by Lactoferrin**

Lactoferrin has a broad range of immunostimulatory properties that have been extensively documented and discussed in the literature. Orally administered lactoferrin can result in substantial systemic immunomodulation, which must be evaluated thoroughly before permitting unsupervised availability of rhLF, especially in pediatric populations. (**Artym 2005, Curran 2006, Fischer 2006, Hwang [a] 2007, Hwang [b] 2007, Kuhara 2006, Legrand 2006, Legrand [a] 2005, Prgomet 2007, Rosa 2008, Spadaro 2008, Spadaro 2007, Takakura 2006, Varadhachary 2006, Varadhachary 2005, Wakabayashi 2006, Wilk 2007, Wolf 2007, Zimecki 2007, Zimecki 2005, Zuccotti 2007**)

\* \* \* \*

In vitro, lactoferrin has been shown to activate macrophages (**Edde 2001**) and has been shown to induce immune maturation and proliferation of a range of immune cells (**Legrand [b] 2005, Shau 1992, Dhennin-Duthille 2000**).



### **Topic: Immunotoxicity Risks**

Immunomodulatory agents (like rhLF) present a distinct risk of immunotoxic effects that require careful preclinical and clinical evaluation. A recent review by a noted immunotoxicologist summarized these concerns (**Descotes 2004**).

### **Utility to Pathogens**

Iron availability is critical to the growth of intestinal pathogens such as *Helicobacter pylori* and *Entamoeba histolytica* – organisms that have evolved a mechanism to acquire iron from lactoferrin. Infection with the later organism can often lead to Amoebic dysentery. Before children are exposed to lactoferrin, special care should be taken to screen for any amoebic parasites. (**Dhaenens 1997, Husson 1993, Johansson 2008, Leon-Sicairos 2005, Olakanmi 2007**)

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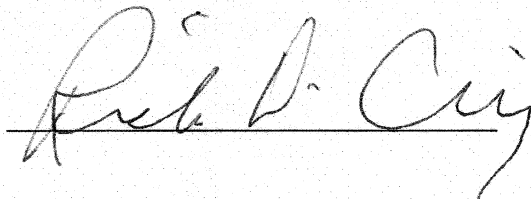
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# Expert Signature Pages

**SAFETY CONCERNS RAISED BY RECOMBINANT HUMAN LACTOFERRIN  
PRODUCED IN RICE: SUPPLEMENTAL SCIENTIFIC ASSESSMENT OF  
GRAS NOTICE NO. 000235 SUBMITTED BY VENTRIA BIOSCIENCE**

The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature:

A handwritten signature in cursive script, appearing to read "Richard D. Cummings", written over a horizontal line.

Name:

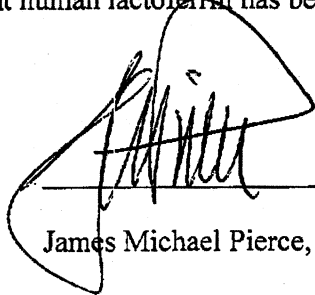
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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature:



\_\_\_\_\_

Name:

James Michael Pierce, Ph.D.

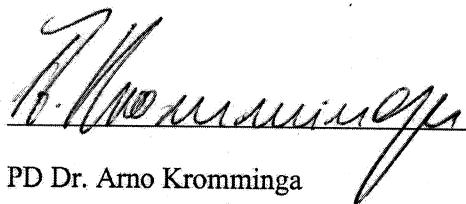
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in Cancer Research  
Member, Complex Carbohydrate Research Center  
University of Georgia

**SAFETY CONCERNS RAISED BY RECOMBINANT HUMAN LACTOFERRIN  
PRODUCED IN RICE: SUPPLEMENTAL SCIENTIFIC ASSESSMENT OF  
GRAS NOTICE NO. 000235 SUBMITTED BY VENTRIA BIOSCIENCE**

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Name:

PD Dr. Arno Kromminga

Title:

Director, Immunology



**SAFETY CONCERNS RAISED BY RECOMBINANT HUMAN LACTOFERRIN  
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Professor of Medicine

**SAFETY CONCERNS RAISED BY RECOMBINANT HUMAN LACTOFERRIN  
PRODUCED IN RICE: SUPPLEMENTAL SCIENTIFIC ASSESSMENT OF  
GRAS NOTICE NO. 000235 SUBMITTED BY VENTRIA BIOSCIENCE**

The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature: Marco van de Weert May 19, 2008

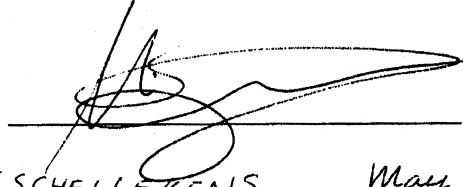
Name: Marco van de Weert

Title: PhD, Associate Professor

**SAFETY CONCERNS RAISED BY RECOMBINANT HUMAN LACTOFERRIN  
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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature:

A handwritten signature in black ink, appearing to be 'H. Schellekens', written over a horizontal line.

Name:

H. SCHELLEKENS

May 19, 2008

Title:

Professor

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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature: *Michael P. Sherman*

Name: **MICHAEL P. SHERMAN, M.D.**

Title: Professor of Pediatrics [tenured], School of Medicine,  
Southern Illinois University, Springfield, IL  
Professor Emeritus (Pediatrics), School of Medicine  
University of California, Davis

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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

*Irma van Die*

Signature: \_\_\_\_\_

Name: Irma van Die

Title: PhD, Associate professor in Glycoimmunology

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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature: SD Roger 18th May 2008

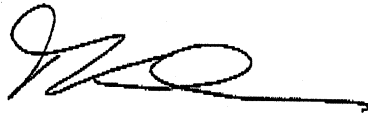
Name: SIMON ROGER MD FRACP

Title: RENAL PHYSICIAN  
DIRECTOR OF NEPHROLOGY  
GOSFORD HOSPITAL  
GOSFORD  
AUSTRALIA.

**SAFETY CONCERNS RAISED BY RECOMBINANT HUMAN LACTOFERRIN  
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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature:



Name:

Prof. Dr. med. Martin K. Kuhlmann, M.D.

Title:

Director, Department of Internal Medicine, Nephrology  
Vivantes Klinikum im Friedrichshain  
Landsberger Allee 49  
Berlin, Germany

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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

*N. Casadevall*

Signature: \_\_\_\_\_

Name: CASADEVALL Nicole


Title: Professor of Hematology  
Hospital SAINT ANTOINE - PARIS



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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature:



Ashraf Mikhail

Name:

Ashraf Mikhail

Title:

Cosultant Nephrologist

Morrison Hospital

Senior Clinical Tutor

Swanbsea University

UK

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The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

Signature: Eugene D. Weinberg

Name: Eugene D. Weinberg, PhD

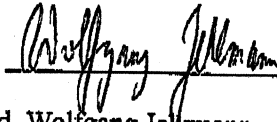
Title: Professor Emeritus  
Biology & Medical Sciences  
Indiana University  
Bloomington, IN 47405 USA

**SAFETY CONCERNS RAISED BY RECOMBINANT HUMAN LACTOFERRIN  
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GRAS NOTICE NO. 000235 SUBMITTED BY VENTRIA BIOSCIENCE**

The preceding scientific assessment of safety issues concerning rice-produced recombinant human lactoferrin has been provided by and reflects the opinion of:

*May 15, 2008*

Signature:



Name: Dr. med. Wolfgang Jelkmann

Title: Professor of Physiology  
Director, Institute of Physiology  
University of Luebeck  
Ratzeburger Allee 160  
D-23538 Luebeck  
Germany



## DEPARTMENT OF HEALTH & HUMAN SERVICES

---

### Food and Drug Administration Center for Drug Evaluation & Research

Date: 6-17-08  
To: Dr. Steven Sundlof, Director, Center for Food Science and Nutrition  
From: Amy S. Rosenberg, M.D. and Daniela Verthelyi, Ph.D., M.D.  
Through: Dr. Steven Kozlowski, Director, OBP/OPS/CDER and Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research  
Re: GRN 000235 and GRN 000191 GRAS Notices

#### Introduction

This document communicates our concerns regarding the decision not to contest the GRAS designation for recombinant human lysozyme (hLZ-R) and recombinant human lactoferrin (hLF-R) produced in rice, in term infant formulas, pre-term infant formulas, “fortifiers”, and oral rehydration solutions for children up to three years of age. We have several important safety concerns regarding the addition of these proteins to formula and oral rehydration solutions:

#### 1. Potential risks:

The first regards the potential that the human immune system will view these proteins as allergens. Drs. Jay Slater and Ron Rabin will address the potential allergenicity of such proteins in a separate report/memo.

The second relates to the potential of these transgenic rice-produced recombinant human proteins, which have endogenous protein counterparts, to elicit immune responses that result in a breach in tolerance to the corresponding endogenous human proteins. Lactoferrin and lysozyme are normally present in multiple body fluids, particularly breast milk. They are considered an important component of the innate immune system with anti-infective, anti-cancer, and anti-inflammatory effects. Lactoferrin and Lysozyme are also prominent components of the secondary granules of neutrophils (PMNs) and are released in infected tissues and blood during inflammatory or infectious processes. Therefore development of antibodies to these proteins that either neutralize or change their bioactivity poses a significant risk. Indeed, several studies show that reduced levels of lactoferrin and/or granzyme are associated with increased susceptibility to infectious diseases (ref).

Antibodies to both lactoferrin and lysozyme have been described in the context of several autoimmune disorders including inflammatory bowel disease, lupus (Caccavo, 2005), Wegener’s granulomatosis (Pradhan, 2005) and rheumatoid arthritis (Manolova, 2003). Early studies show that the presence of antibodies to lactoferrin may contribute to increased vascular permeability (Erga et al, 2000). However, their exact role in autoimmune pathology still unclear as the impact of such antibodies has not been

extensively evaluated. Administration of LF to patients with inflammatory bowel disease is particularly concerning as it has a substantial probability to worsen disease by binding to high affinity, or even to lower affinity intestinal receptors, to which antibody could then bind and potentially fix complement, causing damage and destruction to the intestinal mucosa. The impact of hLF-R and hLZ-R on incidence and course of IBD in infants and children should be evaluated prior to general distribution in the population at large. In vitro modeling supports the activation of leukocytes by LF antibodies, due to the presence of LF on the cell surface of primed PMNs, as well as adherence of LF to cultured endothelial cells (Peen et al 1996) suggesting that PMNs adhering to vessel walls with exposed LF may become targets of circulating LF antibodies. The effect of orally administered LF in these patient populations is unknown. It may increase, decrease, or have no effect on antibody titer and may worsen, improve disease, or simply have no impact. This should be investigated.

2. Neonates and infants are more prone to mounting an immune response to oral antigens:

The risk of eliciting an immune response to these proteins is higher in neonates and infants, as studies have shown that the immature neonatal immune system has a higher capacity to form allergic immune responses to proteins delivered orally (refs). The presence of low titers of antibodies to LF in healthy, exclusively breast fed infants may further reflect the inherent immunogenicity of this protein (Lonnerdal et al 1998 Adv. Exp Med and Biol). However, the presence of antibodies to lysozyme has never been evaluated in infants. Assessment of antibodies to hLf and hLZ should be undertaken in infants prior to consideration of allowing transgenic rice produced lysozyme or lactoferrin in formulas or ORS. Should such antibodies be detected, the response should be followed over time and any correlation with disease states evaluated.

Studies show that, the incidence of food allergy is substantially greater in children than in adults (Sampson H 2004 J. Allergy and Clin Immunol). Moreover, in neonatal rodent models, some proteins delivered orally have been shown to prime rather than tolerize the immune response. For example, oral administration of myelin basic protein to neonates exacerbates the subsequent course of experimental allergic encephalomyelitis, a disease similar to multiple sclerosis (Miller et al 1994 E. JI. Immunol). The relevance of such observations in rodents to human infants is not clear, but does elicit concern. An additional concern when considering the administration of these proteins as ORS, is that exposure to LF and LZ proteins normally occurs in the context of breast milk, which is replete with cytokines, hormones and other immunomodulatory factors (Paramasivank et al 2006 Int J Fertil and Women Med). These factors may reduce or modify the immunogenicity of these proteins, or greatly moderate their potential to elicit immune related toxicity. Therefore, administration of hLF-R and hLZ-R in formula or ORS lacking such cytokines and immunomodulators may elicit a much more significant immune response than they would induce when delivered in human breast milk. As stated above, low levels of antibodies to LF have been reported in healthy infants, suggesting that low level antibodies to human LF are normal in infants, likely benign, and likely resolve over time. However administration of hLF-R, bearing foreign determinants may have the capacity to turn a benign response

into one with adverse consequences by increasing the affinity, the titer, causing isotype switching, or inducing a more sustained response. Lastly, delivery of these proteins in the setting of an inflamed and potentially compromised gut wall such as can happen in children with severe diarrhea may further facilitate the crossing of undegraded protein, believed to be more immunogenic than its degraded peptide fragments, into the gut associated lymphoid tissue where it may prime an immune response. Therefore, the development and fate of antibodies to human LF, in the presence or absence of exposure to rice produced hLF-R must be determined prior to generalized and uncontrolled use of ORS containing this agent.

### 3. Product immunogenicity:

From the data currently available it appears that the proteins produced in rice are not identical to their human, naturally occurring counterparts. Differences may include small differences in primary sequence, product related impurities due to post translational modifications (truncation, oxidation deamidation etc), process related impurities (such as rice related proteins, lipids or carbohydrates, or low levels of immune activators derived from adventitious agents such as bacteria or yeast, and altered glycosylation. All are of great concern as they can create novel epitopes or favor a pathogenic immune response to existing epitopes. To date, the published literature on hLF-R and hLZ-R, shows that only N-terminal sequencing and amino acid composition analysis has been performed. The presence of novel epitopes raises the concern that epitope spreading could ensue leading to breaking of tolerance to the fully human portions of the molecule and the generation of antibodies directed to the endogenous human protein. Thus, the full length of the hLF-r protein should be sequenced and not just the N-terminus. The primary data should be submitted for review by FDA. N-terminal sequencing may be acceptable as a release test for identity, but not as a test for determination of sameness to human LF.

