

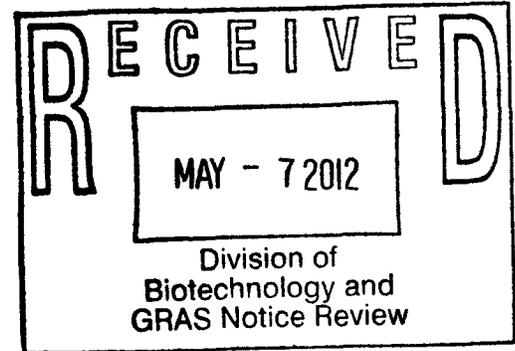
Original Submission



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May 2, 2012

Paulette Gaynor, Ph.D.  
Office of Food Additive Safety (HFS-200)  
Center for Food Safety and Applied Nutrition  
Food And Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835



Dear Dr. Gaynor:

In accordance with 21 CFR 170.36 (62 FR 18960; April 17, 1997), Sterling Technology, Inc. is hereby submitting notice of a claim that the use of two (2) substances derived from bovine colostrum, a whey protein concentrate (to be marketed as Tegrice<sup>TM</sup> or RPM Factors<sup>TM</sup>) and a low molecular weight whey protein fraction (to be marketed as Immune<sup>TM</sup>), in foods as described in the attached notice is generally recognized as safe (GRAS) based on scientific procedures and therefore exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act.

Attached please find three (3) copies of the GRAS notice, each of which includes a comprehensive summary of data supporting the safety of the ingredients, and the signed statement of an expert panel regarding the value of these data in supporting a GRAS determination.

My contact information is provided below. Please feel free to contact me<sup>1</sup> by phone or e-mail if you have any questions regarding this GRAS notice.

Sincerely,

Dilip Patel, PhD  
Director (R&D and Quality)  
E-mail: [Dilip.Patel@SterlingTechnology.com](mailto:Dilip.Patel@SterlingTechnology.com)  
Tel: 605-692-5552; Fax: 605-692-9080; Cell: 605-695-4174

<sup>1</sup> Please note that Sterling Technology has authorized Drs. David Bechtel ([David.Becht@Intertek.com](mailto:David.Becht@Intertek.com)) and Katherine Vega ([Katherine.Vega@Intertek.com](mailto:Katherine.Vega@Intertek.com)) from Intertek Cantox, located at 1011 U.S. Highway 22, Suite 200, Bridgewater, NJ 08827, to engage in discussions about any issues related to the enclosed GRAS notice. Each may be reached by e-mail (shown above), by telephone at (908) 429-9202, or by FAX at (908) 429-9260.

000002



**GRAS Notice:**

THE USE OF TWO SUBSTANCES DERIVED FROM BOVINE COLOSTRUM, A WHEY PROTEIN CONCENTRATE (TEGRICEL™) AND A LOW MOLECULAR WEIGHT WHEY PROTEIN FRACTION (IMMUNEL™), IN HUMAN FOODS IS GENERALLY RECOGNIZED AS SAFE (GRAS)

**Submitted to:**

Food and Drug Administration  
Center for Food Safety and Applied  
Nutrition  
Office of Food Additive Safety

**By:**

Sterling Technology  
133 32nd Ave.  
Brookings, SD 57006

May 2, 2012



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**GRAS EXEMPTION CLAIM**

Sterling Technology, Inc. hereby notifies the U.S. Food and Drug Administration that the use of two (2) substances derived from bovine colostrum, a whey protein concentrate (to be marketed as Tegrice<sup>TM</sup>) and a low molecular weight whey protein fraction (to be marketed as Immune<sup>TM</sup>), in foods as described herein is generally recognized as safe (GRAS) based on scientific procedures and therefore exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act.

Sterling Technology Inc. Representative

Signature (b) (6)  
 Dilip Patel, PhD  
 Director of R & D and Quality

Date May 02/2012

<p><b>NAME AND ADDRESS OF NOTIFIER</b></p> <p>Sterling Technology, Inc.          133 32nd Ave.          Brookings, SD 57006</p>	<p>Contact Name: Dilip Patel, PhD          Phone: 605-692-5552          Fax: 605-692-9080          E-mail: dilip.patel@sterlingtechnology.com</p>
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**DESCRIPTION OF THE GRAS SUBSTANCE**

Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction are derived from bovine whole colostrum whey through methods typically used in cheese-making, along with ultrafiltration to separate the whey proteins from the nonprotein constituents. Tegrice<sup>TM</sup> contains the majority of the proteins. Immune<sup>TM</sup> is a by-product of Tegrice<sup>TM</sup> production, derived from the fraction (*i.e.*, filtrate) remaining after the colostrum whey is subjected to ultrafiltration; it contains primarily nonprotein components and small amounts of low-molecular weight (<500 Daltons) whey proteins. Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction are produced through conventional GMP food industry processes to meet rigid established specifications.

**INTENDED USE**

Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction are intended to be used in foods as direct additives in accordance with the physical or technical functional effects described in 21 CFR §170.3 (o) and under the conditions of current Good Manufacturing Practice (GMP). Uses do not include meat or poultry products.



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### **CONSUMER EXPOSURE**

Tegricel™ colostrum whey protein concentrate and Immunel™ colostrum low molecular weight whey protein fraction are intended for use in foods for the general human population at levels up to 1 g/serving and 100 mg/serving, respectively.

### **BASIS FOR GRAS DETERMINATION**

To make the GRAS determination, Sterling Technology compiled information about the substances, specifications, manufacturing, proposed uses, and evidence of safety into a comprehensive dossier; and sought the opinion of qualified experts (*i.e.*, expert panel) in determining whether there is consensus among their peers that the use of these substances as described entails a reasonable certainty of no harm and is generally recognized as safe. To assess safety, Sterling Technology has relied on the available historical and scientific evidence supporting the safety of the source material, bovine colostrum, and other substances derived from mature cow's milk.

All data and information that are the basis for this GRAS determination are available for FDA's review and copying at reasonable times at Sterling Technology, Inc., 133 32nd Avenue South Brookings, SD 57006, and will be sent to FDA upon request.



***GRAS EXPERT PANEL OPINION  
STATEMENT***

**GRAS Notice:**

THE USE OF TWO SUBSTANCES DERIVED FROM BOVINE COLOSTRUM, A WHEY PROTEIN CONCENTRATE (TEGRICEL™) AND A LOW MOLECULAR WEIGHT WHEY PROTEIN FRACTION (IMMUNEL™), IN HUMAN FOODS IS GENERALLY RECOGNIZED AS SAFE (GRAS)

May 2, 2012

## A NOTE REGARDING DISCONTINUITY IN SOME ELEMENTS OF THE PRESENT GRAS NOTICE

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Due to circumstances beyond Sterling Technology's control, there are some minor differences between the Expert Panel opinion statement and corresponding nomenclature/definition statements in the present GRAS notice. Specifically, the term *Bovine Colostral Whey Protein/Peptide Concentrates (BCWPC)* used in the Expert Opinion document has been changed to *Colostral Whey Protein Concentrate (Tegricel™)* and *Colostral Low Molecular Weight Whey Protein Fraction (Immune!™)*, which more appropriately and accurately describes the GRAS substance(s). This clarification was warranted to allay any perceived misconception regarding the distinctiveness and uniqueness of the two different substances derived from two unique/distinct fractions of bovine colostrum.

It was the intent of Sterling Technology to notify U.S. FDA in 2011 of its determination, with assistance from a panel of experts, that use of the two substances (for simplicity, referred to as Tegricel™ and Immune!™ hereafter) in food for humans is GRAS. To assist with the GRAS affirmation and notification process, Sterling Technology sought the assistance of Lee B. Dexter of Lee B. Dexter and Associates (Austin, TX). This consultant facilitated expert panel review of all the information supporting a GRAS determination. After a successful outcome, an expert panel opinion statement (Expert Opinion, dated June 1, 2010) was prepared and circulated among panel members for signature during January, 2011. GRAS affirmation was successfully completed but, unfortunately, Lee B. Dexter died soon after. Sterling Technology wanted to pursue notification process beyond self affirmation, for which they sought the assistance of Intertek Cantox.

A complete version of the GRAS dossier reviewed by the expert panel could not be located. Therefore, Intertek Cantox attempted to piece together a comprehensive document based on various individual documents that had been provided to Sterling Technology. Because this effort was unsuccessful, Intertek Cantox prepared an entirely new document that included as much of the existing information as possible. This new document, entitled *Summary of Data Supporting a (GRAS) Determination*, is what is included in the present GRAS notice. There are some minor differences between this document and the information that appears in the signed Expert Opinion document [e.g., *Bovine Colostral Whey Protein/Peptide Concentrates (BCWPC)* vs. *Colostral Whey Protein Concentrate (Tegricel™)* and *Colostral Low Molecular Weight Whey Protein Fraction (Immune!™)*] as a result of our attempt to more accurately and appropriately characterize the nature of the GRAS substance(s). These changes were considered minor, *i.e.*, having no significant impact on the overall conclusion that the use of these ingredients in human foods is GRAS, and a new review by the expert panel of the same substances (*Tegricel™* and *Immune!™*) was considered redundant.

**Expert Opinion**

**Sterling Technology, Inc. Bovine Colostral Whey Protein/Peptide Concentrates**

**Expert Opinion**

**Introduction**

An expert panel qualified by scientific training and experience to evaluate the safety of food and food ingredients was assembled to conduct an independent critical evaluation of the safety of Sterling Technology, Inc. Bovine Colostral Whey Protein/Peptide Concentrates (BCWPC) as food ingredients when produced and used in accordance with current Good Manufacturing Practices and meeting the specifications described herein. The panel members included:

<b>Marian Kruzel, Ph.D.</b>	<b>Expert on Colostrum components, Chairman</b>
<b>Christopher Chase, DVM,</b>	<b>Expert on the Immune Development of Young Animals</b>
<b>Eda Shigetoshi, Ph.D.</b>	<b>Expert on the Assessment of Colostrum Fractions</b>
<b>Ramesh Chandan, Ph.D.</b>	<b>Expert on the Fractionation and Separation of Whey Fractions</b>

The qualifications of the members of the Scientific Expert Review Panel (the Panel) are provided in their curricula vitae, which are on file at the offices of Sterling Technology, Inc. 133 32<sup>nd</sup> Avenue South Brookings, South Dakota 57006, USA. . The Panel's qualifications in their respective scientific fields meet the requirements set forth in the Federal Food, Drug, and Cosmetic Act's definition of generally recognized as safe (GRAS) substances (§ 201(s)) and 21 CFR 170.30(a) "Eligibility for classification as generally recognized as safe (GRAS)".

The Panel was charged by Sterling Technology, Inc. to critically evaluate the information and data regarding Bovine Colostral Whey Protein/Peptide Concentrates in general and Sterling Technology's Bovine Colostral Whey Protein/Peptide Concentrates specifically. The Panel would then render an opinion, based on scientific principles, on the generally recognized as safe (GRAS) status of Sterling Technology's Bovine Colostral Whey Protein/Peptide Concentrates. The opinion of the Panel is based on the

**Expert Opinion**

**general use of Sterling Technology's BCWPC in food when manufactured in accordance with U.S. current Good Manufacturing Practices (21 CFR Part 110) and meeting the specifications presented below.**

**Independently, members of the Panel critically evaluated information provided by Sterling Technology, Inc., and other pertinent materials covering BCWPC. The Panel conferred by telephone regarding the pertinent safety and functionality information associated with Sterling Technology's Bovine Colostral Whey Protein Concentrates. This information supported the eligibility of Sterling Technology's BCWPC as GRAS ingredients in accordance with 21 CFR 170.30. The information provided for the Panel's review was presented in the form stipulated in proposed 21 CFR 170.36.**

**Conclusion**

**Based on the Panel's independent and collective critical evaluation of all the information summarized above, it was determined that Sterling Technology's Bovine Colostral Whey Protein/Peptide Concentrates can be considered generally recognized as safe (GRAS), when produced and used in accordance with cGMP as foods in the various major food categories as listed by the United States Department of Agriculture in the *Continuing Survey of Food Intake by Individuals (CSFII)*, and when meeting the specifications described herein.**

Expert Opinion

Signatures

Marian Kruzel, Ph.D., Chairman

Date

(b) (6)

01/07/2011

Christopher Chase, DVM, Ph.D.