In addition, alternative or reduced glycosylation, as evidenced in the Ventria product could contribute to immunogenicity as glycosyl groups present in the endogenous protein may shield protein epitopes from access by the immune system, and changes in sugars may lead to exposure of cryptic epitopes and the generation of an immune response (Sinclair A and Elliot S 2005. J. Pharm Sci). Further, the presence of the plant glycans  $\alpha$ 1,2 xylose;  $\beta$ 1,3 fucose on the hLF-R, could facilitate the breaking of tolerance to the endogenous human protein via collaboration of the plant glycan specific Th cells and autoreactive LF specific B cells, or via the IgE antibodies themselves, which in binding to antigen, may facilitate epitope spreading so that antibodies are generated to conserved human LF determinants (Bardor M et al 2003. Glycobiology).

Similarly, for lysozyme produced in transgenic rice, even if it is allegedly not glycosylated (this needs to be confirmed through appropriate studies by Ventria), there may be post-translational modifications imposed by the rice expression system that may cause truncations, oxidation, deamidation, aggregation or other product related impurities, which may predispose to immune responses. As mentioned above, such modifications leading to enhanced

immunogenicity have been previously observed (Prescott V et al 2005. J. Agric and Food Chem)

#### 4. Testing:

It should be pointed out that the failure to perform clinical trials that validate the safety of these proteins in infant formulas violates key principles set forth by the National Academy of Sciences regarding the evaluation of the safety of new ingredients in infant formulas: “Infant Formula: Evaluating the Safety of New Ingredients”, published in 2004(<http://www.nap.edu/catalog/10935.html>). This guideline underscores: 1) the unique vulnerability of infancy, 2) that infant formulas are consumed by the vast majority of infants and are the sole source of nutrition for a large segment of infants up to the first 6 months of life, 3) that manufacturers are increasingly interested in adding new ingredients to formulas in an attempt to mimic the perceived and potential benefits of human milk and finally, that 4) existing guidelines and safety regulations lack clarity and completeness in adequately addressing the unique growth and development requirements of infants and the vast diversity of potential new ingredients. In this guidance, it specifically states that though the “GRAS process is rigorous, flexible, credible and transparent..., its application **does not clearly address possible concerns for the multitude of potential new ingredients in infant formulas.... including those derived from novel sources or processes (e.g. products of fermentation or biotechnology)**”. The hLF-R and hLZ-R products clearly fall into the category of “new ingredients derived from novel sources”. It further specifically states that allergenicity is a factor that should be considered in a safety assessment: **“Other factors that should be considered for safety are: tolerance, allergenicity, impact of gastrointestinal flora .....**”. In that regard, there have been no evaluations of the allergenicity or immunogenicity of hLZ-R and hLF-R despite the presence on lactoferrin of plant glycosyl groups known to be immunogenic/allergenic. This guidance clearly advocates for extensive testing of these proteins for their capacity to induce allergic and autoimmune responses to both rice produced and to the endogenous human LF and LZ prior to widespread use. The document describes a hierarchical approach to such evaluations and lists as the first two elements to be considered the “reversibility of potential harmful effects and the severity and consequences of adverse effects”. Allergic responses may be severe, life-threatening and not subject to elimination by standard immunotherapy. Also, they may be associated with vasculitis (). The document further recommends safety assessments of Organ Systems, Neurobiological Development and Behavior and specifically states that “..the committee recommends a two level assessment approach to assess organ, immunological and endocrinological systems”. It goes on to state that “In addition, some organ systems (e.g. immune and endocrine) are immature at birth; every effort must be made to ensure that ingredients new to infant formulas will not affect the development of these systems or expression of their function”. An autoimmune response that neutralizes LF or LZ could have a profound effect on the innate immune system (Welsh et al 2002 Nature), of which these factors are critical components, and could engender a suboptimal microbial gut flora with unknown consequences, both short and long term.

We are puzzled as to the justification for the designation of “Generally Recognized as Safe”, as it is clearly not evidence based. In fact, hLF-R has only been administered to 47 children with diarrhea in Peru (45 of whom completed the study) (Zavaleta et al 2007 2007 J. Ped. Gastro and Nutr.44:258) and a total of 4 healthy females (Lonnerdal 2006 Am J Clin Nutr) who were dosed for 42 days in the USA, while hLZ-R was only administered to children in the Peruvian study (Zavaleta et al 2007). Neither study was performed under IND and immunogenicity, including assessment of allergy was not evaluated. Indeed, the Peruvian study was followed by allegations of malpractice by the Peruvian Association of Physicians and the Peruvian Association for Human Rights according to the local press.

Additionally, we think that there are implicit and potentially explicit drug claims regarding addition of these factors to the formulas mentioned: that they will either prevent infection with microbes causing diarrheal illness (presence in infant formulas), or enhance the recovery from such infection (oral rehydration solutions). These claims are based on the highly criticized clinical trial in which the sponsor purported to demonstrate enhanced recovery from diarrheal illness in Peruvian children (Zavaleta et al 2007.). They were further publicized on the Ventria website: “May 1, 2006: A Breakthrough for Second Leading Killer of Children Under Five a Medical Food for Acute Diarrhea”. A In press release it was stated that “Ventria believes that addition of Lactiva (rhuLF) and Lysomin (rhuLZ) to oral rehydration solutions may help improve the health of children suffering from diarrhea.” As explicit, but unverified claims have been made, these products must be studied for safety and effectiveness, particularly in the ORS setting.

Further reason not to approve the GRAS designation of these products comes from the fact that by US laws and regulations, these products fall under the definition of “biological products” as they are analagous to human proteins present in multiple body fluids including serum. As interpreted in 21CFR600.3, which states that a biological product means any virus, therapeutic serum, toxin, anti-toxin, or analagous product applicable to the prevention, treatment, or cure of diseases or injuries of man, rice produced LF and LZ are biological products and require study under IND. Indeed, recombinant human lactoferrin products, produced in aspergillus are currently in clinical trials for presumed immunomodulatory properties in the settings of cancer and wound healing, and have been studied in the past for their effects on pathogenic microbes in the G.I. tract and on wound healing.

In summary, we disagree with the draft FDA letter stating that there are “no concerns about autoimmune responses to hLF-r as a result of “allogenicity” or plant glycosylation because of the limited duration of use, “one to fourteen days”. This neglects the fact that these products will assuredly be used repetitively and not just on a one time basis (at least three times per year is an estimate). Moreover, if tolerance to endogenous human lactoferrin is broken, there may not be a further requirement for exposure to rice produced hLF-r or hLZ-r to perpetuate the response, as exposure to endogenous LF or LZ may perpetuate the response..



Thus, given the concerns listed above, and most importantly, given that these recombinant proteins have only been tested in a very small number of patients in a non-rigorous fashion, substantial risk exists and thus widespread uncontrolled use in the population, including healthy term and preterm infants, and in children recovering from diarrhea, likely comprising millions of children, is not justified. Should adverse events develop when this product is in widespread use, it could be devastating. In this case, risk can be mitigated to a very low level based on adequately sized and powered clinical trials assessing prevention of or time to recovery from infection.



## DEPARTMENT OF HEALTH & HUMAN SERVICES

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### Food and Drug Administration Center for Drug Evaluation & Research

Date: 6-17-08  
To: Dr. Steven Sundlof, Director, Center for Food Science and Nutrition  
From: Amy S. Rosenberg, M.D. and Daniela Verthelyi, Ph.D., M.D.  
Through: Dr. Steven Kozlowski, Director, OBP/OPS/CDER and Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research  
Re: GRN 000235 and GRN 000191 GRAS Notices

#### Introduction

This document communicates our concerns regarding the decision not to contest the GRAS designation for recombinant human lysozyme (hLZ-R) and recombinant human lactoferrin (hLF-R) produced in rice, in term infant formulas, pre-term infant formulas, “fortifiers”, and oral rehydration solutions for children up to three years of age. We have several important safety concerns regarding the addition of these proteins to formula and oral rehydration solutions:

#### 1. Potential risks:

The first regards the potential that the human immune system will view these proteins as allergens. Drs. Jay Slater and Ron Rabin will address the potential allergenicity of such proteins in a separate report/memo.

The second relates to the potential of these transgenic rice-produced recombinant human proteins, which have endogenous protein counterparts, to elicit immune responses that result in a breach in tolerance to the corresponding endogenous human proteins. Lactoferrin and lysozyme are normally present in multiple body fluids, particularly breast milk. They are considered an important component of the innate immune system with anti-infective, anti-cancer, and anti-inflammatory effects. Lactoferrin and Lysozyme are also prominent components of the secondary granules of neutrophils (PMNs) and are released in infected tissues and blood during inflammatory or infectious processes. Therefore development of antibodies to these proteins that either neutralize or change their bioactivity poses a significant risk. Indeed, several studies show that reduced levels of lactoferrin and/or granzyme are associated with increased susceptibility to infectious diseases (ref).

Antibodies to both lactoferrin and lysozyme have been described in the context of several autoimmune disorders including inflammatory bowel disease, lupus (Caccavo, 2005), Wegener’s granulomatosis (Pradhan, 2005) and rheumatoid arthritis (Manolova, 2003). Early studies show that the presence of antibodies to lactoferrin may contribute to increased vascular permeability (Erga et al, 2000). However, their exact role in autoimmune pathology still unclear as the impact of such antibodies has not been

extensively evaluated. Administration of LF to patients with inflammatory bowel disease is particularly concerning as it has a substantial probability to worsen disease by binding to high affinity, or even to lower affinity intestinal receptors, to which antibody could then bind and potentially fix complement, causing damage and destruction to the intestinal mucosa. The impact of hLF-R and hLZ-R on incidence and course of IBD in infants and children should be evaluated prior to general distribution in the population at large. In vitro modeling supports the activation of leukocytes by LF antibodies, due to the presence of LF on the cell surface of primed PMNs, as well as adherence of LF to cultured endothelial cells (Peen et al 1996) suggesting that PMNs adhering to vessel walls with exposed LF may become targets of circulating LF antibodies. The effect of orally administered LF in these patient populations is unknown. It may increase, decrease, or have no effect on antibody titer and may worsen, improve disease, or simply have no impact. This should be investigated.

## 2. Neonates and infants are more prone to mounting an immune response to oral antigens:

The risk of eliciting an immune response to these proteins is higher in neonates and infants, as studies have shown that the immature neonatal immune system has a higher capacity to form allergic immune responses to proteins delivered orally (refs). The presence of low titers of antibodies to LF in healthy, exclusively breast fed infants may further reflect the inherent immunogenicity of this protein (Lonnerdal et al 1998 Adv. Exp Med and Biol). However, the presence of antibodies to lysozyme has never been evaluated in infants. Assessment of antibodies to hLf and hLZ should be undertaken in infants prior to consideration of allowing transgenic rice produced lysozyme or lactoferrin in formulas or ORS. Should such antibodies be detected, the response should be followed over time and any correlation with disease states evaluated.

Studies show that, the incidence of food allergy is substantially greater in children than in adults (Sampson H 2004 J. Allergy and Clin Immunol). Moreover, in neonatal rodent models, some proteins delivered orally have been shown to prime rather than tolerize the immune response. For example, oral administration of myelin basic protein to neonates exacerbates the subsequent course of experimental allergic encephalomyelitis, a disease similar to multiple sclerosis (Miller et al 1994 E. JI. Immunol). The relevance of such observations in rodents to human infants is not clear, but does elicit concern. An additional concern when considering the administration of these proteins as ORS, is that exposure to LF and LZ proteins normally occurs in the context of breast milk, which is replete with cytokines, hormones and other immunomodulatory factors (Paramasivank et al 2006 Int J Fertil and Women Med). These factors may reduce or modify the immunogenicity of these proteins, or greatly moderate their potential to elicit immune related toxicity. Therefore, administration of hLF-R and hLZ-R in formula or ORS lacking such cytokines and immunomodulators may elicit a much more significant immune response than they would induce when delivered in human breast milk. As stated above, low levels of antibodies to LF have been reported in healthy infants, suggesting that low level antibodies to human LF are normal in infants, likely benign, and likely resolve over time. However administration of hLF-R, bearing foreign determinants may have the capacity to turn a benign response

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It should be pointed out that the failure to perform clinical trials that validate the safety of these proteins in infant formulas violates key principles set forth by the National Academy of Sciences regarding the evaluation of the safety of new ingredients in infant formulas: “Infant Formula: Evaluating the Safety of New Ingredients”, published in 2004(<http://www.nap.edu/catalog/10935.html>). This guideline underscores: 1) the unique vulnerability of infancy, 2) that infant formulas are consumed by the vast majority of infants and are the sole source of nutrition for a large segment of infants up to the first 6 months of life, 3) that manufacturers are increasingly interested in adding new ingredients to formulas in an attempt to mimic the perceived and potential benefits of human milk and finally, that 4) existing guidelines and safety regulations lack clarity and completeness in adequately addressing the unique growth and development requirements of infants and the vast diversity of potential new ingredients. In this guidance, it specifically states that though the “GRAS process is rigorous, flexible, credible and transparent..., its application **does not clearly address possible concerns for the multitude of potential new ingredients in infant formulas.... including those derived from novel sources or processes (e.g. products of fermentation or biotechnology)**”. The hLF-R and hLZ-R products clearly fall into the category of “new ingredients derived from novel sources”. It further specifically states that allergenicity is a factor that should be considered in a safety assessment: “**Other factors that should be considered for safety are: tolerance, allergenicity, impact of gastrointestinal flora .....**”. In that regard, there have been no evaluations of the allergenicity or immunogenicity of hLZ-R and hLF-R despite the presence on lactoferrin of plant glycosyl groups known to be immunogenic/allergenic. This guidance clearly advocates for extensive testing of these proteins for their capacity to induce allergic and autoimmune responses to both rice produced and to the endogenous human LF and LZ prior to widespread use. The document describes a hierarchical approach to such evaluations and lists as the first two elements to be considered the “reversibility of potential harmful effects and the severity and consequences of adverse effects”. Allergic responses may be severe, life-threatening and not subject to elimination by standard immunotherapy. Also, they may be associated with vasculitis (). The document further recommends safety assessments of Organ Systems, Neurobiological Development and Behavior and specifically states that “..the committee recommends a two level assessment approach to assess organ, immunological and endocrinological systems”. It goes on to state that “In addition, some organ systems (e.g. immune and endocrine) are immature at birth; every effort must be made to ensure that ingredients new to infant formulas will not affect the development of these systems or expression of their function”. An autoimmune response that neutralizes LF or LZ could have a profound effect on the innate immune system (Welsh et al 2002 Nature), of which these factors are critical components, and could engender a suboptimal microbial gut flora with unknown consequences, both short and long term.

We are puzzled as to the justification for the designation of “Generally Recognized as Safe”, as it is clearly not evidence based. In fact, hLF-R has only been administered to 47 children with diarrhea in Peru (45 of whom completed the study) (Zavaleta et al 2007 2007 J. Ped. Gastro and Nutr.44:258) and a total of 4 healthy females (Lonnerdal 2006 Am J Clin Nutr) who were dosed for 42 days in the USA, while hLZ-R was only administered to children in the Peruvian study (Zavaleta et al 2007). Neither study was performed under IND and immunogenicity, including assessment of allergy was not evaluated. Indeed, the Peruvian study was followed by allegations of malpractice by the Peruvian Association of Physicians and the Peruvian Association for Human Rights according to the local press.

Additionally, we think that there are implicit and potentially explicit drug claims regarding addition of these factors to the formulas mentioned: that they will either prevent infection with microbes causing diarrheal illness (presence in infant formulas), or enhance the recovery from such infection (oral rehydration solutions). These claims are based on the highly criticized clinical trial in which the sponsor purported to demonstrate enhanced recovery from diarrheal illness in Peruvian children (Zavaleta et al 2007.). They were further publicized on the Ventria website: “May 1, 2006: A Breakthrough for Second Leading Killer of Children Under Five a Medical Food for Acute Diarrhea”. A In press release it was stated that “Ventria believes that addition of Lactiva (rhuLF) and Lysomin (rhuLZ) to oral rehydration solutions may help improve the health of children suffering from diarrhea.” As explicit, but unverified claims have been made, these products must be studied for safety and effectiveness, particularly in the ORS setting.

Further reason not to approve the GRAS designation of these products comes from the fact that by US laws and regulations, these products fall under the definition of “biological products” as they are analagous to human proteins present in multiple body fluids including serum. As interpreted in 21CFR600.3, which states that a biological product means any virus, therapeutic serum, toxin, anti-toxin, or analagous product applicable to the prevention, treatment, or cure of diseases or injuries of man, rice produced LF and LZ are biological products and require study under IND. Indeed, recombinant human lactoferrin products, produced in aspergillus are currently in clinical trials for presumed immunomodulatory properties in the settings of cancer and wound healing, and have been studied in the past for their effects on pathogenic microbes in the G.I. tract and on wound healing.

In summary, we disagree with the draft FDA letter stating that there are “no concerns about autoimmune responses to hLF-r as a result of “allogenicity” or plant glycosylation because of the limited duration of use, “one to fourteen days”. This neglects the fact that these products will assuredly be used repetitively and not just on a one time basis (at least three times per year is an estimate). Moreover, if tolerance to endogenous human lactoferrin is broken, there may not be a further requirement for exposure to rice produced hLF-r or hLZ-r to perpetuate the response, as exposure to endogenous LF or LZ may perpetuate the response..

Thus, given the concerns listed above, and most importantly, given that these recombinant proteins have only been tested in a very small number of patients in a non-rigorous fashion, substantial risk exists and thus widespread uncontrolled use in the population, including healthy term and preterm infants, and in children recovering from diarrhea, likely comprising millions of children, is not justified. Should adverse events develop when this product is in widespread use, it could be devastating. In this case, risk can be mitigated to a very low level based on adequately sized and powered clinical trials assessing prevention of or time to recovery from infection.

Memorandum

To: Dr. Stephen F. Sundlof, D.V.M., Ph.D.  
Director, CFSAN

From: Ronald L. Rabin, M.D., DBPAP  
Office of Vaccines Regulation and Research, CBER

Through: Jay E. Slater, M.D., Deputy Director, DBPAP  
Office of Vaccines Regulation and Research, CBER

Re: GRAS designation for recombinant human lysozyme and lactoferrin

Date: June 27, 2008

**APPROVED**

By Ronald L. Rabin, M.D. at 2:47 pm, Jun 27, 2008

Ventria Biosciences proposes use of recombinant human lactoferrin (rhLF) and/or lysozyme (rhLZ) in an oral rehydration formula for infants with diarrhea. These two recombinant proteins are not perfectly identical to their endogenous counterparts, as there may be differences in glycosylation or other post-translational modifications that in turn may be novel epitopes for T cell recognition and activation.

While infectious diarrhea may be due to active secretion of solutes (and the water that follows) or an impairment in absorption of solutes (and water), the mucosal injury associated with infection and inflammation is frequently if not always accompanied by increased permeability of large molecules from the intestinal tract into the blood stream. Since infants may experience 3-6 episodes of diarrhea per year for the first two years of life, inclusion of rhLF and rhLZ in oral rehydration fluids has the potential for repeated intermittent systemic exposure to neoantigens.

Repeated intermittent exposure is precisely the scenario that is known to induce allergic responses to exogenous proteins. Once a T cell response to a neoantigen is established, there is potential for the process of "antigenic spread" to other parts of the recombinant protein that are identical to their endogenous counterparts. Therefore, if the neoantigenic part of rhLF and rhLZ induce an allergic response, it may spread to endogenous LF and/or LZ. Antigenic spread is also associated with induction of autoimmunity that when directed, for example, against pancreatic islet beta cells, ultimately causes Type I diabetes mellitus.

Therefore, it is our opinion that these two recombinants not be considered GRAS, as they have the potential of inducing in infants allergic responses to rhLF and/or rhLZ first, followed by an allergic response to their endogenous counterparts, and possibly may also induce autoimmunity.



**Fasano, Jeremiah**

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**From:** Scott Deeter [sdeeter@ventria.com]  
**Sent:** Tuesday, July 15, 2008 1:09 PM  
**To:** Fasano, Jeremiah  
**Subject:** Plant Glycan - Lactoferrin GRAS

Dear Jeremiah:

The following paper showing the work we sponsored with Ronald van Ree and Adriano Mari regarding plant glycans and lactoferrin was published. As you know, Ronald was on our GRAS panel and is one of the leading experts in the world in this area of science and immunology. This data was previously discussed and presented as a poster session and I have made Rick Goodman aware of this paper, as he had not seen the poster presentation.

I think this reinforces his presentation at the Toxicology Forum and would confirm the safety of Lactoferrin from rice as a GRAS ingredient for foods, especially for pediatric populations.

See below:

[Mari A, Ooievaar-de Heer P, Scala E, Giani M, Pirrotta L, Zuidmeer L, Bethell D, van Ree R.](#)

Evaluation by double-blind placebo-controlled oral challenge of the clinical relevance of IgE antibodies against plant glycans. *Allergy*. 2008 Jul;63(7):891-6.  
PMID: 18588555

Thank you,

Scott E. Deeter  
President & CEO  
Ventria Bioscience  
(970) 420-9598  
[www.Ventria.com](http://www.Ventria.com)

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**Fasano, Jeremiah**

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**From:** Scott Deeter [sdeeter@ventria.com]  
**Sent:** Tuesday, July 15, 2008 8:45 PM  
**To:** McConagha, William; Commissioner FDA  
**Cc:** Mattia, Antonia; Fasano, Jeremiah  
**Subject:** Ventria GRAS - Meeting Follow-up

Dear Commissioner Von Eschenbach and Mr. McConagha:

I wanted to follow-up on our GRAS status and let you know that I attended the Toxicology Forum, which hosted the session: “human proteins as food ingredients”. Thank you for the heads-up regarding this meeting. Below is a recap of the meeting from our perspective and a request for the Commissioner to intervene so that sound science guides the decision-making process at FDA, rather than hypothetical or un-related issues.

Toni Mattia (FDA/CFSAN) chaired the session and there were six speakers on the agenda with two speakers from FDA (Jeremiah Fasano-CFSAN and Daniela Verthelyi – Div. of Therapeutic Proteins). Jeremiah invited the speakers and arranged the session. Although he invited several members that were also members of the breastmilk protein (lactoferrin and lysozyme) GRAS panels, none were available to attend and speak at this meeting due to scheduling conflicts with the July 4<sup>th</sup> Holiday. I believe if they had been present, the level of scientific understanding regarding the subject would have been much improved.

Interestingly, several of the speakers mentioned the published work of several of the breastmilk protein GRAS panel members, so the GRAS panel was well represented in that regard. Each speaker was provided 20 minutes plus 10 minutes of Q&A. The topic was introduced by Jeremiah Fasano. Jeremiah requested the audience to provide input regarding the GRAS status of products in this category. There was not a specific mention of the benefits of adding these ingredients to foods, nor was there a specific mention of which proteins are proposed to be added, although the audience was directed to FDA’s GRAS notices website where Ventria’s GRAS notifications for the breastmilk proteins, lactoferrin and lysozyme, are listed.

Overall, the quality of discussion and dialogue at this meeting was introductory in nature and did not approach the scientific rigor that was employed by the GRAS panel when they reviewed the published data and science and made their conclusion that these proteins are GRAS. The issues that were relevant to the safety that were discussed at this meeting were thoroughly considered by the GRAS panel prior to reaching their conclusion. In this respect, the meeting was a confirmation that the GRAS panel addressed the relevant issues regarding safety of these proteins in foods and, in our view, this should clear the pathway for the completion of the GRAS review with a “no further questions” letter.

Two presenters from biopharmaceutical companies discussed the safety considerations of injectible biopharmaceuticals. They mentioned areas of concern for injectible biopharmaceuticals including injection site reactions, changes in formulation of injectibles, and immunogenicity related to biologic drugs delivered by injection. Neither of these presenters had data related to oral delivery of proteins, and were quite unfamiliar with the scientific literature in this area. They both mentioned that they were not well suited to address the safety issues presented by proteins used in foods, as this was the first time they had been asked to review the topic. The audience also questioned the applicability and relevance of data that was presented by these speakers when considering safety of products for oral consumption.

Another presenter briefly discussed lactoferrin and its application in human health, but spent most of his time discussing other human milk-derived proteins of interest for further development.

Dr. Richard Goodman at FARRP (University of Nebraska), provided a clear approach to the safety assessment (suggested by FARRP) and considering the immunogenicity/allergenicity of protein-based foods. Dr. Goodman’s approach to the safety assessment of

proteins as food ingredients was the only presentation to directly address the question raised by Jeremiah and Toni in the introduction. Dr. Goodman's approach was consistent with the GRAS panel's safety assessment and the safety conclusion by the GRAS panels regarding Ventria's breastmilk protein products.

Daniela Verthelyi, FDA-Div of Therapeutic Proteins mentioned several potential safety issues related to immunogenicity of injectible protein-based drugs. This is hardly relevant to oral consumption of proteins, as mentioned in Dr. Goodman's presentation and as questioned by the audience at the meeting. Clearly, the safety issues for an injectible drug are quite unique due to this route of administration. Daniela claimed in her presentation that the safety issues could be the same, but she had no data or scientific literature to backup her assertion. Rather, it was a unfounded and hypothetical (at best) with no published scientific data to reach a meaningful or relevant hypothesis about the safety of oral consumption.

After the session, a reception was held and myself and our VP of R&D introduced ourselves to Dr. Verthelyi. Very quickly, Dr. Verthelyi revealed her bias against the use of breastmilk proteins in foods and claimed that Ventria's data was not strong enough to show benefit or safety. Of course, the issue currently being reviewed by FDA is the safety of these proteins in foods, not the efficacy/benefit. However, I felt compelled to describe the benefit of breastfeeding and the fact that millions of children are not breastfed for a variety of reasons, so improving infant formula with the addition of proteins found in breastmilk would be a significant benefit for pediatric nutrition. She claimed that Ventria did not have any human studies on this and no history of consumption. I mentioned that children have been consuming these proteins as part of breastmilk and also mentioned a recent published study in *Journal of Pediatric Gastroenterology & Nutrition* (Feb 2007) showing not only the safety of these proteins, but also the benefit of helping children with diarrhea to receive breastmilk proteins as part of a rehydration solution. The results were similar to those seen in children that have been breastfed. Daniela continued to claim that there were problems with our science and I asked her to explain, but she declined. When I repeated my request and suggested that we deserve an explanation, since she represents the FDA, she walked away from the conversation and would not address the question.

This is a very concerning development for Ventria and the FDA. Out of concern for the process, I mentioned this interaction to Jeremiah Fasano and suggested that he share it with Toni Mattia. Jeremiah mentioned that he was "well aware" of the problem with Dr. Verthelyi, so I suspect this is an internal FDA issue and since the CFSAN group is separate from the Division of Therapeutic Proteins, resolution of this may require leadership from the Commissioner.

From our perspective, it is very important that we use science to guide the regulatory process and decision-making utilizing currently available, published and credible science, rather than individual bias.

Senator Harkin and other Congressional representatives have been informed of the above information. I look forward to following up with you on this issue so that we can move forward for the benefit of child health and nutrition.

Very sincerely,

Scott E. Deeter  
President & CEO  
Ventria Bioscience  
(970) 420-9598  
[www.Ventria.com](http://www.Ventria.com)

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9/16/2008

**Fasano, Jeremiah**

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**From:** Fasano, Jeremiah  
**Sent:** Thursday, July 17, 2008 2:23 PM  
**To:** 'Scott Deeter'  
**Subject:** RE: Plant Glycan - Lactoferrin GRAS

Mr. Deeter-

Thank you for passing this on. I had seen a reference to the poster abstract a while back but was unable to readily obtain more information about it. I'll forward it to the team.