Date

(b) (6)

(b) (6)

01-10-2011

Eda Shigetoshi, Ph.D.

Date

(b) (6)

January 12, 2011

Ramesh Chandan, Ph.D.

Date

(b) (6)

01-13-2011

**Expert Opinion**

**In reaching this conclusion, the Panel relied on information summarized below:**

**Chemical Identity and Manufacturing**

- **Bovine Colostral Whey Protein/Peptide Concentrates** comprise bioactive peptides and proteins which historically have been consumed as a part of whole colostrum. Sterling Technology, Inc. produces two products, which are separated from whole colostrum by the removal of fat and casein to obtain bovine colostrum whey, followed by ultrafiltration with a 10,000 Dalton cut-off, and concentration with nanofiltration. The two products can be distinguished based on their membrane retention. The trade names for the two products are Immunel™ [ $<10,000$  Daltons] and Tegriceal™ [ $>10,000$  Daltons].
- Bovine whey derived from milk is a natural by-product of the cheese making process, and is now a familiar consumer product in its dry form. Whey can be separated from whole colostrum via acid precipitation, by fermentation, or by subjecting milk or colostrum to an enzyme system to remove the casein and fat by centrifugation [Yalcin, 2006 and Krissansen, 2007].
- Bovine colostrum whey is known to contain many bioactive proteins, which have been shown to modulate the immune system, and have beneficial effects on many other organ systems, including the gastrointestinal tract [Rokka, *et al.*, 2001 and Wong, *et al.*, 1997].
- Bovine milk contains about 3.5% protein, 80% of which are caseins and the remaining 20% are whey proteins. Whey proteins contain all the essential amino acids and have the highest protein quality rating among other protein sources [Yalcin, 2006 and Krissansen, 2007].
- Many milk or colostrum proteins possess specific biological properties which make them potential ingredients of health-promoting foods [Korhonen, *et al.*, 2007]. These properties are attributed to both native protein molecules and to physiologically active peptides encrypted within larger protein structures.
- Sterling Technology, Inc. has pioneered a fractionation method to separate two mixtures of bioactive proteins and peptides from bovine colostrum whey.

**Expert Opinion**

**This system uses an ultrafiltration system to separate peptides based on their molecular weight. A low molecular weight (<10 kDa) peptide product called Immunel™ has been shown to modulate both animal and human immune systems at very low consumption levels. The higher molecular weight (>10 kDa) whey protein concentrate, Tegricel™, has been shown to positively effect the gastrointestinal tract [Jensen, *et al.*, 2009 and 2010 and Playford, 2004].**

- Unlike some dietary supplements whose composition is precisely defined chemically, bovine colostrums do not have a typical composition profile. The typical composition profile of bovine colostrums varies depending on multiple factors. Breed, health status of the animal, feeding practices and post-parturition time interval have been cited as factors influencing the composition of colostrums (Kelly, 2003). Therefore, Sterling Inc. has standardized its whey protein concentrates around certain key components such as immunoglobulins or proline-rich polypeptides.**
- The Sterling Technology manufacturing plant has a certified Hazards Analysis Critical Control Point Program (HACCP) in place to assure product quality. [Sterling Technology Hazards Analysis Critical Control Point Program, 2006].**
- Final written product specifications for the various Bovine Colostral Whey Protein/Peptide Concentrates have been provided to the Panel. A comparison of the high and low molecular weight colostrum whey protein concentrates is shown below.**

Expert Opinion

**Comparative Final Product Specifications for Sterling  
Tegrice<sup>TM</sup> and Immune<sup>TM</sup>**

<b>Food Grade</b>			
<b>Chemical Parameters</b>			
	<b>Tegrice<sup>TM</sup></b>	<b>Immune<sup>TM</sup> Liquid</b>	<b>Immune<sup>TM</sup> Powder</b>
Moisture	≤6.0 %	>80 %	≤6.0 %
Ash	≤5.0 %	-	-
Fat	≤5.0 %	≤1.0 %	≤1.0 %
Protein	≥70.0 %	≥2.0 %	≥2.0 %
Carbohydrate	-	≤6.0 %	≥78.0 %
Lactose	≥6.0 %	-	-
IgG	≥25.0 %	-	-
Proline-rich Polypeptide (PRP)	-	≥1.8 %	≥0.75 %
Sialic acid	-	-	≥30 mg/100g
<b>Microbiological Parameters</b>			
Total Plate Count	< 10,000 CFU/g	< 1,000 CFU/ml	< 1,000 CFU/ml
<i>Escherichia coli</i>	Negative/g	Negative/ml	Negative/g
Coliform Organisms	Negative/g	Negative/ml	Negative/g
<i>Salmonella sp.</i>	Negative/25 grams	Negative/25 ml	Negative/25 g
<i>Listeria sp.</i>	Negative/25 grams	Negative/25 ml	Negative/25 g
Coagulase positive <i>Staph.</i>	Negative/g	Negative/ml	Negative/g
<i>E. sakazaki</i>	<0.003/g <sup>1</sup>	-	-
<i>B. cereus</i>	Negative/g	-	-
<i>C. perfringens</i>	Negative/g	-	-
Yeast	≤ 10 CFU/g	≤ 10 CFU/ml	≤ 10 CFU/g
Mold	≤ 10 CFU/g	≤ 10 CFU/ml	≤ 10 CFU/g
Antibiotic Resistance	Negative	-	-

<sup>1</sup>Negative indicates that 30 X 10 gram samples were analyzed by ISO method 22964.

- An analysis of four lots of Sterling Technology Bovine Colostral Whey Protein Concentrates has demonstrated that the products can consistently meet their published specifications.

Potential Human Toxicants

**Expert Opinion**

- **Chemical and heavy metals analyses of Sterling Technology products have shown that the products contain no toxicants of concern. Significantly, lead and melamine were below the levels of detection. Sterling Technology Bovine Colostral Whey Protein/Peptide Concentrates contains less chemical and microbiological contaminants than many common food sources.**

**Use and Functionality**

- **Because of the high cost of producing Bovine Colostral Whey Protein/Peptide Concentrates, they have not been historically used as foods or food ingredients in their concentrated forms [Yalcin, 2006 and Krissansen, 2007].**
- **As a food source for humans, it is likely that the raw material for the concentrates, bovine colostrum, was consumed by man starting with the domestication of ruminants some 40,000 years ago [Solomons, 2002]. Settled agriculture led to the availability of colostrum and milk for persons older than infants roughly 10,000 years ago, and consumption of colostrum continues into modern times. For instance, some ethnic cultures and persons in Eastern Europe and in India consume colostrum regularly [Solomons, 2002].**
- **Applications for Bovine Colostral Whey Protein Concentrates include general use in foods as multiple-use direct additives.**
- **A comparison of the nutritional components of the powder forms of the two BCWPC products is shown below. Tegricel™, the product retained on the 10 kDa membrane contains >65% protein, while the membrane permeate, Immunel™, contains at least 2% protein.**

Expert Opinion

**Comparison of Nutritional Components for Low and High  
Molecular Weight  
Bovine Colostral Whey Protein/Peptide Concentrates**

<b>Analysis</b>	<b>Tegricel™</b>	<b>Immunel™</b>
Protein	>65%	2% min
Fat	<5%	<1%
Moisture	<6%	<6%
Ash	<5%	<2%
Carbohydrates	<10%	>78%
<b>Unique Characteristics</b>		
Glycomacropeptide	-	>0.75%
Proline Rich Polypeptides	-	>30 mg/100g
N-Acetyl neuraminic Acid	-	2% min
Nucleotides/Nucleic Acid	-	<1%

- Bovine colostrum whey is known to contain many bioactive proteins, which have been shown to modulate the immune system, and have beneficial effects on many other organ systems, including the gastrointestinal tract [Rokka, *et al.*, 2001 and Wong, *et al.*, 1997].
- Many milk or colostrum proteins possess specific biological properties which make them potential ingredients of health-promoting foods [Korhonen, *et al.*, 2007]. These properties are attributed to both native protein molecules and to physiologically active peptides encrypted within larger protein structures. These bioactive peptides are inactive within the protein sequence but may be released by the action of native proteolytic enzymes from milk, enzymes from lactic acid bacteria or from exogenous sources or they may be released during gastrointestinal digestion or the processing of foods.
- Colostrum extracts, such as the high molecular weight BCWPC, which contain high levels of bioactive components (> 40% immunoglobulins) and growth factors, have been shown to enhance intestinal villus size, maintain the integrity of the mucosa, reduce mucosal permeability, and to repair

Expert Opinion

NSAID's induced gut injury. Insulin-like Growth Factor, IGF-I, found in the low molecular weight BCWPC has been determined to have potential for accelerating intestinal repair and epithelial regrowth [Playford, 2009 and Campbell, *et al.*, 2009].

- Colostrum extracts have been shown to inhibit oxidative stress and tissue damage induced by endurance training [Campbell, *et al.*, 2009]. They have also been shown to assist in muscle mass regulation, both for bodybuilders, and for the frail elderly, or those with conditions associated with muscle wasting [Campbell, *et al.*, 2009].
- Immunel™ has been shown to have a number of effects on the immune system, as well as significant antioxidant activity. In independent studies it acted very rapidly on human phagocytes, causing them to ingest a higher number of particles per cell, and to more efficiently ingest microbe-sized particles. It induced Natural Killer (NK) cells, which expressed much higher amounts of an activation marker called CD69 after treatment with Immunel™. This indicated that the NK cells were activated to be more efficient at attacking target cells. When another well-known stimulus of NK cell activation, namely Interleukin-2 (IL-2) was added to tests with human immune cells, Immunel™ and IL-2 acted in synergy and produced higher levels of NK cell activation. This result provided an indication that when an ongoing immune reaction triggered IL-2 production, Immunel™ supported the immune reaction involving NK cells. Immunel™ also showed a synergistic effect with IL-2 on T-cell activation and treatment of purified human peripheral blood mononuclear cells with Immunel™ resulted in an increase in adhesion among peripheral blood monocytes [Jensen, 2006 and Krieg, *et al.*, 2010].
- Both low and high molecular weight BCWPC products provide mixtures of trophic molecules, which function to enhance the effectiveness of the immune and digestive systems. Currently, these helpful molecules are not available to humans beyond early infancy. Many food scientists have considered Bovine Colostral Whey Protein/Peptide Concentrates a source of health-promoting foods, providing a general recognition of their use and safety [Korhonen, *et al.*, 2007].

Expert Opinion

**Self-Limiting Use in Foods**

- Use of Bovine Colostral Whey Protein Concentrates is expected to be limited by their cost (\$400 to 1,000/kilo) and by the fact that the activity of the peptides may be degraded by exposure to high heat [Godden, *et al.*, 2006].