Regards-

-Jeremiah Fasano

---

Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
DBGNR/OFAS/CFSAN/FDA

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College Park, MD 20740

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**From:** Scott Deeter [mailto:sdeeter@ventria.com]  
**Sent:** Tuesday, July 15, 2008 1:09 PM  
**To:** Fasano, Jeremiah  
**Subject:** Plant Glycan - Lactoferrin GRAS

Dear Jeremiah:

The following paper showing the work we sponsored with Ronald van Ree and Adriano Mari regarding plant glycans and lactoferrin was published. As you know, Ronald was on our GRAS panel and is one of the leading experts in the world in this area of science and immunology. This data was previously discussed and presented as a poster session and I have made Rick Goodman aware of this paper, as he had not seen the poster presentation.

I think this reinforces his presentation at the Toxicology Forum and would confirm the safety of Lactoferrin from rice as a GRAS ingredient for foods, especially for pediatric populations.

See below:

[Mari A, Ooievaar-de Heer P, Scala E, Giani M, Pirrotta L, Zuidmeer L, Bethell D, van Ree R.](#)

Evaluation by double-blind placebo-controlled oral challenge of the clinical relevance of IgE antibodies against plant glycans.

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Thank you,

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August 14, 2008

Laura M. Tarantino, Ph.D. (HFS-200)  
Director, Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
Room 3044, University Station  
5100 Paint Branch Parkway  
College Park, Maryland 20740

**Re: Request for Legal Conclusion that Recombinant Human Lactoferrin from Transgenic Rice GRN No. 000235 (resubmission of GRN No. 000162) Submitted by Ventria Bioscience is *not* Generally Recognized as Safe (GRAS) based on a “Severe Disagreement” among Qualified Experts**

Dear Dr. Tarantino:

On behalf of Agennix, Inc. (Agennix) <sup>1/</sup>, we write to urge the Food and Drug Administration (FDA) to reach the legal conclusion that recombinant human lactoferrin (rhLF) from transgenic rice is *not* generally recognized as safe (GRAS) for use in oral rehydration solutions and pediatric medical foods, due to a “severe disagreement” among qualified experts as to whether it is safe for these food uses. For that reason alone, GRN No. 235, submitted by Ventria Biosciences (“Ventria”) to FDA’s Center for Food Safety and Applied Nutrition (CFSAN), should be denied—based solely on legal grounds.

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<sup>1/</sup> Agennix is a Houston, Texas-based biotechnology company and is the pioneer innovator of recombinant human lactoferrin as a pharmaceutical product. Agennix began clinical testing of rhLF in 1996 under the FDA’s investigational new drug (IND) program. Agennix has completed blinded, placebo-controlled Phase II clinical trials with rhLF that met their primary endpoints in indications including non-small cell lung cancer and diabetic foot ulcers. In advanced renal cell carcinoma (RCC), rhLF has also been successfully tested in a Phase II open label trial to evaluate its effects in patients whose disease had progressed after receiving at least one prior regimen of systemic therapy. Additionally, the Company has initiated an NIH-funded, randomized, placebo-controlled, multi-center Phase II trial in patients with severe sepsis. Agennix obtained FDA Orphan Drug designation for rhLF for indications including graft versus host disease (Aug. 2003), non-small cell lung cancer (Aug. 2007), and renal cell carcinoma (Sept. 2006). Agennix also obtained Fast Track designation from the FDA for two different non-small cell lung cancer (NSCLC) indications (first-line in combination with chemotherapy [Sept. 2006] and third-line as monotherapy [Oct. 2007]), and is starting Phase III trials in these indications. Agennix obtained approval of a Special Protocol Assessment (SPA) from the FDA for its first-line trial of rhLF in combination with chemotherapy in NSCLC patients (Nov. 2008).

Agennix has already filed extensive scientific comments regarding significant, unresolved safety issues with the use of rhLF in food. <sup>2/</sup> Those submissions were supported by the opinions of 14 prominent scientific and medical experts that rhLF is *not* GRAS for these food uses. These scientific and medical experts are from disciplines directly applicable to the safety assessment of rhLF—including the fields of glycobiology, immunology, and medicine, particularly pediatric medicine. Moreover, these scientific and medical experts are leaders in their respective fields, based on their many years of experience, prestigious academic posts, extensive publications, and numerous positions on government panels and editorial boards. They are regularly sought after as speakers at national and international conferences precisely because they are thought leaders whose opinions are highly respected.

Today's submission is tantamount to a "motion for summary judgment" because there are no material facts in dispute (i.e., it is a matter of record that there are two groups of experts expressing diametrically opposing views) and so the Agency may rightfully decide this issue as a matter of law. Furthermore, this letter is based solely on the third prong of the GRAS test—namely, that there be a consensus among qualified experts that the food ingredient is safe. <sup>3/</sup> We are asking FDA to determine, as a matter of law, that rhLF from transgenic rice is *not* GRAS for use in oral rehydration solutions and pediatric medical foods because Ventria has failed to demonstrate that there is a scientific consensus among qualified experts that the substance is safe.

The law is clear: a substance must meet all three prongs of the GRAS test to qualify as generally recognized as safe. An Agency determination that any one of the three elements is not met eliminates the need to evaluate and resolve the other two. As described below, Ventria so clearly fails to meet its burden of establishing a scientific consensus among experts that its GRAS notification for its rice-based rhLF must be denied on this basis alone. <sup>4/</sup>

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<sup>2/</sup> Agennix submitted to CFSAN its original Scientific Assessment on GRN No. 000162 on November 9, 2005, a subsequent response to additional Ventria comments on September 11, 2006, and a recent Supplemental Scientific Assessment to address new data submitted by Ventria regarding a South American pediatric rhLF clinical trial on June 3, 2008.

<sup>3/</sup> This letter does not rely on either of the first two prongs of the GRAS test—namely, that there be technical evidence of safety and that the data relied upon be publicly available. Those prongs are addressed in previous comments filed by Agennix to the scientific staff in CFSAN. Because all three prongs are required for a GRAS determination, the Agency does not need to reach a conclusion on the first two prongs if FDA determines, as a matter of law, that the third prong of expert consensus is not met.

<sup>4/</sup> Should the FDA agree that there is a severe disagreement among qualified experts, not only would there be no need for FDA to reach a conclusion on the complex scientific issues surrounding its technical evidence of safety, but FDA also would not have to reach a conclusion on the effect of Section 912 of the Food and Drug Administration Amendments of 2007 (FDAAA) on Ventria's GRAS notification (see letter of October 31, 2007 from Joseph A. Levitt, Counsel to Agennix).

## I. The GRAS Standard Requires A Consensus Among Qualified Experts

As you are aware, a substance added to food is a “food additive” for which FDA pre-market approval is required unless the substance is GRAS or qualifies for another statutory exemption. The intended use of a substance is GRAS if it is—

generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use . . . [5/](#)

As the statutory language states, a GRAS determination may be based on “scientific procedures.” FDA has advised that a GRAS determination based on scientific procedures requires three elements:

1. Evidence that a substance is safe for its intended use;
2. A basis for concluding that such evidence of safety is generally available;  
and
3. A basis for concluding that such evidence of safety is the subject of scientific *consensus among qualified scientific experts*.

FDA refers to the first element as “technical evidence of safety”; the second and third criteria collectively constitute the “common knowledge” element of the GRAS standard. All three elements must be demonstrated or the GRAS notice is considered incomplete. [6/](#) Further, the common knowledge elements of scientific consensus and publication apply to all of the evidence that is the basis for the determination of safety. [7/](#)

Technical evidence of safety requires a showing that “there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.” [8/](#) This is frequently paraphrased as demonstrating that there is a “reasonable certainty of no harm.” The second element, general availability, requires publication of key data or information in peer-reviewed scientific journals, general reference materials, textbooks, or other

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[5/](#) FFDC A § 201(s).

[6/](#) 62 Fed. Reg. at 18937, 18948 (Apr. 17, 1997) (stating “A notice summary that fully describes the technical evidence of safety, but does not provide a basis to conclude that the technical evidence is generally available and accepted [by experts], would be incomplete”).

[7/](#) *Id.*

[8/](#) 21 C.F.R. § 170.3(i); 62 Fed. Reg. at 18948.



appropriate sources. <sup>9/</sup> Although we believe that Ventria also fails on the first two counts of the GRAS standard, this submission is limited to the third prong of the GRAS standard—the common knowledge element of scientific consensus among qualified experts.

## II. A Scientific Consensus Does Not Exist If There Is A “Severe Disagreement” Among Qualified Scientific Experts

It is well-settled law that a “consensus” of qualified experts does *not* exist if there is a “severe disagreement” among such experts as to whether the food ingredient is safe for its intended use. The very fact that Agennix has identified 14 prominent, highly qualified scientific and medical experts who all believe there are significant, unresolved safety issues and that rhLF has *not* been shown to be safe for its intended uses, unequivocally demonstrates that a “severe disagreement” exists on this pivotal point. Accordingly, Ventria has failed to demonstrate that the safety of its proposed uses of rhLF from rice is the subject of expert consensus.

FDA’s 1997 proposed rule on “Substances Generally Recognized as Safe” provides clear guidance on criteria for the basis of concluding expert consensus, <sup>10/</sup> and that the existence of a “severe conflict” among experts will preclude a GRAS determination. <sup>11/</sup>

As discussed in FDA’s GRAS proposal and the pertinent case law, a proponent of a GRAS claim bears the burden of establishing expert consensus (i.e., that experts “generally” consider the ingredient at issue to be safe). The courts and FDA have interpreted this to mean that, although a mere divergence of views will not necessarily preclude GRAS status (as “even properly conducted studies may produce disagreement” <sup>12/</sup>) a “severe conflict” of expert opinion will *prevent* a finding of general recognition. <sup>13/</sup>

Although there is no bright-line test for identifying what constitutes a “severe conflict,” courts have readily found a “severe conflict” to exist after evaluating the facts at hand. In one case, even where the proponent of a GRAS claim presented the testimony of seven experts supportive of GRAS status, general recognition was found to be lacking in light of persuasive

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<sup>9/</sup> 21 C.F.R. § 170.30(b); 62 Fed. Reg. at 18942-43.

<sup>10/</sup> 62 Fed. Reg. at 18948-49.

<sup>11/</sup> See 62 Fed. Reg. at 18939 (citing *United States v. An Article of Drug . . . 4,680 Pills*, 725 F.2d 976, 990 (5th Cir. 1984); *Premo Pharma. Labs. v. United States*, 629 F.2d 795, 803 (2d Cir. 1980). Significantly, according to the Proposed Rule, “an ongoing scientific discussion or controversy about safety concerns . . . would make it difficult to provide a basis about the safety of a substance for an intended use.” *Id.* at 18949.

<sup>12/</sup> See, e.g., *United States v. Articles of Food and Drug . . . “Coli-Trol 80,”* 518 F.2d 743, 746 (5th Cir. 1975).

<sup>13/</sup> 62 Fed. Reg. at 18939 (citing *United States v. Articles of Drug . . . 5,906 boxes*, 745 F.2d 105, 119 n. 22 (1st Cir. 1984); *4,680 Pills*, 725 F.2d at 990; *Coli-Trol 80*, 518 F.2d at 746 (5th Cir. 1975); *United States v. Articles of Drug . . . Promise Toothpaste*, 624 F. Supp. 776, 782 (N.D. Ill. 1985), *aff’d* 826 F.2d 564 (7th Cir. 1987)).

opposing views offered by “several” government experts. [14/](#) In another case, “sharply divided testimony” was found to present a severe conflict of opinion. [15/](#) Expert testimony critical of general recognition in that case suggested that the studies presented did not prove safety or meet other criteria contained in FDA’s regulations. [16/](#) Another court failed to find a consensus where there was a “sharp difference of opinion” between experts regarding the methods and results of the available studies. [17/](#) Although these and other cases addressing expert consensus involve drug products, the expert consensus standard is exactly the same for both food and drugs. [18/](#) For both food products and drugs, the key is whether there is a “severe disagreement” of views among qualified experts.

As described further below, these judicial characterizations of “sharply divided testimony” and “sharp difference of opinion” perfectly describe the current case—i.e., whether rhLF is generally recognized as safe for its intended food uses. The experts presented by Ventria express one view, and the experts presented by Agennix express the very opposite view. Indeed, it is hard to imagine a scenario where the experts are any more “sharply divided.” In such cases, the courts have consistently found that expert consensus does not exist, and FDA should reach the same conclusion here.

Expert credentials play an important role when assessing whether expert consensus exists. In one case evaluating the status of a drug for a particular treatment, the court gave great weight to the opinions of several chairmen of leading medical departments from that specialty area. The court stated that “it cannot be denied that the affidavits of five of the leading doctors in the field which deny general recognition creates more than a ‘mere’ conflict . . . [i]t is inconceivable that a drug such as this could be considered generally recognized in the face of such learned non-recognition.” [19/](#)

Once again, the court has very much described the current case. As detailed below, and reinforced in the collection of expert CVs already on file with CFSAN [20/](#), the 14 scientific and medical experts presented by Agennix have national and international stature. They hold prestigious academic posts, direct cutting edge scientific and medical centers, serve on important

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[14/](#) See, e.g., *Pails*, 725 F.2d at 990 (holding that presentation by the United States of the views of “several experts” that a drug was not generally recognized as effective showed a “severe conflict” in the expert testimony and precluded general recognition).

[15/](#) *United States v. An Article of Drug . . . X-Otag Plus Tablets*, 441 F. Supp. 105, 113-114 (D. Colo. 1977).

[16/](#) *Id.* at 113.

[17/](#) *Premo Pharma. Labs.*, 629 F.2d 795 at 804.

[18/](#) See, e.g., 62 *Fed. Reg.* at 18938-18939 (citing drug and food precedent in discussion of meaning of GRAS standard under section 201(s) of the FFDCFA).

[19/](#) *United States v. An Article of Drug . . . “Mykocert,”* 345 F. Supp. 571, 575 (N.D. Ill. 1972).

[20/](#) These CVs were all submitted to CFSAN with the June 3, 2008 Supplemental Scientific Assessment.

governmental committees, and publish extensively in leading journals. In short, they are quintessential examples of “leading doctors [and scientists] in the field” so that a finding of GRAS is virtually precluded “in the face of such learned non-recognition.”

Agennix, the clear worldwide leader in research, development and production of rhLF, has consulted leading national and international experts on lactoferrin and issues relevant to the safety of rhLF from transgenic rice. These experts are primarily from the fields of: (a) glycosylation/glycobiology; (b) immunology; and (c) medicine, including pediatric medicine. Included among these are experts who have conducted research directly with recombinant human lactoferrin, so they have first hand knowledge of its safety profile. These 14 highly qualified experts have expressed serious and specific concerns regarding the safety of the Notifier’s proposed uses of rhLF from rice, demonstrating a “severe conflict” with the expert opinions and conclusions submitted by Ventria. We feel strongly that all of our experts are qualified to opine on various issues related to the GRAS status of rhLF from rice and their credentials speak for themselves. These are notable opinion leaders in various fields of science and medicine expressing widely-held safety concerns. We believe their opinions—as contrasted to those of Ventria’s experts—demonstrate there is a “severe disagreement” among qualified experts and that there is no “consensus” of the scientific community on the safety of rhLF for its intended uses.

### **III. Agennix has Provided the Opinions of 14 Prominent Physicians and Scientists that Rice-based Recombinant Human Lactoferrin is *Not* GRAS.**

Agennix has provided FDA with the opinions of 14 prominent physicians and scientists that rhLF is *not* GRAS for its intended uses. These experts were selected based on their recognized subject matter expertise, professional reputation, and experience in areas that have a high degree of relevance to the safety, biologic activity, and mechanism of action of rhLF, including glycobiology, immunology, and medicine (including pediatrics). These experts include renowned professors at universities in the United States, Europe and Australia, chairs of their respective departments or group, directors of scientific or medical centers, and practicing physicians. Collectively, they have published over 1,500 scientific articles, abstracts or book chapters, including a number of studies on recombinant human lactoferrin. The background and experience of each of these 14 experts may be summarized as follows:

- 1. Richard D. Cummings, Ph.D.:** Dr. Cummings is a preeminent leader in the field of Glycobiology with over 30 years of research and academic experience. He is William Patterson Timmie Professor and Chair of the Department of Biochemistry at Emory University School of Medicine. He and his research labs have made numerous significant discoveries and contributions at the forefront of this emerging field. Dr. Cummings founded and directed two major centers for Glycobiology at Emory University School of Medicine and the University of Oklahoma Health Sciences Center. He is co-editor of the first textbook on Glycobiology. Dr. Cummings has published over 170 peer-reviewed articles, over 30 review articles, eleven textbook chapters, and owns 27 different U.S. patents.

Dr. Cummings is an internationally known lecturer and speaker on issues related to Glycobiology. He has been an invited speaker of over 125 organizations and institutions. He has organized or chaired various national and international meetings and symposia on glycomics. He is a former President of the Society of Glycomics and is active in numerous professional societies. Dr. Cummings has been awarded various prestigious research fellowships from the National Institutes of Health (NIH) and National Science Foundation. He has served in an editorial capacity on ten different scientific journals. Dr. Cummings and his labs have been the recipient of seven current and seventeen prior NIH research grants, and twelve other research grants from various public and private institutions. He has provided government service in many different roles as an NIH reviewer, panel member, and study section member.

**2. James Michael Pierce, Ph.D.:** Dr. Pierce is a Professor of Biochemistry and Molecular Biology at the University of Georgia and Director of the University of Georgia Cancer Center. He is a tenured professor with over 25 years in academia. Dr. Pierce's research focuses on the function of complex carbohydrates in human health with an emphasis on cancer progression and diagnosis. He has conducted extensive research in the area of glycobiology. He is the editor of the *Handbook of Glycomics* and an officer in the Society of Glycobiology. Dr. Pierce's work has been supported by the NIH and the National Cancer Institute. He has published over 65 peer-reviewed articles. He has served as a reviewer for various NIH, NCI, and American Cancer Society study sections and project reviews. Dr. Pierce is also a reviewer at leading publications including *Nature*, *Biochemistry*, *Gene*, *Glycobiology*, *Glycoconjugate Journal*, and the *International Journal of Cancer*. Dr. Pierce has been an invited speaker or lecturer at over 70 major seminars/symposia in the U.S. and abroad. He also holds eleven U.S. patents.

**3. Irma van Die, Ph.D.:** Dr. van Die is Head of the Glycoimmunology Group in the Department of Molecular Cell Biology & Immunology at Vrije University Medical Center in Amsterdam. She has written over 100 publications in the areas of glycobiology and immunology and has been a professor for over fifteen years. Dr. van Die has done extensive work for various sections of the Netherlands Organization for Scientific Research (NWO), the Dutch government organization that funds research at top universities and institutes. She is a regular reviewer for major journals including: *European Journal of Biochemistry*, *Glycoconjugate Journal*, *Glycobiology*, *Journal of Biological Chemistry* and a grant reviewer for the NWO. She has been a board member and is the current Secretary of the Dutch Society of Glycobiology, and is a member of various other professional societies. Dr. van Die's research is supported by numerous major public and private grants. Research at her glycoimmunology department has made a significant contribution to the present understanding and knowledge of glycan function.

**4. Hubertus Schellekens, M.D.:** Dr. Schellekens is a professor of Pharmaceutical Sciences at Utrecht University in the Netherlands. Dr. Schellekens has written more than 200 peer-reviewed journal articles concerning the preclinical development of biotechnology-derived therapeutic proteins. His most recent work focuses on immunogenicity of therapeutic proteins and biosimilars. He is the editor-in-chief of *Biotherapy*. Dr. Schellekens is very active in the Netherlands Commission on Genetic Modification (COGEM), serving as chairman of several subcommittees. COGEM provides scientific advice to the government on the risks to human health and environment regarding the production and use of bioengineered compounds. He also serves as an expert in rDNA pharmaceuticals for the European Medicines Agency (EMA), and as chairman of the Dutch Society of Microbiology's Committee for Biological Safety and deputy chair of its Committee on Biotechnology in Animals.

**5. Arno Kromminga, Ph.D.:** Dr. Kromminga serves as Director of Immunology at the Institute for Immunology, Clinical Pathology, and Molecular Medicine (IPM) in Hamburg, Germany. IPM's work focuses on resolving immunogenicity issues by antibody detection against biopharmaceuticals using a broad range of methods and different assay formats. It is dedicated to the development, validation and application of innovative methods in molecular and immunological diagnostics including immunogenicity. He is an international leader in the field of immunology. Dr. Kromminga has written over 25 publications and presented over 40 lectures at major symposia around the world.

**6. Michael P. Sherman, M.D.:** Dr. Sherman is a Professor of Pediatrics at Southern Illinois University School of Medicine and Professor Emeritus at the University of California, Davis. He has practiced academic medicine for over thirty years with a focus on neonatology. Dr. Sherman has a longstanding interest in lactoferrin and is uniquely qualified to express medical opinions on the use of rhLF in humans and the potential risks to children and neonates (a proposed use by Ventria).

Dr. Sherman's research has been published in over 80 peer-reviewed publications. He has written 19 book chapters and holds two U.S. patents. He has been a reviewer or member of several NIH study sections, a reviewer for thirty-six scientific journals and a member of the editorial board of three journals. He has been an invited lecturer at over fifty conferences/symposia since 1988. A sample of the subjects he has lectured on includes: "Lactoferrin and Neonatal Gut Related Infections," "Lactoferrin and Macrophage Biology and Biochemistry," and "Neonatal Small Bowel Epithelia: Fortifying Anti-bacterial Defense with Lactoferrin and Lactobacillus GC." Dr. Sherman has obtained NIH and Children's Miracle Network grants for research specific to lactoferrin.

Dr. Sherman has published or submitted manuscripts for publication for several articles on various issues related to lactoferrin. Some of these articles include: "Effect of lactoferrin and lactobacillus prophylaxis on small bowel infection by *Escherichia coli* in newborn rats," "Lactoferrin-enhanced Anoikis: A Defense against Neonatal Necrotizing Enterocolitis," "Lactoferrin protects neonatal rats from gut-related system infection," and "Lactoferrin and recognition of enteric bacteria by rat bronchoalveolar macrophages." In addition, he has presented twenty-eight abstracts or poster presentations concerning lactoferrin.

**7. E.D. Weinberg, Ph.D.:** Dr. Weinberg is Professor Emeritus in Microbiology at Indiana University and the Scientific Advisory Board Chair for the Iron Disorders Institute. He was a professor for over 40 years for more than 15,000 students. He has published over 150 research papers or book chapters. Two of his papers have been designated as Benchmark Papers in Microbiology. Dr. Weinberg has presented thirty-six invited lectures at national and international meetings and attended over forty invited seminars throughout the world.

Dr. Weinberg has conducted important research on lactoferrin over decades and is particularly qualified to advise on the safety issues related to human use of rhLF. Three of his publications include: "Human lactoferrin: a novel therapeutic with broad spectrum potential," "Therapeutic potential of human transferrin and human recombinant lactoferrin," and "The therapeutic potential of lactoferrin."

**8. Sidney E. Grossberg, M.D.:** Dr. Grossberg is Walter Schroeder Professor of Microbiology and Molecular Genetics and Professor of Medicine at the Medical College of Wisconsin. He served as Chairman of the Department of Microbiology for thirty-one years and has been a medical professor for over fifty years. Dr. Grossberg has been published in over 170 peer-reviewed publications. He has served as an advisor or reviewer for the National Cancer Institute, National Institute of Allergy and Infectious Diseases, the World Health Organization, and the National Board of Medical Examiners. His expertise includes microbiology and immunology.

**9. Marco van de Weert, Ph.D.:** Dr. van de Weert is a professor in the Department of Pharmaceutics and Analytical Chemistry and is Biomacromolecules Group Leader at the Danish University of Pharmaceutical Sciences. He has been a professor for six years and focuses his research on protein formulation and drug delivery. He has written over 20 publications and three book chapters. Dr. van de Weert is a regular reviewer for scientific journals, including the *European Journal of Pharmaceutical Sciences*, the *Journal of Pharmaceutical Sciences*, and the *International Journal of Pharmaceutics*. He is also a member of the European Working Party on Biosimilars, the group that advises the European Medicines Agency on issues related to comparability testing for follow-on biologics and any other clinical and non-clinical matters relating directly or indirectly to the safety and efficacy of biosimilar therapies.

**10. Wolfgang E.B. Jelkmann, M.D.:** Dr. Jelkmann is Professor of Physiology and Director of the Institute of Physiology at the University of Luebeck in Germany. He has over thirty years of academic medical experience and focuses his research on the production and action of inflammatory cytokines and hemopoietic growth factors, with an emphasis on erythropoietin. Dr. Jelkmann has written over 120 original publications, over fifty book chapters and reviews, and edited three books regarding the pathophysiology, pharmacology, molecular biology and clinical use of erythropoietin. He is on the editorial board of six journals.

**11. Martin K. Kuhlmann, M.D.:** Dr. Kuhlmann is an Associate Professor of Medicine and Nephrology and Director of Internal Medicine - Nephrology at Vivantes Clinical Center-Friedrichshain in Berlin. He has been a professor of nephrology for fifteen years, with

research focusing on various issues related to hemodialysis, peritoneal dialysis, and cytoprotection from ischemic/toxic renal injury. Dr. Kuhlmann is a reviewer for fourteen different scientific journals. He has written thirty peer-reviewed publications, over forty review articles, and has been an invited presenter at over 100 international conferences and symposia.

**12. Simon D. Roger, M.D.:** Dr. Roger is a renal physician and Director of Nephrology at Gosford Hospital in Australia and a Clinical Associate Professor in the Department of Medicine and Health Sciences at Newcastle University. He has written over forty publications and a book chapter. Dr. Roger's research focuses on the management of anemia/chronic kidney disease, erythropoietin use and renal failure, and biosimilars.

**13. Ashfar I. Mikhail, M.D.:** Dr. Mikhail is a renal physician at Morriston Hospital and Senior Clinical Tutor at Swansea University in Wales. Dr. Mikhail's main areas of research include the impact of introducing biosimilar epoetins on the quality of anemia management in hemodialysis patients and the role of cytokines in modulating the response to erythropoietin therapy. He has published fourteen articles in peer-reviewed journals and two book chapters.

**14. Nicole Casadevall, M.D.:** Dr. Casadevall is Professor of Hematology at Saint Antoine Hospital in Paris. Her areas of research have centered on hemodialysis with special emphasis on erythropoiesis, erythropoietin, and myeloproliferative and myelodysplastic syndromes. She has served a member of the Medical Committee for the French Health Products Safety Agency (AFSSAPS) and as Scientific President of the French Society of Hematology.

Agennix sought out these experts solely for the purpose of obtaining an independent evaluation of the safety of rhLF for use in food. In doing so, Agennix sought a broad range of perspectives and experience including: (1) topical experts from research and academia (experts who are leaders in their respective fields and who are familiar with state-of-the art in these fields); (2) seasoned medical professionals in academia (physicians from teaching hospitals and/or medical professors); (3) practicing medical doctors (providing a perspective from frontline clinicians); and (4) experts in proteins, in general, and recombinant human lactoferrin, in particular. The mix was selected to provide both technical and practical depth. Complete CVs of these experts are already on file with CFSAN.

Although the opinions of just a few of these experts would be compelling, the opinions of this broad array of experts concurring in their scientific assessments unambiguously demonstrates a "severe conflict" that precludes GRAS status.

#### **IV. These Expert Opinions Create a “Severe Disagreement” with those of Ventria’s Experts on the Key Issues Affecting GRAS Evaluation.**

The opinions of 14 prominent experts submitted by Agennix quite clearly demonstrate there is a “severe disagreement” among experts regarding whether the use of rhLF from rice in oral rehydration solutions and pediatric medical foods is safe. These experts have raised legitimate concerns regarding important, unanswered safety questions as well as regarding the safety of long-term use of rhLF in food. Thus, given that these experts have expressed an opinion diametrically opposed to that offered by Ventria’s experts, a consensus definitely does *not* exist in the medical and scientific communities.