**Exposure**

- Sterling Technology, Inc. has provided an estimate of exposure to its Bovine Colostral Whey Protein/Peptide Concentrate products. Additional exposure to BCWPC may result from their use as dietary supplements [Enns, *et al.*, 1997].
- The calculation for the mean and the 90<sup>th</sup> percentile of estimated exposure to Sterling, Inc. Bovine Colostral Whey Protein Concentrates assumes that 100% of consumers are "eaters" of Bovine Colostral Whey Protein Concentrates-containing products within a given food category, and that all foods within a given category contain Colostral Whey Protein/Peptide Concentrates.
- The mean and the 90<sup>th</sup> percentile of estimated exposure to Sterling, Inc. Bovine Colostral Whey Protein/Peptide Concentrates amounts to 15 and 30 mg respectively [Enns, *et al.*, 1997].
- The recommended dose of Sterling, Inc. Bovine Colostral Whey Protein Concentrates as dietary supplements is 10 to 20 mg per day. This dosage has been recommended based on the results of clinical trials with human volunteers [Jensen, 2006 a and b].

**Current Usage**

- Other products derived from bovine colostrum whey have been marketed to consumers, particularly in Europe. For instance, a Finnish company has manufactured a bovine colostrum whey product, called Bioenervi. On April 04, 1994, a U.S. federal trademark registration was filed for BIOENERVI. This trademark was owned at the time by Valio Biotuotteet Oy, Tykistokatu 6, Biocity, FIN-20520 Turku. The correspondent listed for BIOENERVI is Adrienne L. White of Burns, Doane, Swecker & Mathis, Post Office Box 1404,

Expert Opinion

Alexandria, VA 22313-1404. The BIOENERVI trademark is filed in the category of Pharmaceutical Products, Meats and Processed Food Products . The description provided to the USPTO for BIOENERVI is nutritional supplements and whey based food supplements. The USPTO has given the BIOENERVI trademark serial number of 74508269. This substance was the subject of several clinical and animal studies [Loimaranta, *et al.*, 2001 and Playford, *et al.*, 2001]



General Recognition of Safety through Experience

- Bovine colostrum, the raw material for the low and high molecular weight colostrum whey protein concentrates has a General Recognition of Safety through Experience as encoded at 21 CFR §170.30(c)(1). As mentioned above, whole colostrum has been in the human food chain for thousands of years [Solomons, 2002]. Thus the burden for maintaining that safety falls to the extraction processes for the low and high molecular weight Colostral Whey Protein/Peptide Concentrates.
- Separation of the two products from whole colostrum requires the removal of fat and casein via processes already widely used in the food industry. The ultrafiltration step, used to separate the low and high molecular weight, Colostral Whey Protein/Peptide Concentrates has been considered safe for dairy food processing [Kosikowski, *et al.*, 1990].

Safety

- The high and low molecular weight end products resulting from ultrafiltration of colostrum have undergone various clinical studies, which are summarized below. These studies demonstrate that the final products to be consumed by humans pose no threat to consumers.
- A classic 90-day animal feeding study was conducted in young rats by a research group from New Zealand. In this study, the potential detrimental effects of two different oral doses of bovine colostrum were assessed when colostrum was supplemented at 3% and 10% of a normal rat chow. A control group received no supplementation. After 90 days the authors

Expert Opinion

found no difference between colostrum-fed animals and the control group in body weight, food consumption, clinical signs, hematology and most parameters of blood chemistry including carbohydrate metabolism, liver function and kidney function. The authors explained that the only effects of statistical significance were a decrease in serum cholesterol concentration in the rats receiving 10% colostrum ( $p < 0.025$ ), and a 33% increase in serum triglyceride concentration in the rats receiving 3% colostrum ( $p < 0.005$ ). Further, histological examination of most organs and tissues confirmed that there were no apparent differences between the animals receiving colostrum compared to controls. Based on these results, the authors concluded that young growing rats had no observed toxicological or histopathological abnormalities caused by ingestion of colostrum at the levels of supplementation [Davis, *et al.*, 2006].

- Sterling Technology, Inc. sponsored a study to test the effects of colostrum-derived protein food supplements in human and animal health. The study was conducted under South Dakota CITE Grant #219. In this study, the research team tested the ability of colostrum derivatives to protect animals from the consequences of infection with pathogenic organisms. The effects of colostrum whey fractions with molecular weights greater than 50 kDa and as well as low molecular weight fractions were examined. The studies indicated that both colostrum whey fractions were kill several bacterial pathogens of economic importance. Gnotobiotic piglets supplemented with 10% bovine colostrum whey for 14 days were challenged with pathogenic *E. coli* on day 2 of the experiment. All animals being supplemented were found to have better antibody response to antigens, and had a shorter less severe course of the disease. The researchers also reported that calves supplemented with bovine colostrum whey had less problems with scouring, and as shown especially in veal calves had improved uptake and utilization of iron and improved levels of hemoglobin and hematocrit. No adverse reactions were reported in the test animals [Hurley, 1994].
- Researchers at the German Red Cross' Center for Transfusion Medicine in Muenster, Germany reviewed the value of bovine colostrum as a biologic in medicine. The ability of bovine colostrum concentrates (BCC) to

Expert Opinion

neutralize lipopolysaccharides (LPS), i.e. endotoxins arising from Gram-negative bacterial pathogens and to inhibit enterogenic endotoxemia in animal models was found to have its counterpart in patient therapy, according to the authors. Clinical trials with BCC provided evidence that oral application reduced the influx of LPS from the gut and this appeared to be a major mechanism underlying the therapeutic effect of BCC in patients at risk for Gram-negative septic shock. Data from two well-controlled clinical studies with a total of 100 surgical patients had shown that the inhibition of intestinal LPS absorption measured after the application of BCC not only reduced the LPS levels in the peripheral blood but also inflammatory parameters like IL-6 and C-reactive protein. The normal daily dose of a commercially available BCC preparation, LactobinA (LC1) was cited as 10 to 20 g daily, but higher doses could be given to the majority of patients because of the low incidence of intolerance problems. BCC was also found to be effective in infants with hemorrhagic diarrhea caused by infections with enterohemorrhagic *E. coli*. BCC was reported to reduce the likelihood of the disease progressing to a hemolytic uremic syndrome. The authors stated that the safety of newer BCC products obtained from BSE-free regions seemed to be beyond contention now. In the case of the product LC1, which was used as a commercial dietary foodstuff in Germany until 1992 and was tested in three Phase 1 and 5 clinical studies (two trials in patients with secondary immunodeficiencies, one in surgical patients with gastrointestinal disorders, one in patients undergoing open heart surgery and one in pediatric patients with EHEC infections), there were no cases of BSE-associated disease such as the new variant of Creutzfeldt-Jakob disease. Side effects of clinical relevance were limited to possible intolerance to lactose and sensitivity to milk proteins, but the researchers explained that these food ingredients were also present in many commonly used foodstuffs [Struff, *et al.*, 2008].

- A group of Finnish researchers conducted a study to obtain additional information on the immunomodulatory effect of orally administered bovine colostrum whey in healthy subjects. The aim of the study was to assess whether a bovine colostrum whey supplement had immune response enhancing effects in subjects orally immunized with *Salmonella typhi* Ty21a oral vaccine. The subjects were given 100 ml per day of colostrum

Expert Opinion

whey supplements prior to and after the vaccine intake. Eighteen healthy volunteers were randomized into two treatment groups and consumed liquid prepackaged bovine colostrum whey or placebo for 7 days. On days 1, 3 and 5, an attenuated *Salmonella typhi* Ty21a oral vaccine was given to all subjects to mimic an enteropathogenic infection. The circulating antibody secreting cells and the expression of phagocytosis receptors of the subjects before and after oral immunization were measured with the ELISPOT assay and flow cytometry. All subjects responded well to the vaccine. No significant differences were observed in ELISPOT values for IgA, IgG, IgM, FcQ and CR receptor expression on neutrophils and monocytes between the two groups. There was a trend towards a greater increase in specific IgA among the subjects receiving their vaccine with bovine colostrum whey. These results suggested to the authors that bovine colostrum may possess some potential to enhance human special immune responses. Taken together these factors suggest that the potent immunomodulatory effect of bovine colostrum whey observed in the present study may be related to its ability to promote the integrity of the human epithelium. No adverse reactions were reported in the subjects [He, *et al.*, 2001].

- Sterling Technology sponsored studies in which the two BCWPC products were tested for their ability to influence repair of the intestinal lining. Those studies showed positive effects on several areas of the repair process (migration, proliferation, and reduced overall injury). The findings of effects in multiple repair pathways strengthen claims of activity and increase the likelihood of potential therapeutic benefit against multiple aggressive factors. Indomethacin, for instance, causes damage to the gastrointestinal tract by several mechanisms including reduction of mucosal prostaglandin levels, reduction of mucosal blood flow, stimulation of neutrophil activation and possibly also stimulation of apoptosis. It is likely that many of these mechanisms will be influenced by the numerous growth factors present in the colostrum preparation. The author had previously shown that several of these peptides, e.g. EGF and transforming growth factor were susceptible to digestion from luminal proteases when administered alone and that peptides involved in mucosal repair can act in a synergistic fashion if co-administered. The author explained that there are therefore

**Expert Opinion**

several reasons why the use of BCWPC preparations, as opposed to giving a single recombinant peptide, might be particularly beneficial [Playford, 2009]. In this group of studies the human colonic cancer cell line, HT-29, was grown in DMEM containing glutamine and 10% fetal calf serum. The effects of the colostrals samples and EGF (positive control) were subsequently tested under serum-starved conditions. To assess the percentage of cells entering DNA synthesis, [<sup>3</sup>H]-thymidine (2 μCi/well) was included twenty-four hours after the addition of the test factors and cells were left for a further 24 hours. For each condition, the stimulatory or inhibitory effect of the solutions was measured in quadruplet in six separate wells. Cell viability, determined by the ability to exclude 0.2% trypan blue, was greater than 90%. The author concluded that the BCWPC products tested were biologically active and showed positive results when used in various models of wound injury and repair. No adverse results in cell viability were reported at doses ranging from 1-5 mg of protein per milliliter [Playford, 2009].

**At Risk Populations**

- Both the high and low molecular weight BCWPC products may contain proteins, to which persons with milk sensitivities may react. Therefore, both Tegricel™ and Immunel™ will be labeled as "Contains milk products".



***Summary of Data Supporting a  
(GRAS) Determination***

**GRAS Notice:**

THE USE OF TWO SUBSTANCES DERIVED FROM BOVINE COLOSTRUM, A WHEY PROTEIN CONCENTRATE (TEGRICEL™) AND A LOW MOLECULAR WEIGHT WHEY PROTEIN FRACTION (IMMUNEL™), IN HUMAN FOODS IS GENERALLY RECOGNIZED AS SAFE (GRAS)

May 2, 2012

## **Summary of Data Supporting a (GRAS) Determination**

### **Table of Contents**

	<b>Page</b>
1.0 INTRODUCTION.....	25
1.1 Background .....	25
1.2 Objective.....	26
1.3 Comparison to Other GRAS Substances .....	26
2.0 SUBSTANCE CHARACTERIZATION .....	27
3.0 MANUFACTURING AND QUALITY CONTROL & ASSURANCE .....	29
3.1 Manufacturing Process .....	29
3.2 Specifications .....	29
3.2 Product Specifications .....	29
4.0 INTENDED USE AND PROJECTED EXPOSURE .....	40
4.1 Intended Use .....	40
4.2 Exposure Estimates .....	43
5.0 SAFETY .....	52
5.1 Overview.....	52
5.2 Nonclinical Safety .....	52
5.3 Clinical Safety .....	53
5.4 At-risk Populations.....	53
6.0 SUPPORTING EVIDENCE .....	54
6.1 Experimental Animal Studies .....	54
6.2 Clinical Studies .....	54
6.3 Marketed Products.....	55
7.0 SUMMARY AND CONCLUSION.....	58
8.0 REFERENCES.....	59

### **List of Appendices**

APPENDIX 1: RESULTS OF HEAVY METALS ANALYSES OF BOVINE COLOSTRUM WHEY USED TO PRODUCE TEGRICEL™ COLOSTRAL WHEY PROTEIN CONCENTRATE AND IMMUNEL™ COLOSTRAL WHEY NONPROTEIN FRACTION.....	61
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## List of Tables and Figures

	<b>Page</b>
Table 1-1 Comparison between whey protein concentrate and Tegrice <sup>TM</sup> colostr <sup>TM</sup> whey protein concentrate .....	27
Table 2-1 General characteristics of Sterling Technology colostr <sup>TM</sup> whey-derived products .....	27
Table 2-2 Primary components of Sterling Technology's bovine colostr <sup>TM</sup> -derived products .....	28
Table 2-3 Protein and related constituents present in Tegrice <sup>TM</sup> colostr <sup>TM</sup> whey protein concentrate .....	28
Table 2-4 Bioactive factors present in liquid and solid forms of Immunel <sup>TM</sup> .....	28
Table 3-1 Specifications for Tegrice <sup>TM</sup> colostr <sup>TM</sup> whey protein concentrate .....	32
Table 3-2 Specifications for Immunel <sup>TM</sup> liquid colostr <sup>TM</sup> low molecular weight whey protein fraction .....	32
Table 3-3 Specifications for Immunel <sup>TM</sup> powder colostr <sup>TM</sup> low molecular weight whey protein fraction .....	33
Table 3-4 Molecular weight distribution of proteins in Immunel <sup>TM</sup> colostr <sup>TM</sup> bovine low molecular weight whey protein fraction .....	33
Table 3-5 Analyses of multiple lots of Tegrice <sup>TM</sup> colostr <sup>TM</sup> whey protein concentrate .....	37
Table 3-6 Analyses of multiple lots of Immunel <sup>TM</sup> liquid colostr <sup>TM</sup> low molecular weight whey protein fraction .....	38
Table 3-7 Analyses of multiple lots of Immunel <sup>TM</sup> powder colostr <sup>TM</sup> low molecular weight whey protein fraction .....	39
Table 4-1 Examples of foods in which Tegrice <sup>TM</sup> or Immunel <sup>TM</sup> may be used .....	41
Table 4-2 Components of bovine colostr <sup>TM</sup> and associated physiological activity .....	42
Table 4-3 Estimated intakes of colostr <sup>TM</sup> elements based on the use of Tegrice <sup>TM</sup> colostr <sup>TM</sup> whey protein concentrate and Immunel <sup>TM</sup> colostr <sup>TM</sup> low molecular weight whey protein fraction in foods .....	44
Table 4-4a Use of Tegrice <sup>TM</sup> colostr <sup>TM</sup> whey protein concentrate in food categories listed by the US FDA in 21 CFR §170.3 (n) .....	45
Table 4-4b Use of Immunel <sup>TM</sup> colostr <sup>TM</sup> low molecular weight whey protein fraction in food categories listed by the US FDA in 21 CFR §170.3 (n) .....	46

Table 4-5a	Estimated Intake of Tegrice1™ colostrat whey protein concentrate in selected food categories .....	47
Table 4-5b	Estimated Intake of Immunel™ colostrat low molecular weight whey protein fraction in selected food categories.....	49
Table 4-6a	Tegrice1™ colostrat whey protein concentrate--USDA major food categories and corresponding categories from 21 CFR 170.3 (n) .....	51
Table 4-6b	Immunel™ colostrat low molecular weight whey protein fraction--USDA major food categories and corresponding categories from 21 CFR 170.3 (n) .....	51
Table 6-1	Subset of human studies reviewed by Kelly (2003) that examined the use of bovine colostrum for specific conditions.....	56
Table 6-2	List of marketed colostrum-derived nutritional supplement products .....	57
Figure 3-1	Overview of manufacturing process for Tegrice1™ colostrat whey protein concentrate.....	30
Figure 3-2	Overview of manufacturing process for Immunel™ colostrat whey nonprotein fraction.....	31

THE USE OF TWO SUBSTANCES DERIVED FROM BOVINE  
COLOSTRUM, A WHEY PROTEIN CONCENTRATE (TEGRICEL™) AND  
A LOW MOLECULAR WEIGHT WHEY PROTEIN FRACTION  
(IMMUNEL™), IN HUMAN FOODS IS GENERALLY RECOGNIZED AS  
SAFE (GRAS)

**Summary of Data Supporting a (GRAS) Determination**

**1.0 INTRODUCTION**

**1.1 Background**

Sterling Technology, Inc. (Sterling Technology hereafter) has developed two products, to be marketed under the names Tegricel™ or RPM factors™ and Immunel™, that are derived from bovine whole colostrum whey through methods typically used in cheese-making, along with ultrafiltration to separate the whey proteins from the nonprotein constituents. Tegricel™ (also interchangeably called RPM factors™) contains the majority of the proteins. Immunel™ is a by-product of Tegricel™ production, derived from the fraction (*i.e.*, filtrate) remaining after the colostrum whey is subjected to ultrafiltration; it contains nonprotein components and small amounts of low-molecular weight (<500 Daltons) whey proteins.

With assistance from an Expert Panel specifically convened for the purpose of reviewing information regarding safety, specifications, manufacturing, proposed uses, *etc.*, Sterling Technology has affirmed that the use of Tegricel™ and Immunel™ in foods for the general population is generally recognized as safe (GRAS) and exempt from the premarket approval requirements for food additives. Bovine colostrum has been consumed as a component of food for thousands of years. However, because these isolates *per se* have not been consumed as such, a GRAS determination through scientific procedures, rather than through common use in foods, would be more appropriate.

Tegricel™ colostrum whey protein concentrate (≥70% proteins, most >10,000 Daltons molecular weight) is considered similar to *whey protein concentrate*, a direct food substance affirmed as generally recognized as safe (GRAS) as described in 21 CFR 184.1979c; Tegricel™ differs in that it is derived from colostrum. Colostrum is a form of mammalian milk whose production and release from the mammary glands generally coincides with the birth of the offspring and is temporary as production transitions within days into mature milk. This “early” milk has a nutrient profile and immunological composition substantially different from “mature” milk. In addition to the macronutrients found in milk (protein, carbohydrate, fat, vitamins, and minerals), colostrum contains oligosaccharides, growth factors, antimicrobial compounds, and immune-regulating constituents either not present in milk or present in mature milk in substantially lower concentrations (Kelly, 2003).

## 1.2 Objective

Sterling Technology has affirmed that the use of Tegrice<sup>™</sup> colostrum whey protein concentrate and Immunel<sup>™</sup> colostrum low molecular weight whey protein fraction in human foods at levels up to 1 g/serving and 100 mg/serving, respectively, is generally recognized as safe (GRAS) by qualified experts, as shown through scientific procedures. Tegrice<sup>™</sup> colostrum whey protein concentrate and Immunel<sup>™</sup> colostrum low molecular weight whey protein fraction would therefore be exempt from the definition of “food additive” and thus from the premarket approval requirements outlined in section 201(s) of the Federal Food, Drug, and Cosmetic Act.

To make this GRAS determination, Sterling Technology: (1) compiled information regarding the nature of the substance, specifications, manufacturing, proposed conditions of use, and technical evidence of safety into a comprehensive dossier (GRAS dossier); and (2) obtained the opinion of an Expert Panel specifically convened for the purpose of reviewing the information therein to determine whether there is a consensus among qualified experts that the use of Tegrice<sup>™</sup> colostrum whey protein concentrate and Immunel<sup>™</sup> colostrum low molecular weight whey protein fraction as described entails a reasonable certainty of no harm and is GRAS. The use of these substances would be considered GRAS based on the following:

- All available scientific information indicates that consumption of colostrum and colostrum-derived substances is not associated with any adverse effects in humans or other animal species.
- Colostrum, the source material for these whey protein isolates, is a naturally-occurring substance produced by all mammals, including humans, and history indicates it has been present in the human diet.
- Substantial equivalence to other milk-derived products.

## 1.3 Comparison to Other GRAS Substances

As mentioned previously, Tegrice<sup>™</sup> whey protein concentrate is similar to *whey protein concentrate* already considered GRAS, except it is derived from *colostrum* whey. Table 1-1 compares Tegrice<sup>™</sup> to whey protein concentrate as described in §184.1979c. Immunel<sup>™</sup> is a by-product of Tegrice<sup>™</sup> production.

Other related substances whose GRAS status has been evaluated, generating no questions from U.S. FDA, include whey protein isolate and dairy products solids (GRAS Notice No. GRN 000037), and whey mineral concentrate (GRN 000052).

**Table 1-1 Comparison between whey protein concentrate and Tegrice<sup>TM</sup> colostr whey protein concentrate**

Criterion	Whey protein concentrate (§184.1979c)	Tegrice <sup>TM</sup> Powder
<b>Definition</b>	[S]ubstance obtained by the removal of sufficient nonprotein constituents from whey so that the finished dry product contains not less than 25 percent protein.	Substance obtained by the removal of nonprotein constituents by filtration from <i>colostral</i> whey so that the finished dry product contains not less than 25 percent protein.
<b>Specifications</b>		
Protein (%)	≥25	≥70
Fat (%)	1-10	≤8
Ash (%)	2-15	≤5
Lactose (%)	≤60	≤9
Moisture (%)	1-6	≤6
Heavy metals (as lead)	≤10 ppm (0.001%)	None detected <sup>1</sup>
Pasteurized before using in food or derived from pasteurized milk	Yes	Yes

<sup>1</sup>No heavy metals were detected in multiple samples of bovine colostrum, the source material (see Appendix 1).

## 2.0 SUBSTANCE CHARACTERIZATION

Sterling Technology's products, marketed under the names Tegrice<sup>TM</sup> RPM factors<sup>TM</sup> and Immune<sup>TM</sup>, are isolates of bovine whole colostrum whey derived through methods typically used in cheese-making, along with ultrafiltration to separate the whey proteins from the largely nonprotein constituents. The general characteristics of Tegrice<sup>TM</sup> colostr whey protein concentrate and Immune<sup>TM</sup> colostr low molecular weight whey protein fraction are shown in Table 2-1.

**Table 2-1 General characteristics of Sterling Technology colostrum whey-derived products**

<b>Trade Name:</b>	Tegrice <sup>TM</sup> or RPM factors <sup>TM</sup>	Immune <sup>TM</sup>
<b>Generic Name:</b>	Colostr whey protein concentrate	Colostr low molecular weight whey protein fraction
<b>Chemical Composition:</b>	Mixture of whey proteins with molecular weight above 10 kilo Daltons (>10 kDa)	Mixture of whey protein and nonprotein constituents <sup>†</sup>
<b>Form(s):</b>	Dry product	Fluid and dry product

<sup>†</sup> Contains small amounts of proteins, most (>70%) with molecular weight below 500 Daltons.

Tegrice<sup>TM</sup> colostr<sup>al</sup> whey protein concentrate contains the majority of the whey proteins ( $\geq 70\%$  proteins) and is considered similar to *whey protein concentrate*, a direct food substance affirmed as generally recognized as safe (GRAS) as described in 21 CFR 184.1979c, except that Tegrice<sup>TM</sup> is derived from bovine colostr<sup>um</sup>, a form of milk produced at the time the calf is born and for a short period thereafter. Immunel<sup>TM</sup> is derived from what remains after isolation of the whey proteins; it contains nonprotein constituents and small amounts of low-molecular weight (<500 kDa) proteins. Table 2-2 provides an overview of the composition of each of the products.