The expert opinions provided by Agennix raise concerns in a number of areas, particularly concerning: (1) risks specifically associated with the glycosylation of rhLF from rice; (2) risks of immunogenicity and allergenicity with rhLF from rice; and (3) risks associated with feeding rice-based rhLF to young children, including infants. <sup>21/</sup> These 14 prominent scientific and medical experts have all endorsed the entire Supplemental Scientific Assessment submitted to FDA on June 3, 2008. The summary below highlights particular expertise that certain experts bring to each of the major issues presented.

Fundamental to the concerns raised by these experts is the genuine opinion and belief that the safety of this compound cannot be established in the absence of appropriately powered long-term human clinical studies. Of particular concern was the need to determine (again through appropriately powered long-term human clinical studies) rhLF’s safety in uniquely vulnerable patient populations, including children and immunocompromised subjects such as those with autoimmune disease. Moreover, the opinions of these experts, many of whom have been evaluating this particular issue since 2005, have not wavered during the intervening 3 years, despite attempts by Ventria to reposition its GRAS filing.

##### **1. Risks specifically associated with the glycosylation of rhLF from rice.**

Our experts strongly disagree with Ventria’s experts on whether the safety profiles of rice-derived lactoferrin and native human lactoferrin are equivalent and whether the structural differences and major changes in glycosylation patterns can pose significant, long-term health risks. We have consulted some of the most prominent leaders in the field of glycobiology (Dr. Cummings, Dr. Pierce, and Dr. Schellekens) who concluded that the data presented in Ventria’s GRAS notice did not substantiate the safety of rice-produced rhLF. Rather, comprehensive studies characterizing the long-term safety risks related to exposure to foreign rice glycans are necessary before any consensus on its safety can be reached. The glycosylation issue is of particular concern, according to these experts, because Ventria’s rhLF consists of allergenic plant glycans attached to a human protein sequence. As these experts have explained in submissions

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<sup>21/</sup> These experts have also expressed concern about the absence of adequate safety studies conducted with rhLF from rice; risks of rice-based rhLF exacerbating autoimmune disease; and other risks associated with extended dosing with any rhLF, including the risk of toxicity in individuals with iron overload.



to CFSAN, evaluation of the safety of plant glycans and of human lactoferrin separately does not replace the need to evaluate the safety of rhLF that combines plant glycosylation with the human protein sequence. Rather, these experts believe that the novel structure of rice glycosylated human lactoferrin may create new risks relating to the recombinant protein's processing and recognition by the human immune system that can only be adequately assessed by long-term human clinical studies with the rice-derived recombinant protein.

Dr. Cummings is one of the preeminent scholars on glycosylation and the resulting effect on the function of and safety of therapeutic proteins. As noted above, he holds the prestigious position as the William Patterson Timmie Professor at the Emory University School of Medicine, where he also chairs the Department of Biochemistry. He founded and directed two major centers for glycobiology at leading universities. He has published over 170 peer-reviewed articles and is co-editor of the first textbook on Glycobiology. He is also a former President of the Society of Glycomics. In short, any "who's who" in the field of glycobiology would start with Dr. Cummings.

Dr. Pierce is also a prominent expert on glycobiology and carbohydrates. He has spent 25 years in academia and is currently a Professor of Biochemistry and Molecular Biology at the University of Georgia and is Director of the University's Cancer Center. He has published over 65 peer-reviewed articles, is the editor of the *Handbook of Glycomics* and is a reviewer for several leading scientific journals, including *Nature* and *Glycobiology*.

Dr. Schellekens is a physician and a professor of pharmaceutical sciences at Utrecht University in the Netherlands. He has extensive experience on the effect of glycosylation on the immunogenicity of proteins. He has published more than 200 peer-reviewed journal articles and is editor-in-chief of *Biotherapy*. He serves as an expert to the European Medicines Agency and is chairman of the Dutch Society of Microbiology's Committee for Biological Safety.

In the individual and collective opinions of these experts, there is no justification for Ventria's experts to ignore evidence that foreign glycoforms may have an effect on the safety of rhLF from rice. Further, our experts disagree with Ventria's experts' basic assertions that carbohydrates are not generally considered allergens and have poor biological activity. Moreover, according to our experts, risks related to plant-derived glycans including IgE-mediated responses may even be amplified by the administration of rice-based lactoferrin which could serve as a vector to deliver cross-reactive plant glycans directly to immune cells in the gut. Our experts also believe there is a further increase in immunogenicity and allergenicity risk in the context of infantile or childhood gastroenteritis, where there is an increase in gut permeability.

These unresolved safety issues present an "ongoing scientific discussion or controversy about safety concerns" as stated in the Agency's 1997 Proposed Rule, that should clearly stand in the way of establishing the safety of an intended use. The impeccable credentials of our glycosylation experts should solidify the validity of their opinions and preclude a finding of scientific consensus, as established by the *Mycocert* court. In that case, it was "inconceivable" that a substance could be GRAS given the "learned non-recognition" of several chairmen of

leading specialty medical departments. <sup>22/</sup> Here, too, we have a severe disagreement among prominent experts and a sharp difference of opinion on the key issue of the potential consequences of the glycosylation of rice-derived rhLF. Failure of these learned experts to recognize Ventria's rhLF as GRAS is demonstrative of a "severe disagreement" in the scientific community.

## **2. Risks of immunogenicity and allergenicity with rhLF from rice.**

Drs. van Die, Kromminga, and Schellekens are well-known and esteemed experts in the field of immunology, and Drs. Weinberg and van de Weert are notable researchers who have addressed protein immunogenicity in their published work. These experts all strongly disagree that Ventria has provided sufficient human data to resolve the safety concerns of immunogenicity, induction of anti-lactoferrin antibodies and exacerbation of autoimmune diseases that are associated with anti-lactoferrin antibodies. Indeed, these experts believe that Ventria and its experts may be basing their conclusions on a dated understanding of the mechanism and activity of human lactoferrin. Our experts have evaluated several published, peer-reviewed studies conducted by Agennix which have further strengthened their conclusion that long-term human studies are needed to accurately understand the actual safety profile of rhLF.

Dr. van Die is Head of the Glycoimmunology Group in the Department of Molecular Cell Biology & Immunology at Vrije University Medical Center in Amsterdam. She has been a professor for over 15 years and has written over 100 publications in the areas of glycobiology and immunology. She is a regular reviewer for major scientific journals and is a grant reviewer for the Netherlands Organization for Scientific Research. She is a former board member and current Secretary of the Dutch Society of Glycobiology.

Dr. Kromminga is Director of Immunology at the Institute of Immunology, Clinical Pathology, and Molecular Medicine in Hamburg, Germany, where he focuses on resolving important immunogenicity issues. He is an international leader in the field and has written over 25 publications and presented over 40 lectures at major symposia around the world.

Dr. Schellekens' extensive scientific and medical expertise is summarized in the previous section. Dr. Weinberg has researched lactoferrin for decades and has noted immunogenicity and other risks from lactoferrin administration in scientific publications. Dr. van de Weert's research and publications on the development of protein-based drugs include relevant concerns relating to immunogenicity.

Our experts strongly disagree with Ventria's experts' assertion that possible allergenic properties of rhLF cannot be the basis to deny a GRAS petition. Known allergenic/immunogenic properties are a significant safety concern and should be questioned when determining if a substance is GRAS. Our experts have provided the equivalent of the "sharply divided

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<sup>22/</sup> *United States v. An Article of Drug . . . "Mykocert"*, 345 F. Supp. 571, 575 (N.D. Ill. 1972).

testimony” from the *X-Otag* case on the issue of whether exogenous lactoferrin can cause allergenic responses in humans. <sup>23/</sup> According to our experts, long-term studies are the only credible way to identify and quantify health risks associated with immunogenicity and allergenicity. Our experts fervently believe that the conclusions reached in Ventria’s GRAS Notice are not supportable. Thus, an ongoing scientific controversy clearly exists on these issues, and the experts from Ventria and Agennix maintain an unresolved and severe conflict of opinion on these subjects.

### **3. Risks to young children, including infants.**

Ventria specifically proposes to use its rhLF in pediatric medical foods. As detailed in our June 2008 submission, our experts opined that the trial conducted by Ventria in South America in a relatively small number of children receiving very short term administration did not establish the safety of pediatric use of rice-derived rhLF, and, in fact, raised more safety questions than it answered.

Dr. Sherman is a highly respected pediatrician and academic with extensive research experience with lactoferrin and with gut infections in neonates. He is a Professor of Pediatrics at Southern Illinois University of Medicine and Professor Emeritus at the University of California, Davis. He has practiced in the field for over 30 years and has a specialty in neonatology. He has published over 80 peer-reviewed articles and has written 19 book chapters. Importantly, he is a true expert on lactoferrin and on gut infections in neonates, having conducted NIH-funded research in both areas and having written and presented extensively on the subject. It is particularly significant that Dr. Sherman, who has published research specifically on the beneficial effect that lactoferrin has in neonatal animal models, still believes strongly that it would not be appropriate to consider rhLF as GRAS without evidence from long-term clinical studies.

Dr. Sherman is joined by a host of other practicing physicians we consulted, including Dr. Sidney Grossberg (Medical College of Wisconsin), Wolfgang E. B. Jelkmann (University of Leubeck in Germany), Martin Kuhlmann (Director of Internal Medicine-Nephrology at Vivantes clinical Center-Friedrichshain in Berlin), Simon Roger (Newcastle University), Ashfar Mikhail (Swansea University in Wales) and Nicole Casadevall (Saint Antoine Hospital in Paris, France).

These experts strongly disagree with Ventria’s experts’ view that the results of the pediatric clinical trial with rice-based rhLF conducted in South America support a conclusion that Ventria’s rice-based rhLF is safe for its intended use. In particular, these experts believe that Ventria’s trial in South America was not designed to address the serious safety concerns they had identified. The experts cited the fact that the children received only a single cycle of only a few days of treatment, that the number of children receiving treatment with Ventria’s rhLF was small, and that the children did not receive adequate follow-up. Moreover, according to these experts,

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<sup>23/</sup> *United States v. An Article of Drug . . . X-Otag Plus Tablets*, 441 F. Supp. 105, 113-114 (D. Colo. 1977).

published reports of allergic reactions in the trial – even though the trial involved administration of Ventria’s rhLF to only a small number of children and for only a few days of treatment – only adds to the safety concerns. The possibility of acute allergic reactions was raised previously by many of these experts in the initial Scientific Assessment we submitted to CFSAN dated November 9, 2005. It was also concerning to these experts that insufficient follow-up monitoring was conducted to determine whether other delayed reactions or allergic sensitization may have occurred.

These experts had a number of other concerns, which were articulated in the Supplemental Scientific Assessment dated June 3, 2008, about the way the trial was conducted (including among other things, informed consent issues, and the use of a “control group” that received in about half the cases an ORS that is well known to be inferior to the ORS base received by all the infants in the rhLF/rhLZ “treated group”). They were also concerned that the occurrence of allergic reactions, and the higher frequency of bacterial pathogen isolation in the stool of children receiving the rhLF/rhLZ-ORS, do not appear to have been disclosed by Ventria to CFSAN when they would clearly be relevant to Ventria’s GRAS petition.

Furthermore, even if there had not been serious safety concerns raised by the South American trial, these experts strongly believe that long-term human studies are necessary to assess the risks of immunogenicity. Some of the immunogenicity risks include:

- the risk of immunogenicity and the breaking of B-cell tolerance, which may take over a year to manifest;
- the risk of inducing anti-lactoferrin antibodies, which could both cross-neutralize endogenous lactoferrin with negative biological effects and neutralize the efficacy of exogenous lactoferrin, which could compromise future treatments; and
- the risk of exacerbating autoimmune diseases that are associated with anti-lactoferrin antibodies.

This impressive list of medical experts all agree that the safety concerns related to glycosylation and immunogenicity/allergenicity are magnified when targeting vulnerable pediatric populations. These experts believe that autoimmune diseases and other immunogenicity concerns may be a greater threat to infants and children with developing immune systems, particularly those with gastrointestinal infections where gut permeability can be further increased. These qualified experts do not believe that administration of compounds containing Ventria’s rhLF is considered safe for neonates and children.

Thus, like in the *Premo Pharmaceutical Laboratories* case cited above, there is a “sharp difference of opinion” between experts regarding the methods and results of the available study. [24/](#) A severe disagreement exists concerning whether rice-derived rhLF is safe for use in

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[24/](#) *Premo Pharma. Labs.*, 629 F.2d at 804.

Laura M. Tarantino, Ph.D.  
August 14, 2008  
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children, and much more robust clinical data is needed to establish any type of informed consensus on the issue.

In summary, the clear lack of scientific consensus that rhLF is GRAS is evidenced by the compelling opinions of these 14 prominent scientific and medical experts, raising legitimate safety questions about the safety of feeding rice-based rhLF to young children and infants. That so many, and such highly qualified, experts have repeatedly expressed serious concern about the proposed uses of rhLF demonstrates a “severe conflict” of expert opinion and precludes GRAS status for rhLF from rice.

### **III. Conclusion**

Based on Ventria’s failure to demonstrate that there is a scientific consensus among qualified experts that rhLF from transgenic rice is GRAS, we are asking CFSAN to determine, as a matter of law, that rhLF from transgenic rice is *not* GRAS for use in oral rehydration solutions and pediatric medical foods.

Agennix appreciates CFSAN’s consideration of this important information as Ventria’s GRAS notification for rhLF from rice is considered. Please do not hesitate to contact us if there are any questions or if additional information would be useful.

Sincerely,



Rick Barsky  
Chief Executive Officer

cc: Jeremiah Fasano (HFS-255)  
Consumer Safety Officer  
Division of Biotechnology and GRAS Notice Review

Stephen F. Sundlof, D.V.M., Ph.D. (HFS-001)  
Director, CFSAN

Michael M. Landa (HFS-001)  
Deputy Director for Regulatory Affairs, CFSAN

Gerald F. Masoudi (GCF-1)  
FDA Chief Counsel

**Fasano, Jeremiah**

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**From:** Levitt, Joseph A. [JALevitt@HHLAW.com]  
**Sent:** Friday, August 15, 2008 12:36 PM  
**To:** Fasano, Jeremiah  
**Cc:** Tarantino, Laura M  
**Subject:** Agennix "Summary Judgment" Letter on GRN 235  
**Attachments:** Agennix Summary Judgment letter aug 14.pdf

Dear Jeremiah--

Attached is an electronic copy of a letter being delivered to your office today. The letter requests that FDA reach the legal conclusion that recombinant human lactoferrin (rhLF) from transgenic rice, GRN No. 000235 (resubmission of GRN No. 000162) submitted by Ventria Bioscience, is *not* Generally Recognized as Safe (GRAS) based on a "severe disagreement" among qualified experts.

Agennix has approached this as being tantamount to a legal motion for summary judgment because there are no material facts in dispute (i.e., it is a matter of record that there are two groups of experts expressing diametrically opposing views) and so the Agency may rightfully decide this issue as a matter of law. Furthermore, this letter is based solely on the third prong of the GRAS test—namely, that there be a consensus among qualified experts that the food ingredient is safe. Agennix is asking FDA to determine, as a matter of law, that rhLF from transgenic rice is *not* GRAS for use in oral rehydration solutions and pediatric medical foods solely because Ventria has failed to demonstrate that there is a scientific consensus among qualified experts that the substance is safe.

The letter also notes that, if FDA were to take this approach, then it would obviate the need to address the rhLF issue in the context of Section 912 of the FDAAA.

Please let me know if you have any questions. FYI, I am sending similar notes to others named as cc's on the letter.

Best regards,

Joe

JOSEPH LEVITT, PARTNER  
HOGAN & HARTSON LLP  
Columbia Square, 555 Thirteenth Street, NW, Washington, DC 20004  
direct +1.202.637.5759 | tel +1.202.637.5600 | fax +1.202.637.5910  
[jlevitt@hhlaw.com](mailto:jlevitt@hhlaw.com) | <http://www.hhlaw.com>

"EMF <HHLAW.COM>" made the following annotations.

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8/20/2008

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=====

**Fasano, Jeremiah**

---

**From:** Fasano, Jeremiah  
**Sent:** Wednesday, August 20, 2008 11:27 AM  
**To:** 'Levitt, Joseph A.'  
**Subject:** RE: Agennix "Summary Judgment" Letter on GRN 235

Mr. Levitt-

I just wanted to acknowledge receipt of both the electronic version of your letter and the hard copy, which has now reached me. We will add the letter to our files and consider its contents.

Regards-

-Jeremiah Fasano

---

Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
DBGNR/OFAS/CFSAN/FDA

[jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov)

Phone: 301-436-1173

Fax: 301-436-2964

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5100 Paint Branch Parkway  
College Park, MD 20740

---

**From:** Levitt, Joseph A. [mailto:JALevitt@HHLAW.com]  
**Sent:** Friday, August 15, 2008 12:36 PM  
**To:** Fasano, Jeremiah  
**Cc:** Tarantino, Laura M  
**Subject:** Agennix "Summary Judgment" Letter on GRN 235

Dear Jeremiah--

Attached is an electronic copy of a letter being delivered to your office today. The letter requests that FDA reach the legal conclusion that recombinant human lactoferrin (rhLF) from transgenic rice, GRN No. 000235 (resubmission of GRN No. 000162) submitted by Ventria Bioscience, is *not* Generally Recognized as Safe (GRAS) based on a "severe disagreement" among qualified experts.

Agennix has approached this as being tantamount to a legal motion for summary judgment because there are no material facts in dispute (i.e., it is a matter of record that there are two groups of experts expressing diametrically opposing views) and so the Agency may rightfully decide this issue as a matter of law. Furthermore, this letter is based solely on the third prong of the GRAS test—namely, that there be a consensus among qualified experts that the food ingredient is safe. Agennix is asking FDA to determine, as a matter of law, that rhLF from transgenic rice is *not* GRAS for use in oral rehydration solutions and pediatric medical foods solely because Ventria has failed to demonstrate that there is a scientific consensus among qualified experts that the substance is safe.

9/16/2008



The letter also notes that, if FDA were to take this approach, then it would obviate the need to address the rhLF issue in the context of Section 912 of the FDAAA.

Please let me know if you have any questions. FYI, I am sending similar notes to others named as cc's on the letter.

Best regards,

Joe

JOSEPH LEVITT, PARTNER  
HOGAN & HARTSON LLP  
Columbia Square, 555 Thirteenth Street, NW, Washington, DC 20004  
direct +1.202.637.5759 | tel +1.202.637.5600 | fax +1.202.637.5910  
[jlevitt@hhlaw.com](mailto:jlevitt@hhlaw.com) | <http://www.hhlaw.com>

"EMF <HHLAW.COM>" made the following annotations.

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=====



We discussed several points relevant to the question we had identified and the points Mr. Deeter had raised, including the difference between oral and non-oral exposures and the significance of hLF and hLZ exposure via human milk. We acknowledged that all known adverse alloimmunization events stemming from human protein use were the result of non-oral therapeutic use. However, we also noted that:

- In the context of ingredients added to food, Ventria's intended uses of human proteins are novel,
- the evidence that Ventria and its panel relied on to establish safety was indirect and limited by confounding factors (such as the presence of many other immunomodulatory components of human milk which might prevent alloimmunization or alter its consequences), and
- we were unable to find sufficient data or analyses in the notices or scientific literature that address the potential for adverse alloimmunization effects by novel human protein food ingredients and demonstrate their safety.

We noted that the potential for alloimmunization-based autoimmune effects, although poorly understood, appears to be related to alterations that might disrupt normal immune tolerance to self proteins. On that basis, we suggested that it should be possible to eliminate all significant concerns with respect to Ventria's hLZ, if it could be shown to be biochemically identical to native hLZ at the point of consumption. Ventria's data were consistent with this possibility for hLZ (though not for hLF). We stated that we were willing to schedule a meeting soon to discuss this possibility further if Ventria was interested. We also noted that we had questions about the intended use level of hLZ in infant formula relative to levels found in human milk, though we did not consider this a key question. We encouraged Mr. Deeter to discuss the questions we had identified with Ventria's panel.

Mr. Deeter stated that he was disappointed with the results of the guidance that Ventria had been given by CFSAN regarding its products, and that he questioned whether CFSAN was inappropriately applying drug standards to a food ingredient. He also stated that he was not aware of any expert in immunology or food safety who would disagree with the members of Ventria's GRAS panel.

We concluded the discussion conveying our regret for the length of time taken to evaluate Ventria's various human protein notices, noting that they had presented multiple novel and challenging issues to CFSAN. We offered to provide a written outline of our comments. Mr. Deeter declined our offer, and said that he would communicate with CFSAN again once Ventria had evaluated this new information. Mr. McConagha offered to relay the contents of the discussion to interested parties in Congress with whom Ventria had been in contact. Mr. Deeter agreed that this was acceptable.

Jeremiah Fasano

R/D:HFS-255:JMFasano:10/03/2008  
Comments/Init:HFS-255:JGGlew:10/06/2008  
Comments/Init:HFS-255:AMattia:10/07/2008  
Comments/Init:HFS-255:PMGaynor:10/09/2008  
Sent:BMcConagha:10/15/2008  
Init:HFS-23:EFlamm:10/15/2008  
F/T:HFS-255:JMFasano:03/04/2010

(b) (4)

(b) (4)

(b) (4)

February 24, 2009

**CONFIDENTIAL**

**VIA UPS AND ELECTRONIC MAIL**

Ms. Laura M. Tarantino  
Director, Office of Food Additives  
U.S. Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Rm. 3044, HFS-200  
5100 Paint Branch Pkwy  
College Park, MD 20740  
[laura.tarantino@fda.hhs.gov](mailto:laura.tarantino@fda.hhs.gov)

**Re: Meeting Request for Pending GRAS Notifications (GRN 235 and GRN 191) for Ventria Bioscience**

Dear Ms. Tarantino:

I wanted to thank you for taking the time to speak with me regarding the GRAS Notifications, referenced above, submitted by Ventria Bioscience ("Ventria"). On behalf of my client, I am requesting a meeting to discuss the status of the pending GRAS Notifications and any issues that may prevent these notifications from receiving approval. We ask that this meeting be conducted any day (at any time) during the weeks of March 2 or 9, 2009.

Thank you in advance for your consideration of this meeting request submitted on behalf of Ventria. Should you require additional information, prior to the scheduling of this meeting, please feel free to contact me at (b) (4).

Respectfully submitted,

(b) (4)

Counsel to Ventria Bioscience

cc: Scott E. Deeter  
President and CEO, Ventria Bioscience

Pennsylvania :: New York :: Washington, DC :: Virginia :: Florida :: New Jersey :: Delaware :: Ohio :: California

## Fasano, Jeremiah

---

**From:** Fasano, Jeremiah  
**Sent:** Monday, March 02, 2009 11:25 AM  
**To:** 'edward.allera@bipc.com'  
**Subject:** Re: Meeting request on behalf of Ventria

Mr. Allera-

I'm Jeremiah Fasano, the Consumer Safety Officer assigned to arrange the meeting you've requested in your February 24th letter to Laura Tarantino. I'm still checking availability of a few parties who might attend, but I wanted to let you know that I'm working on it and to give you my direct contact information. The week of the 9th looks pretty promising, and I will likely be back in touch in the next day or so to lock in a date. Are there any days or times of day during that week that would definitely *not* work for you?

My understanding (based on a few words from Dr. Tarantino) is that you would like to come in and discuss with us the history of Ventria's submissions to date and their current status. Is this basically correct? Please let me know at your convenience if that's so, or if I've missed something getting it second-hand. Also, will anyone else be with you? (I need to provide names to the lobby guard).

I'll be in touch very soon.

Regards-

-Jeremiah Fasano

---

Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
Division of Biotechnology and GRAS Notice Review  
Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
Phone: 301-436-1173  
Fax: 301-436-2964  
Email: [jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov)  
Mailing Address:  
HFS-255  
5100 Paint Branch Parkway  
College Park, MD 20740

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# VENTRIA BIOSCIENCE

March 6, 2009

**CONFIDENTIAL**

**VIA FACSIMILE (301) 436-2964**

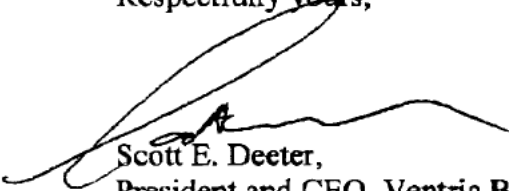
Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
U.S. Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Rm. 2051, HFS-255  
5100 Paint Branch Parkway  
College Park, MD 20740  
[jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov)

Re: **Legal Representation by (b) (4)**

Dear Dr. Fasano,

I am writing this letter to inform you that (b) (4) is serving as our legal representation with regard to any matter relating to our GRAS Notifications, including but not limited to pending GRAS notifications GRN 235 and GRN 191.

Respectfully yours,

  
Scott E. Deeter,  
President and CEO, Ventria Bioscience

cc: (b) (4)

From: [Fasano, Jeremiah](#)  
To: ["Allera, Edward John"; "Scott Deeter";](#)  
cc: [Gaynor, Paulette M;](#)  
Subject: Confidentiality of recent correspondence associated with GRN 191/235  
Date: Wednesday, June 24, 2009 7:59:04 PM  
Attachments: [2009-02-24 - Letter from Ventria to OFAS requesting meeting and notifying of new counsel.pdf](#)  
[2009-03-06 - Letter from Ventria confirming new counsel.pdf](#)

---

Mr. Allera and Mr. Deeter-

We recently received a Freedom of Information Act request that would encompass two recent letters our office received from you (attached), both marked 'Confidential.' Before preparing our response to this FOIA request, we wanted to consult with you, in accordance with our regulations governing such requests, about the aspects and content of these letters that you would consider confidential.

Dr. Paulette Gaynor and I are each managing one of the relevant GRAS notices and will both be away from our desks with different schedules for the next several weeks, so please direct your response, at your convenience, to both of us.

Sincerely-

-Jeremiah Fasano

---

Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
Division of Biotechnology and GRAS Notice Review  
Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
Phone: 301-436-1173  
Fax: 301-436-2964  
Email: [jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov)

Mailing Address:  
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**From:** [Gaynor, Paulette M](#)  
**To:** ["Scott Deeter"; Allera, Edward John;](#)  
**cc:** [Fasano, Jeremiah;](#)  
**Subject:** RE: Confidentiality of recent correspondence associated with GRN 191/235  
**Date:** Thursday, June 25, 2009 1:56:09 PM

---

Dear Mr. Deeter,

Thank you for getting back to us about the confidential information in these two letters.

Sincerely,

Paulette Gaynor, Ph.D.

---

**From:** Scott Deeter [mailto:sdeeter@ventria.com]  
**Sent:** Thursday, June 25, 2009 12:07 AM  
**To:** Fasano, Jeremiah; Allera, Edward John  
**Cc:** Gaynor, Paulette M  
**Subject:** RE: Confidentiality of recent correspondence associated with GRN 191/235

Dear Jeremiah:

It is good to hear from you. The contents of the letter that are confidential are the firm name, contact name, signature and contact information referencing our counsel (Buchanon, Ingersoll & Rooney and Ed Allera). Otherwise, the rest of the information is not confidential.

Sincerely,

Scott Deeter  
President & CEO  
Ventria Bioscience

---

**From:** Fasano, Jeremiah [mailto:Jeremiah.Fasano@fda.hhs.gov]  
**Sent:** Wednesday, June 24, 2009 5:59 PM  
**To:** Allera, Edward John; Scott Deeter  
**Cc:** Gaynor, Paulette M  
**Subject:** Confidentiality of recent correspondence associated with GRN 191/235

Mr. Allera and Mr. Deeter-

We recently received a Freedom of Information Act request that would encompass two recent letters our office received from you (attached), both marked 'Confidential.' Before preparing our response to this FOIA request, we wanted to consult with you, in accordance with our regulations governing such requests, about the aspects and content of these letters that you would consider confidential.