**Table 2-2 Primary components of Sterling Technology's bovine colostr<sup>um</sup>-derived products**

Component	Tegrice <sup>TM</sup> Powder	Immunel <sup>TM</sup> Liquid	Immunel <sup>TM</sup> Powder
Moisture	$\leq 6.0\%$	$\geq 80.0\%$	$\leq 6.0\%$
Ash	$\leq 5.0\%$	$\leq 1.0\%$	$\leq 1.0\%$
Fat	$\leq 8.0\%$	$\leq 1.0\%$	$\leq 1.0\%$
Carbohydrate	$\leq 9.0\%$	$\leq 6.0\%$	$\geq 80.0\%$
Protein	$\geq 70.0\%$	$\geq 2.0\%$	$\geq 1.0\%$

Tegrice<sup>TM</sup> colostr<sup>al</sup> whey protein concentrate and Immunel<sup>TM</sup> colostr<sup>al</sup> low molecular weight whey protein fraction are typically characterized by two principal factors, molecular weight and the prevalence of immunoglobulins. As Tables 2-3 and 2-4 illustrate, Tegrice<sup>TM</sup> contains the majority of the immunoglobulins, while Immunel<sup>TM</sup> contains the majority of the growth factors and other bioactive molecules.

**Table 2-3 Protein and related constituents present in Tegrice<sup>TM</sup> colostr<sup>al</sup> whey protein concentrate**

Component	Analytical results
Immunoglobulins (IG)	> 25%
Non-IG whey proteins	< 65%
Lactoferrin	Present
Peptides	Present

**Table 2-4 Bioactive factors present in liquid and solid forms of Immunel<sup>TM</sup>**

Component	Analytical results	
	Liquid	Solid
Proteins	< 2%	< 2%
Insulin-like growth factor 1 (IGF-I)	43 ng/mL	1.95 ng/mg total solids
Other factors (<10 kDa)	Present	Present

## **3.0 MANUFACTURING AND QUALITY CONTROL & ASSURANCE**

### **3.1 Manufacturing Process**

Tegricel™ colostrum whey protein concentrate and Immunel™ colostrum low molecular weight whey protein fraction are derived from bovine whole colostrum using methods typically used in cheese-making, along with ultrafiltration to separate the whey proteins from the largely nonprotein constituents. Figures 3-1 and 3-2 provide an overview of the process.

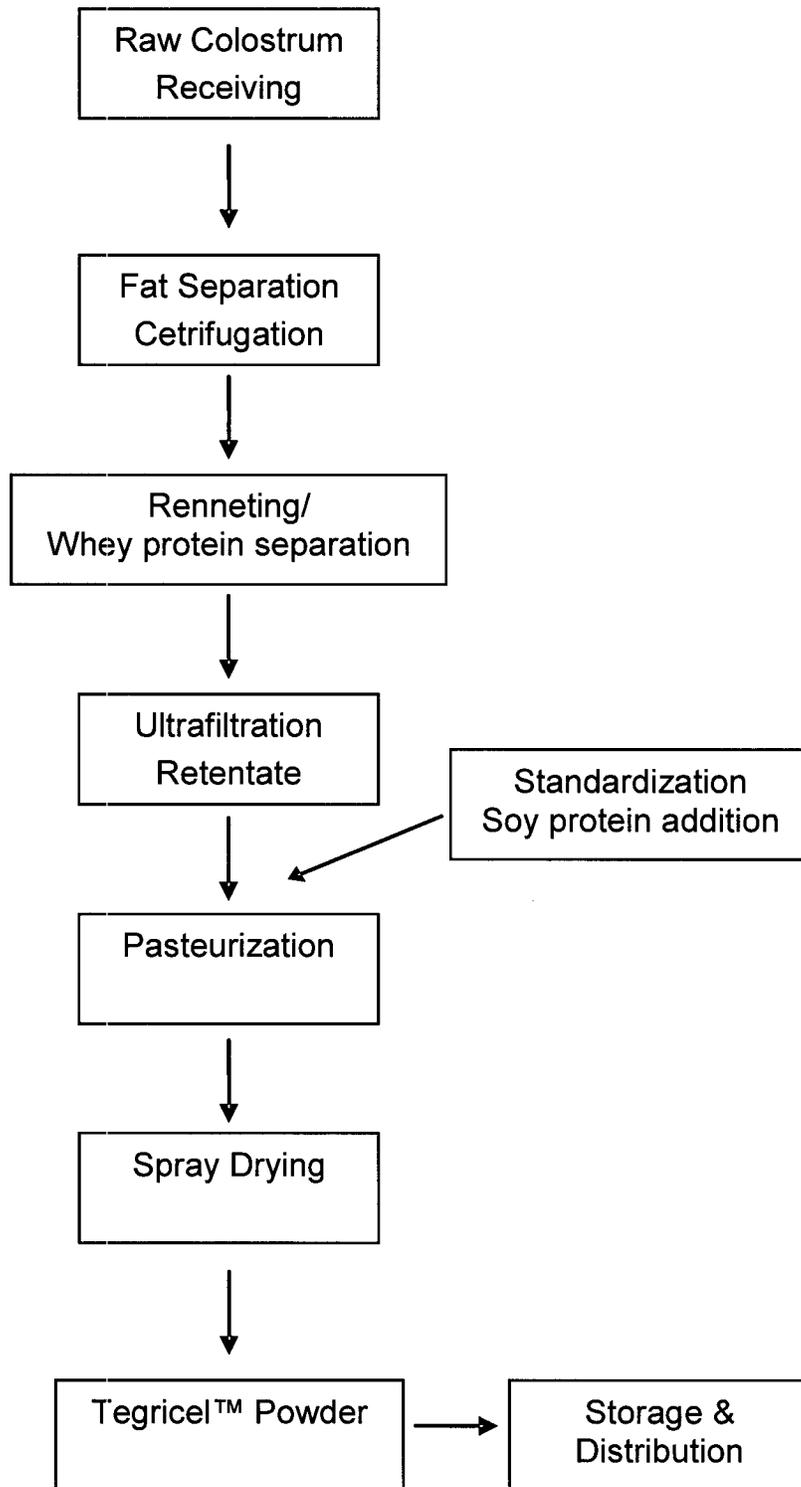
Production begins with thawing of frozen whole bovine colostrum (less than 48 hrs post-parturition). The fat fraction is then separated from the raw colostrum with a cream separator. The skimmed colostrum is then heated to 35°C and the caseins are precipitated with the addition of double-strength microbial 20 rennet (Danisco, Madison, WI, USA) for 20 minutes. A combination of low pH and or renneting may be used to separate whey. The resulting curds are separated from the colostrum whey by centrifugation. The casein fines are then removed from the colostrum whey with a cream separator. The purified whey is heated to 50°C and subjected to an ultrafiltration step using a 10,000 molecular weight cut-off (MWCO) spiral wound membrane, intended to retain the majority of the whey proteins with molecular weight >10,000 Daltons. The whey protein concentrate remaining on the membrane is then collected and spray-dried. The liquid filtrate, which contains primarily nonprotein components and small amounts of lower-molecular weight whey proteins, is acidified, concentrated by nano-filtration, and spray- or freeze-dried (Kjelden *et al.*, 2009). As described in Section 3.3.1.2, maltodextrin and soy lecithin are used in the production of Immunel™ and Tegricel™, respectively, to facilitate blending and to normalize protein content. As appropriate, a warning regarding soy allergy will appear on the product label.

### **3.2 Specifications**

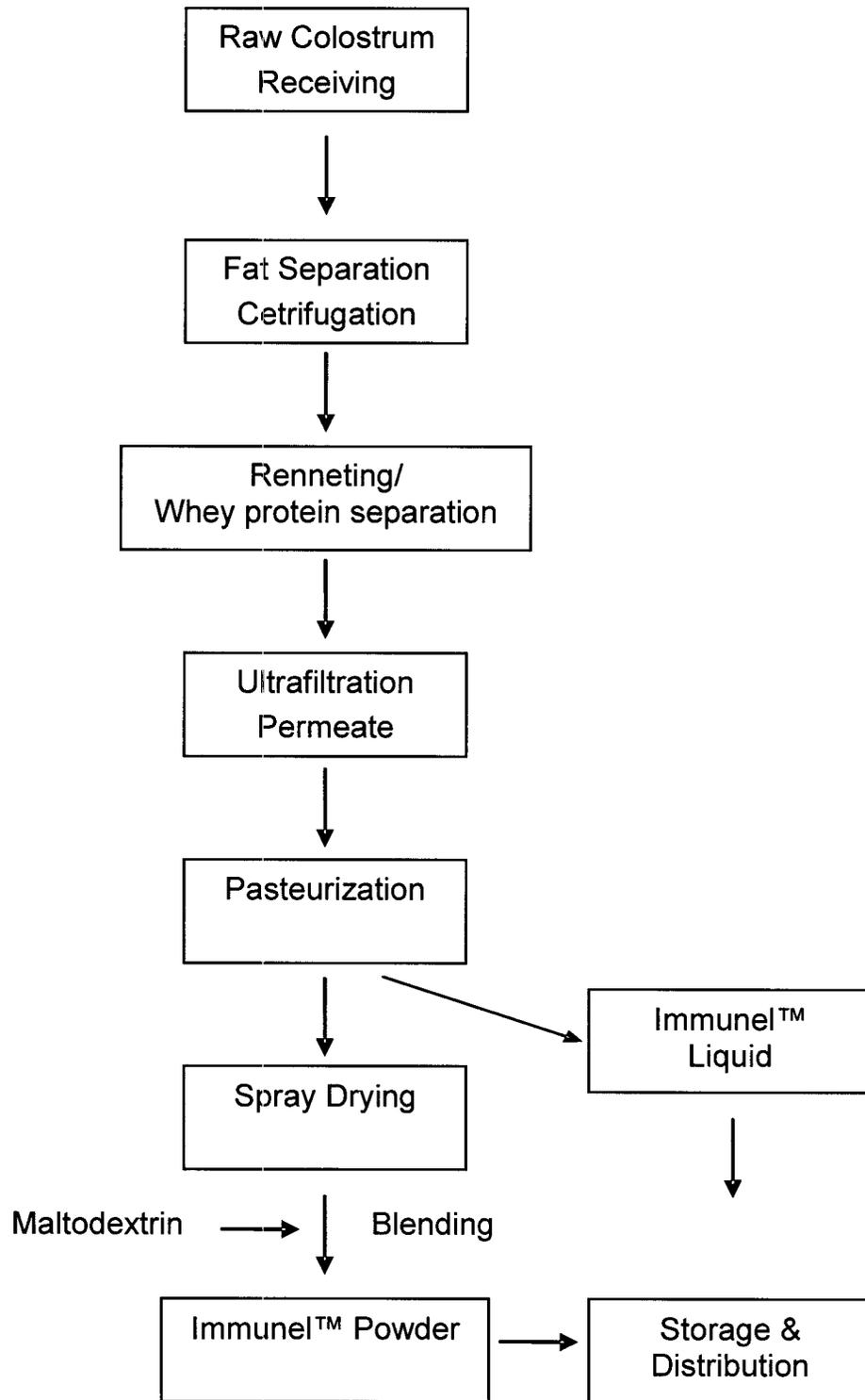
#### **3.2 Product Specifications**

As the specification in Table 3-1 show, Tegricel™ colostrum whey protein concentrate contains at least 70% total proteins. Tables 3-2 and 3-3 provide the specifications for the liquid and powder forms of Immunel™ colostrum low molecular weight whey protein fraction, respectively. Both forms of the Immunel™ colostrum low molecular weight whey protein fraction contain some proteins ( $\geq 2.0\%$ ), including proline-rich polypeptide (PRP). However, as Table 3-4 illustrates, the majority of these proteins were low-molecular weight (<500 Dalton) proteins.

**Figure 3-1 Overview of manufacturing process for Tegrice<sup>TM</sup> colostrum whey protein concentrate**



**Figure 3-2 Overview of manufacturing process for Immunel™ colostrum whey nonprotein fraction**



**Table 3-1 Specifications for Tegrice<sup>TM</sup> colostrum whey protein concentrate**

Parameter	Specification
<b>Chemical</b>	
Moisture (%)	≤6.0
Fat (%)	≤8.0
Ash (%)	≤5.0
Protein (%)	≥70.0
Carbohydrate (%)	≤9.0
Immunoglobulins (%)	≥25.0
Sialic acid	≥800 mg/100 g
Neutral Oligosaccharides	≥100 mg/100 g
<b>Microbiological</b>	
Total Plate Count	< 10,000 CFU/g
<i>Escherichia coli</i>	Negative/g
Coliform organisms	Negative/g
<i>Salmonella sp.</i> 25 grams	Negative/25 g
<i>Listeria sp.</i>	Negative/25 g
Coagulase positive <i>Staph.</i>	Negative/g
<i>E. sakazaki</i> <sup>1</sup>	<0.003/g <sup>†</sup>
<i>B. cereus</i>	<20 CFU/g
<i>C. perfringens</i>	Negative/g
Yeast	< 10 CFU/g
Mold	< 10 CFU/g

**Table 3-2 Specifications for Immunel<sup>TM</sup> liquid colostrum low molecular weight whey protein fraction**

Parameter	Specification
<b>Chemical</b>	
Moisture (%)	≥80.0
Fat (%)	≤1.0
Ash (%)	≤1.0
Protein (%)	≥2.0
Carbohydrate (%)	≤6.0
Proline-rich Polypeptide (PRP) (%)	≥1.0
Sialic acid	≥1 mg/100 mL
Neutral Oligosaccharides	≥1 mg/100 mL
<b>Microbiological</b>	
Total Plate Count	< 1,000 CFU/mL
<i>Escherichia coli</i>	Negative/mL
Coliform organisms	Negative/mL
<i>Salmonella sp.</i> 25 grams	Negative/25 mL
<i>Listeria sp.</i>	Negative/25 mL
Coagulase positive <i>Staph.</i>	Negative/mL
Yeast	< 10 CFU/mL
Mold	< 10 CFU/mL

**Table 3-3 Specifications for Immunel™ powder colostrum low molecular weight whey protein fraction**

Parameter	Specification
<b>Chemical</b>	
Moisture (%)	≤6.0
Fat (%)	≤1.0
Ash (%)	≤1.0
Protein (%)	≥1.0
Carbohydrate (%)	≥80.0
Proline-rich Polypeptide (PRP) (%)	≥0.003
Sialic acid	≥50 mg/100 g
Neutral Oligosaccharides	≥10 mg/100 g
<b>Microbiological</b>	
Total Plate Count	< 1,000 CFU/g
<i>Escherichia coli</i>	Negative/g
Coliform organisms	Negative/g
<i>Salmonella sp.</i> 25 grams	Negative/25 g
<i>Listeria sp.</i>	Negative/25 g
Coagulase positive <i>Staph.</i>	Negative/g
Yeast	< 10 CFU/g
Mold	< 10 CFU/g

**Table 3-4 Molecular weight distribution of proteins in Immunel™ colostrum bovine low molecular weight whey protein fraction**

Molecular Weight (Daltons)	Amount
<500	74%
500-1000	8%
1000-2000	8%
2000-5000	8%
5000-10,000	3%
10,000-20,000	2%
20,000-50,000	0.5%

Method: Samples were solubilized in HPLC-grade water and passed through a 0.2-µm pore filter. Sample was passed through a TSK-GEL, Guard SWXL (6.0 5 i.d. x 40 mm) pre-column and a TSK-GEL, G2000 SWXL (7.8 i.d. x 300 mm) column at a flow rate of 0.6 mL/minute using a Waters HPLC containing two pumps (model 600), a controller (model 600E) and a UV detector (model 486). The results were analyzed with Millennium 10 32 software (Kjelden *et al.*, 2009).

### **3.3 Quality and Stability**

Sterling Technology has developed a sophisticated quality assurance system and Hazards Analysis Critical Control Point (HACCP) Program to ensure product quality and purity (Sterling Technology Hazards Analysis Critical Control Point Program, 2006). This program provides assurance that Sterling Technology is operating under Good Manufacturing Practice (GMP) conditions.

Sterling Technology provided its staff with a set of written Standard Operating Procedures (SOPs) and Quality Assurance (QA) Protocols, which require annual reviews of the procedures. Each responsible employee must read, understand and sign off on each protocol. Further, Sterling Technology has written procedures for returns, complaints, and recalls.

Storage conditions are controlled in order to prevent heat-induced denaturation of the whey proteins. Storage and handling conditions are comparable to normal dairy powder handling. Instructions are provided along with certificate of analysis to adhere to GMP standards of handling and storage.

#### **3.3.1 Raw Materials**

##### **3.3.1.1 *Bovine Colostrum***

The colostrum used by Sterling Technology for production of Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immunel<sup>TM</sup> colostrum low molecular weight whey protein fraction is collected only from cattle raised in the United States on USDA- and FDA-inspected dairy farms. The cattle are from healthy, nutritionally-supplemented herds fed a nutritionally sound diet containing the proper balance of legumes and grasses, along with minerals and trace nutrients. The manufacturing plant is located at 133 32<sup>nd</sup> Avenue South, Brookings, SD 57006.

Sterling Technology has established standard operating procedures for inspection of colostrum prior to processing (Procedure # 013 Inspection of Received Colostrum) and for antibody residue testing (QC 9.0 Charm Testing for Antibiotic Residues).

Each pail of colostrum that is received must be inspected and can be rejected if the following conditions are observed:

- Manure observed in the colostrum or on the outside of the pail or lid.
- Mold growth on the inside and outside of the pail.
- Blood in the colostrum.
- Colostrum received in any other container than those provided by Sterling.
- Colostrum exhibiting a sour smell.
- Straw and other foreign matter in the colostrum.

- Any pails without a producer tag.

Any pails of colostrum showing any of the above conditions will be rejected and put into an animal-grade batch.

### 3.3.1.2 Processing Aids

In addition to bovine colostrum, Sterling Technology uses soy lecithin and soy protein powder in the production of Tegrice<sup>™</sup> colostrum whey protein concentrate and Immune<sup>™</sup> colostrum low molecular weight whey protein fraction. Both ingredients are food-grade materials and would be used in accordance with current Good Manufacturing Practices (21 CFR 110.80(a)). The specifications established by Sterling Technology for each of the processing aids are as follows.

#### **Soy Lecithin**

<u>Variables</u>	<u>Specifications</u>
Acetone Insoluble	97% (Min)
Soybean Oil	2.00 % (Max)
Moisture	1.00 % (Max)
Hexane Insolubles	0.05% (Max)
Form	Powder or Granule

Source: ADM Ultralec ®

#### **Isolated Soy Protein Powder**

<u>Variables</u>	<u>Specifications</u>
Moisture	6.0% (Max)
Protein	78% (Min)
Fat (via Acid Hydrolysis)	5.5% (Max)
Ash	5.0% (Max)
Dietary Fiber	8.5%
pH (1:10 disp. In water)	6.8-7.2
Calories (per 100 grams)	350
Standard Plate Count	10,000 (Max)
<i>Salmonella sp.</i>	Negative per 25 g
<i>E. coli</i>	Negative

Source: ADM Product Code 066-050

As indicated previously, a warning regarding soy allergy will appear on the product label.

### **3.3.2 Batch Analyses**

The results of analyses of multiple lots of Tegrice!™ colostrum whey protein concentrate and Immunel™ colostrum low molecular weight whey protein fraction are listed in Tables 3-5 through 3-7. The data show that the samples produced at various times were in compliance with the established product specifications.

No heavy metals were detected in multiple samples of the Sterling Technology bovine colostrum source material. Actual reports are provided in Appendix 1.

**Table 3-5 Analyses of multiple lots of Tegrigel™ colostrum whey protein concentrate**

Parameters	Written Specifications	Lot Number: 10471629	Lot Number: 10478112	Lot Number: 10478115	Lot Number: 10478117	Mean of 4 Lots
		Date Manufactured: 10/27/2009	Date Manufactured: 11/12/2009	Date Manufactured: 11/18/2009	Date Manufactured: 12/17/2009	
<b>Chemical</b>						
Moisture (%)	≤6.0	4.50	4.41	4.71	4.58	4.55
Fat (%)	≤5.0	2.76	2.76	2.68	2.85	2.76
Ash (%)	≤5.0	4.54	4.30	3.72	3.40	3.99
Protein (%)	≥70.0	77.51	76.32	79.33	79.14	78.07
Carbohydrate (%)	≤9.0	6.88	8.18	7.98	8.12	7.79
Immunoglobulins (%)	≥25.0	29.50	25.50	26.73	25.00	26.68
Sialic acid (mg/100 g)	≥800	1100	1300	1180	1240	1205
Neutral Oligosaccharides (mg/100g)	≥100	500	600	550	600	550
<b>Microbiological</b>						
Total Plate Count (CFU/g)	<10,000	308	1320	600	4122	1588
<i>Escherichia coli</i>	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g
Coliform organisms	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g
<i>Salmonella sp.</i> 25 grams	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g
<i>Listeria sp.</i>	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g
Coagulase positive <i>Staph.</i>	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g
<i>E. sakazaki</i> <sup>1</sup>	<0.003/g <sup>1</sup>	<0.003/g	<0.003/g	<0.003/g	<0.003/g	<0.003/g
<i>B. cereus</i> (CFU/g)	<20/g	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g
<i>C. perfringens</i>	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g
Yeast (CFU/g)	<10	<10	<10	<10	<10	<10
Mold (CFU/g)	<10	<10	<10	<10	<10	<10

<sup>1</sup>Negative indicates that 30 x 10 gram samples were analyzed by ISO method 22964.