Dr. Paulette Gaynor and I are each managing one of the relevant GRAS notices and will both be away from our desks with different schedules for the next several weeks, so please direct your response, at your convenience, to both of us.

Sincerely-

-Jeremiah Fasano

<<2009-02-24 - Letter from Ventria to OFAS requesting meeting and notifying of new counsel.pdf>> <<2009-03-06 - Letter from Ventria confirming new counsel.pdf>>

---

Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
Division of Biotechnology and GRAS Notice Review  
Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
Phone: 301-436-1173  
Fax: 301-436-2964  
Email: [jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov)

Mailing Address:

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College Park, MD 20740

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**From:** [Scott Deeter](#)  
**To:** [Fasano, Jeremiah](#); [Allera, Edward John](#);  
**cc:** [Gaynor, Paulette M](#);  
**Subject:** RE: Confidentiality of recent correspondence associated with GRN 191/235  
**Date:** Thursday, June 25, 2009 12:07:25 AM

---

Dear Jeremiah:

It is good to hear from you. The contents of the letter that are confidential are the firm name, contact name, signature and contact information referencing our counsel (Buchanon, Ingersoll & Rooney and Ed Allera). Otherwise, the rest of the information is not confidential.

Sincerely,

Scott Deeter  
President & CEO  
Ventria Bioscience

---

**From:** Fasano, Jeremiah [mailto:Jeremiah.Fasano@fda.hhs.gov]  
**Sent:** Wednesday, June 24, 2009 5:59 PM  
**To:** Allera, Edward John; Scott Deeter  
**Cc:** Gaynor, Paulette M  
**Subject:** Confidentiality of recent correspondence associated with GRN 191/235

Mr. Allera and Mr. Deeter-

We recently received a Freedom of Information Act request that would encompass two recent letters our office received from you (attached), both marked 'Confidential.' Before preparing our response to this FOIA request, we wanted to consult with you, in accordance with our regulations governing such requests, about the aspects and content of these letters that you would consider confidential.

Dr. Paulette Gaynor and I are each managing one of the relevant GRAS notices and will both be away from our desks with different schedules for the next several weeks, so please direct your response, at your convenience, to both of us.

Sincerely-

-Jeremiah Fasano

<<2009-02-24 - Letter from Ventria to OFAS requesting meeting and notifying of

new counsel.pdf>> <<2009-03-06 - Letter from Ventria confirming new counsel.  
pdf>>

---

Jeremiah Fasano, Ph.D.  
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**From:** [Fasano, Jeremiah](#)  
**To:** ["Scott Deeter";](#)  
**Subject:** RE: Counsel to FDA - Ventria GRAS Submissions  
**Date:** Monday, November 23, 2009 5:04:52 PM

---

Mr. Deeter-

Thank you for keeping us up to date. I'll pass the information along to the appropriate parties as necessary.

Regards-

-Jeremiah Fasano

---

Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
DBGNR/OFAS/CFSAN/FDA

[jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov)

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Fax: 301-436-2964

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---

**From:** Scott Deeter [mailto:sdeeter@ventria.com]  
**Sent:** Friday, November 20, 2009 1:45 PM  
**To:** Fasano, Jeremiah  
**Subject:** FW: Counsel to FDA - Ventria GRAS Submissions

Dear Jeremiah:  
FYI. Please inform others at FDA, if necessary.

---

**From:** Scott Deeter  
**Sent:** Friday, November 20, 2009 11:43 AM  
**To:** Allera, Edward John  
**Cc:** Ann Swan; Randy Semadeni  
**Subject:** Counsel to FDA - Ventria GRAS Submissions

Dear Ed:  
Thank you for your advice related to our GRAS submissions. By way of this email, I wanted to inform you that we no longer require Buchanan, Ingersoll & Rooney's counsel on this matter and our relationship is no longer active. Please inform your team and if required, inform any contacts you made at FDA on our behalf. I enjoyed working with you and your team.

Thanks for your help. Maybe we can work together in the future.

All the best,

**Scott Deeter**  
President & CEO  
(970) 420-9598  
[Ventria Bioscience](#)  
Pediatric Health

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**From:** [Scott Deeter](#)  
**To:** [Fasano, Jeremiah;](#)  
**cc:** [Nancy L. Buc;](#)  
**Subject:** Letter  
**Date:** Tuesday, December 15, 2009 11:28:21 AM  
**Attachments:** [Letter-FDA-Buc-BeardsleyNotice-Dec09.pdf](#)

---

Dear Jeremiah:

I hope this finds you well. We look forward to seeing you on Jan 15<sup>th</sup> to discuss the notices. Thank you for allowing us your time for this meeting. Attached, please find a formal notice of our representation by Buc & Beardsley, LLC.

Have a happy holiday!

Sincerely,

Scott E. Deeter  
President & CEO  
Ventria Bioscience  
(970) 420-9598  
[www.Ventria.com](http://www.Ventria.com)

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Ventria requested a stay of the letter until the firm and its newest counsel, retained since the March 11, 2009 meeting, could discuss the situation with OFAS staff. OFAS agreed to this request and the meeting took place on January 15, 2010.

At this meeting, OFAS discussed our previous conclusions with respect to Ventria's notices. We explained the core immunological issue that we had identified in our review, and we reiterated our view that this issue was very difficult to dismiss without evidence that it had been publicly and critically examined from a food safety perspective, which we had not been able to identify. We also stated that we did not believe it would be appropriate to conduct an examination of this type within the context of an open GRAS notice.

Ventria acknowledged that FDA had offered them multiple opportunities to respond to the points we had raised. Nevertheless, Ventria requested one final chance to provide a substantive response, explaining that the firm had not previously understood the agency's concerns clearly.

We ultimately agreed to provide them with 60 days to respond to the points we had raised, with the understanding that:

- Ventria would within the next few working days provide a letter to FDA stating that GRN 191 and GRN 235 should be automatically considered withdrawn without further action by the firm if the agency had not received a response by March 19, 2010;
- FDA considered that it would be extremely difficult to address the issue satisfactorily within the framework described; and
- if the response did not adequately address FDA's concerns, both Ventria and FDA would consider the matter closed and Ventria would either promptly withdraw or receive a 'no basis' letter.

Jeremiah Fasano

cc: GRN 235 GRN 191  
R/D:HFS-255:JMFasano:01/15/2010  
Comment/Init:HFS-200:MCheeseman:01/18/2010  
Edit/Init:HFS-255:PGaynor:01/26/2010  
Comment:HFS-255:AMattia:01/27/2010  
Edit:HFS-255:JMFasano:01/28/2010  
F/T:HFS-255:JMFasano:03/04/2010

**From:** [Nancy L. Buc](#)  
**To:** [Fasano, Jeremiah;](#)  
**cc:** ["Scott Deeter";](#)  
**Subject:** Followup to our meeting  
**Date:** Monday, January 25, 2010 8:39:59 PM

---

Dear Dr. Fasano -

Scott Deeter, Bill Rutter, and I appreciated the opportunity on behalf of my client, Ventria Biosciences, to meet with you and your colleagues to discuss issues pertaining to the two Ventria GRAS notices, GRN 235 for recombinant human lactoferrin derived from rice, and GRN 291 for recombinant human lysozyme derived from rice, both for use in pediatric medical foods and other pediatric foods such as infant formula. We found the discussion both enlightening and helpful.

At the meeting, Ventria asked to be allowed to make further submissions to the pending GRAS notices before CFSAN takes any action on them, and you agreed to that so long as the submission is made on or before March 22, 2010. Ventria also agreed that if it has not made its submission(s) by that date, it will withdraw the GRAS notice(s) for which a submission has not been made.

I will get you the above in hard copy as soon as possible, and may also want to ask some further questions and make some further suggestions about how to proceed from here. In the meantime, please accept this e-mail version.

Thank you.

Nancy L. Buc

**From:** [Fasano, Jeremiah](#)  
**To:** [Nancy L. Buc](#);  
**cc:** ["Scott Deeter"](#); [Cheeseman, Mitchell A](#);  
[Mattia, Antonia](#);  
**Subject:** RE: Followup to our meeting  
**Date:** Wednesday, January 27, 2010 3:44:18 PM

---

Ms. Buc-

We wanted to take this opportunity to clarify our understanding of the agreement we reached at our January 15th meeting. As a minor point, we understood that Ventria would provide a substantive amendment by the 19th of March, rather than the 22nd. More importantly, Ventria's GRAS notices would be considered automatically withdrawn without any further action on Ventria's part if a substantive amendment is not received by close of business on the final day of the agreed-upon timeframe. This is not clearly articulated in the email you sent to us.

We would be willing to respond to specific questions or comment on suggestions if that will be helpful to you in assembling a substantive amendment, though we would not consider such interactions to comprise a substantive amendment sufficient to preclude automatic withdrawal of the GRAS notices, or to "extend the clock" past the agreed-upon timeframe.

We would appreciate it if the formal letter you send to us is explicit about these points.

Although FDA is very interested in continuing to engage constructively with industry on issues associated with the use of human proteins as food ingredients, if the substantive amendment submitted by Ventria does not resolve the issues we discussed at our January 15th meeting, we do not intend to engage in any further iteration within the framework of these two specific GRAS notices.

Please feel free to contact me with any questions you may have.

Sincerely,

Jeremiah Fasano

---

Jeremiah Fasano, Ph.D.  
Consumer Safety Officer

DBGNR/OFAS/CFSAN/FDA

[jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov)

Phone: 301-436-1173

Fax: 301-436-2964

HFS-255

5100 Paint Branch Parkway

College Park, MD 20740

---

**From:** Nancy L. Buc [mailto:[nlb@bucbeardsley.com](mailto:nlb@bucbeardsley.com)]

**Sent:** Monday, January 25, 2010 8:35 PM

**To:** Fasano, Jeremiah

**Cc:** 'Scott Deeter'

**Subject:** Followup to our meeting

Dear Dr. Fasano -

Scott Deeter, Bill Rutter, and I appreciated the opportunity on behalf of my client, Ventria Biosciences, to meet with you and your colleagues to discuss issues pertaining to the two Ventria GRAS notices, GRN 235 for recombinant human lactoferrin derived from rice, and GRN 291 for recombinant human lysozyme derived from rice, both for use in pediatric medical foods and other pediatric foods such as infant formula. We found the discussion both enlightening and helpful.

At the meeting, Ventria asked to be allowed to make further submissions to the pending GRAS notices before CFSAN takes any action on them, and you agreed to that so long as the submission is made on or before March 22, 2010. Ventria also agreed that if it has not made its submission(s) by that date, it will withdraw the GRAS notice(s) for which a submission has not been made.

I will get you the above in hard copy as soon as possible, and may also want to ask some further questions and make some further suggestions about how to proceed from here. In the meantime, please accept this e-mail version.

Thank you.

Nancy L. Buc







I reminded Mr. Deeter that his proposal was not consistent with the agreement reached by Ventria and FDA at the January 15, 2010 meeting, which was predicated on receipt of a self-contained amendment within two months. I reiterated FDA's interest in public discussion of the issues we had raised, particularly in the scientific literature, but stated that such discussion would take significant time and thus would not meet Ventria's immediate need.

Mr. Deeter agreed to send a written withdrawal of GRN 000191 and 000235.

Jeremiah Fasano

Drafted:HFS-255:JMFasano:03/02/2010  
Edit/Init:HFS-255:CMcMahon:03/03/2010  
F/T:HFS-255:JMFasano:03/04/2010

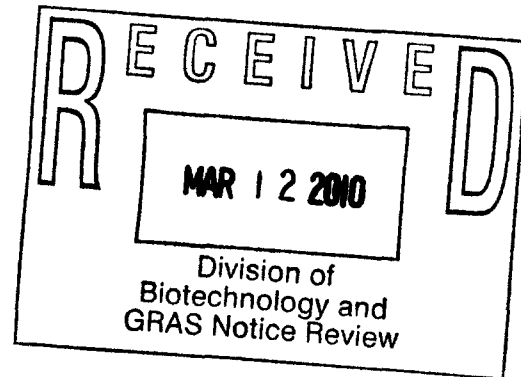
# VENTRIA BIOSCIENCE

2120 Milestone Drive, Fort Collins, CO 80525

(970) 420-9598

March 5, 2010

Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
Food & Drug Administration  
CFSAN/Food Additive Safety/DBGNR  
HFS-255  
5100 Paint Branch Parkway  
College Park, MD 20740



Dear Jeremiah:

This letter is to inform FDA/CFSAN that Ventria Bioscience requests the withdrawal of two GRAS notices, GRN 191 and GRN 235. Please, at notifier's request, discontinue the FDA/CFSAN review of these notices.

Please confirm your receipt by reply email to myself.

Sincerely,



Scott E. Deeter  
President & CEO

**From:** [Fasano, Jeremiah](#)  
**To:** ["Scott Deeter";](#)  
**Subject:** RE: Withdrawal of GRAS Notices  
**Date:** Friday, March 12, 2010 12:11:12 PM

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Mr. Deeter-

I just wanted to let you know that we have received your withdrawal letter. A more formal acknowledgement should be on its way soon.

Regards-

-Jeremiah Fasano

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Jeremiah Fasano, Ph.D.  
Consumer Safety Officer  
DBGNR/OFAS/CFSAN/FDA

[jeremiah.fasano@fda.hhs.gov](mailto:jeremiah.fasano@fda.hhs.gov)

Phone: 301-436-1173

Fax: 301-436-2964

HFS-255  
5100 Paint Branch Parkway  
College Park, MD 20740

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**From:** Scott Deeter [mailto:sdeeter@ventria.com]  
**Sent:** Saturday, March 06, 2010 4:11 PM  
**To:** Fasano, Jeremiah  
**Subject:** Withdrawal of GRAS Notices

Dear Jeremiah:

This email confirms notice is being sent to you for the withdrawal of GRN 291 and GRN 235. A formal withdrawal letter is on its way to you.

Sincerely,

Scott E. Deeter  
President & CEO  
Ventria Bioscience  
(970) 420-9598  
[www.Ventria.com](http://www.Ventria.com)

*Your Life. Our Passion.*

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