000039

**Table 3-6 Analyses of multiple lots of Immunel™ liquid colostrum low molecular weight whey protein fraction**

Parameters	Written Specifications	Lot Number: 12480309  Date Manufactured: 12/17/2009	Lot Number: 8958  Date Manufactured: 12/17/2009	Lot Number: 8959  Date Manufactured: 12/18/2009	Lot Number: 12480409  Date Manufactured: 12/22/2009	Mean of 4 Lots
<b>Chemical</b>						
Moisture (%)	≥80.0	90.84	92.15	92.15	90.84	91.50
Fat (%)	≤1.0	0.25	0.10	0.10	0.25	0.35
Ash (%)	≤1.0	0.2	0.3	0.3	0.2	0.25
Protein (%)	≥2.0	2.05	2.10	2.10	2.05	2.08
Carbohydrate (%)	≤6.0	5.92	5.65	5.65	5.92	5.79
Proline-rich Polypeptide (PRP) (%)	≥1.0	2.00	2.10	2.10	2.00	2.05
Sialic acid (mg/100 mL)	≥1	2	3	3	2	2.5
Neutral Oligosaccharides (mg/100 mL)	≥1	2	2	3	2	2
<b>Microbiological</b>						
Total Plate Count (CFU/mL)	<1,000	<1	1	<1	1	1
<i>Escherichia coli</i>	Negative/mL	Negative/mL	Negative/mL	Negative/mL	Negative/mL	Negative/mL
Coliform organisms	Negative/mL	Negative/mL	Negative/mL	Negative/mL	Negative/mL	Negative/mL
<i>Salmonella sp.</i> 25 mL	Negative/25 mL	Negative/ 25 mL	Negative/ 25 mL	Negative/ 25 mL	Negative/ 25 mL	Negative/ 25 mL
<i>Listeria sp.</i>	Negative/25 mL	Negative/ 25 mL	Negative/ 25 mL	Negative/ 25 mL	Negative/ 25 mL	Negative/ 25 mL
Coagulase positive <i>Staph.</i>	Negative/mL	Negative/mL	Negative/mL	Negative/mL	Negative/mL	Negative/mL
Yeast (CFU/mL)	<10	<1	<1	<1	<1	<1
Mold (CFU/mL)	<10	<1	<1	<1	<1	<1

000040

**Table 3-7 Analyses of multiple lots of Immunel™ powder colostral low molecular weight whey protein fraction**

Parameters	Written Specifications	Lot Number: 1649-10	Lot Number: 1696-9	Lot Number: 1697-9	Lot Number: 1700-9	Mean of 4 Lots
		Date Manufactured: 12/23/2009	Date Manufactured: 7/13/2010	Date Manufactured: 7/28/2010	Date Manufactured: 6/8/2010	
<b>Chemical</b>						
Moisture (%)	≤6.0	5.0	5.0	4.5	4.0	4.6
Fat (%)	≤1.0	0.05	0.05	0.1	0.1	0.075
Ash (%)	≤1.0	0.1	0.1	0.2	0.1	0.125
Protein (%)	≥1.0	1.2	1.1	1.3	1.1	1.2
Carbohydrate (%)	≥80.0	93.8	93.7	93.9	94.7	94.03
Proline-rich Polypeptide (PRP) (%)	≥0.003	0.004	0.005	0.004	0.003	0.004
Sialic acid (mg/100 g)	≥50	150	130	130	150	140
Neutral Oligosaccharides (mg/100 g)	≥10	70	60	60	70	70
<b>Microbiological</b>						
Total Plate Count (CFU/g)	< 1,000	< 100	100	< 100	100	100
<i>Escherichia coli</i>	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g
Coliform organisms	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g
<i>Salmonella sp.</i> 25 grams	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g
<i>Listeria sp.</i>	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g
Coagulase positive <i>Staph.</i>	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g	Negative/g
Yeast (CFU/g)	< 10	< 10	< 10	< 10	< 10	< 10
Mold (CFU/g)	< 10	< 10	< 10	< 10	< 10	< 10

000041

## 4.0 INTENDED USE AND PROJECTED EXPOSURE

### 4.1 Intended Use

Tegricel™ colostrum whey protein concentrate and Immunel™ colostrum low molecular weight whey protein fraction are intended to be used in foods for the general human population as multiple-use direct additives under the conditions of current Good Manufacturing Practice. Uses do not include meat or poultry products.

In accordance with 21 CFR §170.3 (o), the physical or technical functional effects for which Tegricel™ and Immunel™ may be used include:

**Antimicrobial agents:** Substances used to preserve food by preventing the growth of microorganisms and subsequent spoilage, including fungistats, mold and rope spore inhibitors, and the effects listed by the National Academy of Sciences/National Research Council under “preservatives.”

**Antioxidants:** Substances used to preserve food by retarding deterioration, rancidity, or discoloration due to oxidation.

**Formulation aids:** Substances used to promote or produce a desired physical state or texture in food, including carriers, binders, fillers, plasticizers, film-formers, and tableting aids, *etc.*

**Nutrient supplements:** Substances which are necessary for the body’s nutritional and metabolic processes. Bovine colostrum contains many trophic molecules to assure the health and maturation of the newborn calf. Table 4-2 shows some of the components of bovine colostrum and their biological activity. Tegricel™ colostrum whey protein concentrate and Immunel™ colostrum low molecular weight whey protein fraction are intended to be used in foods for the general human population as substances with proteins and other factors that provide general nutritive value.

**Processing aids:** Substances used as manufacturing aids to enhance the appeal or utility of a food or food component, including clarifying agents, clouding agents, catalysts, flocculants, filter aids, and crystallization inhibitors, *etc.*

**Surface-active agents:** substances used to modify surface properties of liquid food components for a variety of effects, other than emulsifiers, but including solubilizing agents, dispersants, detergents, wetting agents, rehydration enhancers, whipping agents, foaming agents, and defoaming agents, *etc.*

**Synergists:** Substances used to act or react with another food ingredient to produce a total effect different or greater than the sum of the effects produced by the individual ingredients.

The levels of use of Tegrice<sup>TM</sup> colostr<sup>TM</sup> whey protein concentrate and Immunel<sup>TM</sup> colostr<sup>TM</sup> low molecular weight whey protein fraction in food will vary. Sterling Technology estimates that the amount of Tegrice<sup>TM</sup> that is incorporated into a particular food category will not exceed 1 gram per 8-ounce serving; Immunel<sup>TM</sup> is expected to be used at levels not exceeding 100 milligrams per 8-ounce serving. The ingredients are intended for use in many food categories, some examples of which are shown in Table 4-1. However, it is important to also consider the following factors, which may limit the use of Tegrice<sup>TM</sup> and Immunel<sup>TM</sup>:

- Bovine colostrum is reported to have a bitter taste that must be masked with other flavorings (Solomons, 2002). The same may be true of Tegrice<sup>TM</sup> and/or Immunel<sup>TM</sup>.
- Whey proteins in general are susceptible to heat denaturation. As such, incorporation of Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> into foods that are subjected to sustained high heat (*e.g.*, cooking, baking) would be unadvisable.
- Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> cost between \$400 to \$1000 USD per kilogram. It is therefore expected that, in seeking the most economical food applications, food manufacturers will be very selective about the types of foods into which Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> are incorporated and the amounts used.

**Table 4-1 Examples of foods in which Tegrice<sup>TM</sup> or Immunel<sup>TM</sup> may be used**

Food Category	Amount per 8-ounce serving	
	Tegrice <sup>TM</sup>	Immunel <sup>TM</sup>
Baked goods, baking mixes*	1 g	100 mg
Beverages and beverage bases, non-alcoholic		
Breakfast Cereals		
Dairy product substitutes		
Fruits and fruit juices		
Frozen dairy desserts and mixes		
Fruit and water ices		
Gelatins, puddings and fillings		
Hard candy		
Milk products		
Processed fruits and fruit juices		
Processed vegetables and vegetable juices		
Snack foods		
Soft Candy		

\*Use would be limited to food subcategories that do not require cooking or heating, such as grain-based bars.

**Table 4-2 Components of bovine colostrum and associated physiological activity**

Component	Antiviral	Antifungal	Antibacterial	Enhance Phago-cytosis	Macrophage Activation	Immune Stimulator	Immune Modulator	Anti-body Production	T- and B-Cell Growth	T-Cell Activation	Tissue Repair
Growth Factors						♦	♦				♦
Immunoglobulins (IgGs)	♦	♦	♦	♦	♦	♦	♦				
Interferon- $\gamma$	♦	♦	♦		♦	♦					
Interleukin-1					♦					♦	
Interleukin-2						♦	♦	♦	♦		
Interleukin-6	♦	♦	♦			♦	♦	♦	♦		
Lactoferrin	♦	♦	♦				♦				
Lactoperoxidase	♦	♦	♦								
Lysozyme	♦	♦	♦								
Proline-Rich-Polypeptide						♦	♦				

Source: Sterling Technology Technical Bulletin (2009).

000044

## 4.2 Exposure Estimates

Sterling, Inc. is providing a realistic estimate of exposure to Tegrice<sup>TM</sup> colostr<sup>al</sup> whey protein concentrate and Immunel<sup>TM</sup> colostr<sup>al</sup> low molecular weight whey protein fraction. The FDA's guidance document entitled *Estimating Exposure to Direct Food Additives and Chemical Contaminants in the Diet*, USDA's *Continuing Survey of Food Intakes by Individuals* (CSFII, 1996), and recent market surveys were used as references to estimate the realistic exposure to Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> produced by Sterling, Inc. (Enns, *et al.*, 1997).

In order to estimate the probable human exposure to Tegrice<sup>TM</sup> colostr<sup>al</sup> whey protein concentrate and Immunel<sup>TM</sup> colostr<sup>al</sup> low molecular weight whey protein fraction on a continual daily basis, Sterling, Inc. has relied upon examples of commercial formulations, examples of the potential for uses of these ingredients based on recent published studies, the patent literature, and the results of its own food technology research. Exposure to Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> was estimated in accordance with the agency's guidance document, cited above, "*Estimating Exposure to Direct Food Additives and Chemical Contaminants in the Diet*" [FDA, September 1995]. Use of the material was estimated for the 94 NAS food categories, on a working Table entitled *GRAS Food Additive Categories and Sub-Categories* (data not shown). Use levels for the final food products were then estimated across food subcategories to yield averages for the major food groups. Tables 4-4a and 4-4b list the 43 food categories in 21 CFR §170.3 (n) in which Tegrice<sup>TM</sup> and Immunel<sup>TM</sup>, respectively, may be used; since these sources do not provide any food intake data, the average use levels for the food subcategories shown on Tables 4-4a and 4-4b were then re-averaged, if necessary, so that they were consistent with the food categories listed in USDA's *Continuing Survey of Food Intakes by Individuals* (CSFII) (Enns, *et al.*, 1997). Tables 4-5a and 4-5b list CSFII food categories and subcategories, mean food intakes, and the intake levels for Tegrice<sup>TM</sup> and Immunel<sup>TM</sup>, respectively. The data provided are for adults 20 years and over (eaters only).

Since the CSFII intake data are statistically valid, use levels for Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> may be multiplied by the mean intakes indicated in the CSFII database to yield an estimated exposure to the ingredients from a given food category. The resulting totals for each food category were then summed to yield a total mean daily intake.

Note that zeros were entered for certain food categories where Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> are unlikely to be used (*e.g.*, in heated products, such as baked goods). The total daily mean intakes from Tables 4-5a and 4-5b were doubled to estimate the 90<sup>th</sup> percentile of exposure (in accordance with the guidance document).

The results of these calculations and exposure estimates for Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> are summarized at the bottom of Tables 4-5a and 4-5b. For Tegrice<sup>TM</sup>, the mean daily and 90<sup>th</sup> percentile intake values were estimated to be 1.27 g and 2.55 g, respectively. The mean and 90<sup>th</sup> percentile daily intake estimates for Immunel<sup>TM</sup> were 0.32 g and 0.64 g, respectively. The

resulting intakes of colostral proteins and immunoglobulins, summarized in Table 4-3, are considerably lower than amounts safely administered to human subjects during the course of clinical studies.

**Table 4-3 Estimated intakes of colostral elements based on the use of TegriceI™ colostral whey protein concentrate and ImmuneI™ colostral low molecular weight whey protein fraction in foods**

	TegriceI™		ImmuneI™	
	Mean	90 <sup>th</sup> Percentile	Mean	90 <sup>th</sup> Percentile
<b>Total exposure from food (g)</b>	1.27	2.55	0.32	0.64
<b>Protein fraction<sup>1</sup> (g)</b> (assumes 70% protein in TegriceI™)	0.89	1.78		
<b>Low molecular weight protein fraction (g)</b> (assumes 1 to 2% low molecular weight protein in ImmuneI™)			0.0032 to 0.0064	0.0064 to 0.0128
<b>Immunoglobulin fraction<sup>1</sup> (g)</b> (assumes 25% immunoglobulins in TegriceI™)	0.32	0.64		

<sup>1</sup>Treatment regimens in studies reviewed by Marnila and Korhonen (2011) included oral administration of 60 g colostral protein to adults for 8 weeks, and of bovine IgG at up to 0.5 g/kg bw/day to infants and children (equivalent to 30 g/day in a 60-kg person).

While the use level assigned to each food subcategory was considered realistic, this exposure estimate remains conservative because 100 percent market penetration was assumed, and TegriceI™ colostral whey protein concentrate and ImmuneI™ colostral low molecular weight whey protein fraction were assumed to be included in all products in a given subcategory. Additionally, the values presented below assumes that 100 percent of consumers are “eaters” of TegriceI™- and ImmuneI™-containing products within a given food category.

In reality, TegriceI™ and ImmuneI™ are expected to be used in only certain products within a given subcategory. Further, use within a subcategory will be limited by economics and physicochemical considerations. Market development in the US is likely to be directed towards the nutritional and functional properties, and certain functional properties may not be appropriate for a given consumer product.

The correlation between the major food categories derived from the USDA food survey, and those listed in § 170.3 (n) is shown in Tables 4-5a and 4-5b.

**Table 4-4a Use of Tegrice<sup>TM</sup> colostr<sup>TM</sup> whey protein concentrate in food categories listed by the US FDA in 21 CFR §170.3 (n)**

	Food Categories	Realistic Use in the US Market per 8 ounce serving
		Tegrice <sup>TM</sup>
01	Baked Goods, Baking Mixes	1 g
02	Beverages alcoholic	0
03	Beverages and beverage bases, non-alcoholic	1 g
04	Breakfast Cereals	1 g
05	Cheeses	0
06	Chewing Gum	0
07	Coffee and tea	0
08	Condiments and relishes	0
09	Confections and frostings	0
10	Dairy product analogs	1 g
11	Egg Products	0
12	Fats and oils	0
13	Fish Products	0
14	Fresh eggs	0
15	Fresh fish	0
16	Fresh fruits and fruit juices	1 g
17	Fresh Meats	0
18	Fresh poultry	0
19	Fresh vegetables	0
20	Frozen dairy desserts and mixes	1 g
21	Fruit and water ices	1 g
22	Gelatins, puddings and fillings	1 g
23	Grain products and pastas	0
24	Gravies and Sauces	0
25	Hard candy	1 g
26	Herbs, seeds, spices, seasonings, blends	0
27	Jams and jellies, home prepared	0
28	Jams and jellies commercial	0
29	Meat products	0
30	Milk, whole and skim	0
31	Milk products	1 g
32	Nuts and Nut products	0
33	Plant protein products	0
34	Poultry products	0
35	Processed fruits and fruit juices	1 g
36	Processed vegetables and vegetable juices	1 g
37	Snack foods	1 g
38	Soft Candy	1 g
39	Soups, home prepared	0
40	Soups and soup mixes	1 g
41	Sugar, white granulated	0
42	Sugar substitutes	0
43	Sweet Sauces, toppings, and syrups	0

**Table 4-4b Use of Immune<sup>TM</sup> colostral low molecular weight whey protein fraction in food categories listed by the US FDA in 21 CFR §170.3 (n)**

	Food Categories	Realistic Use in the US Market per 8-ounce serving
		Immune <sup>TM</sup>
01	Baked Goods, Baking Mixes	0
02	Beverages alcoholic	0
03	Beverages and beverage bases, non-alcoholic	100 mg
04	Breakfast Cereals	100 mg
05	Cheeses	0
06	Chewing Gum	100 mg
07	Coffee and tea	100 mg
08	Condiments and relishes	0
09	Confections and frostings	0
10	Dairy product analogs	100 mg
11	Egg Products	0
12	Fats and oils	0
13	Fish Products	0
14	Fresh eggs	0
15	Fresh fish	0
16	Fresh fruits and fruit juices	100 mg
17	Fresh Meats	0
18	Fresh poultry	0
19	Fresh vegetables	0
20	Frozen dairy desserts and mixes	100 mg
21	Fruit and water ices	100 mg
22	Gelatins, puddings and fillings	100 mg
23	Grain products and pastas	0
24	Gravies and Sauces	0
25	Hard candy	100 mg
26	Herbs, seeds, spices, seasonings, blends	0
27	Jams and jellies, home prepared	0
28	Jams and jellies commercial	0
29	Meat products	0
30	Milk, whole and skim	0
31	Milk products	100 mg
32	Nuts and Nut products	0
33	Plant protein products	0
34	Poultry products	0
35	Processed fruits and fruit juices	100 mg
36	Processed vegetables and vegetable juices	100 mg
37	Snack foods	100 mg
38	Soft Candy	100 mg
39	Soups, home prepared	0
40	Soups and soup mixes	0
41	Sugar, white granulated	0
42	Sugar substitutes	0
43	Sweet Sauces, toppings, and syrups	0

**Table 4-5a Estimated Intake of Tegrice<sup>TM</sup> colostr<sup>al</sup> whey protein concentrate in selected food categories**

Food Coding Scheme- USDA/ARS/BHNRC Food Surveys Research Group	Food Category	Tegrice <sup>TM</sup> Use Level (g/8-oz. serving)	Food Intake (g/d)	Tegrice <sup>TM</sup> Intake (g/day)	CSFII
	<b>Baked goods, baking mixes</b>				
51	Yeast Breads and Rolls		50	0	1996
52, 55	Quick breads, pancakes, etc.		20	0	1996
53	Cakes, cookies, pastries, pies <sup>1</sup>	1	38	0.1696	1996
58	Mixtures mainly grain		107	0	1996
	<b>Breakfast cereals</b>				
571-574, 578	Ready-to-eat cereals	1	17	0.075	1996
	<b>Grain products and pastas</b>				
562	Rice		19	0	1996
561	Pasta		21	0	1996
54	Snack foods (crackers, chips)	1	12	0.053	1996
	<b>Total Vegetables</b>		132		1996
	Fresh vegetables <sup>2</sup>		45	0	1996
	Processed vegetables, juices	1	14	0.0618	1996
72	Dark Green Vegetables		13	0	
	<b>Total Fruits</b>				1996
612	Citrus juices <sup>3</sup>	1	17.7	0.0783	1996
621	Dried fruits	0	0	0	1996
641,642	Non-citrus juices and nectars	1	26	0.1150	1996
	Fruits and mixtures	0	0	0	1996
	<b>Milk products</b>				
114	Yogurt	1	8	0.0354	1996
131,132, 133, 134	Milk desserts <sup>4</sup>	1	24	0.1062	1996
140-147	Cheese		8	0	1996
116, 118	Milk-Based Beverages <sup>5</sup>	1	34	0.1054	1966
	<b>Meat Products</b>				
252	Sausages, processed meats		21	0	
	Fresh Meat		34	0	
	Poultry		20	0	
	Fish		11	0	
	<b>Eggs</b>				
321,323,324, 33, 34	Egg Products <sup>6</sup>		9	0	
	<b>Legumes</b>				
	Legumes <sup>7</sup>		1.8	0	
	<b>Nuts and Nut Products</b>				
	Nuts and Nut Products		3	0	
	<b>Fats and Oils</b>				
832	Salad dressings		8	0	
	<b>Total sugars and sweets</b>				
917,918	Candy (Soft and Hard) <sup>8</sup>	1	7	0.031	
911-916	Other Sugar Products <sup>9</sup>		15	0	
	<b>Beverages Non-Alcoholic</b>				
	Coffee	0	254	0	
923	Teas	0	128	0	
925	Regular Fruit Drinks and Ades	1	82	0.363	

**Table 4-5a Estimated Intake of Tegrice1™ colostrai whey protein concentrate in selected food categories (Cont'd)**

<b>Food Coding Scheme- USDA/ARS/BHNRC Food Surveys Research Group</b>	<b>Food Category</b>	<b>Tegrice1™ Use Level (g/8-oz. serving)</b>	<b>Food Intake (g/d)</b>	<b>Tegrice1™ Intake (g/day)</b>	<b>CSFII</b>
	<b>Beverages Non-Alcoholic</b>				
9252-9255, 9256	Low Cal. Fruit Drinks and Ades	1	18	0.0796	
924	Regular Carbonated Soft Drinks	0	267	0	
924	Low Cal. Carbonated Drinks	0	74	0	
<b>Total Mean Intake (grams)</b>				<b>1.2733</b>	
<b>90th Percentile</b>				<b>2.5466</b>	

<sup>1</sup>Includes dietetic bars

<sup>2</sup>Includes tomatoes and lettuce products

<sup>3</sup>Includes citrus juices with pulp

<sup>4</sup>Includes low-fat ice creams etc.

<sup>5</sup>Includes only skim milk products

<sup>6</sup>Includes processed egg products

<sup>7</sup>Includes only tofu and similar products

<sup>8</sup>Includes chewing gum

<sup>9</sup>Includes jams, jellies, etc.

**Table 4-5b Estimated Intake of Immunel™ colostral low molecular weight whey protein fraction in selected food categories**

Food Coding Scheme- USDA/ARS/BHNRC Food Surveys Research Group	Food Category	Immunel™ Use Level (g/8-oz. serving)	Food Intake (g/d)	Immunel™ Intake (g/day)	CSFII
	<b>Baked goods, baking mixes</b>				
51	Yeast Breads and Rolls		50	0	1996
52, 55	Quick breads, pancakes, etc.		20	0	1996
53	Cakes, cookies, pastries, pies <sup>1</sup>		38	0	1996
58	Mixtures mainly grain		107	0	1996
	<b>Breakfast cereals</b>				
571 - 574, 578	Ready-to-eat cereals	0.010	17	0.0075	1996
	<b>Grain products and pastas</b>				
562	Rice		19	0	1996
561	Pasta		21	0	1996
54	Snack foods (crackers, chips)	0.010	12	0.0053	1996
	<b>Total Vegetables</b>		132		1996
	Fresh vegetables <sup>2</sup>		45	0	1996
	Processed vegetables, juices	0.010	14	0.00618	1996
72	Dark Green Vegetables		13	0	
	<b>Total Fruits</b>				1996
612	Citrus juices <sup>3</sup>	0.010	17.7	0.00783	1996
621	Dried fruits	0	0	0	1996
641,642	Non-citrus juices and nectars	0.010	26	0.01150	1996
	Fruits and mixtures	0	0	0	1996
	<b>Milk products</b>				
114	Yogurt	0.010	8	0.00354	1996
131,132, 133, 134	Milk desserts <sup>4</sup>	0.010	24	0.01062	1996
140-147	Cheese		8	0	1996
116, 118	Milk-Based Beverages <sup>5</sup>	0.010	34	0.01054	1966
	<b>Meat Products</b>				
252	Sausages, processed meats		21	0	
	Fresh Meat		34	0	
	Poultry		20	0	
	Fish		11	0	
	<b>Eggs</b>				
321,323,324, 33,34	Egg Products <sup>6</sup>		9	0	
	<b>Legumes</b>				
	Legumes <sup>7</sup>		1.8	0	
	<b>Nuts and Nut Products</b>				
	Nuts and Nut Products		3	0	
	<b>Fats and Oils</b>				
832	Salad dressings		8	0	
	<b>Total sugars and sweets</b>				
917,918	Candy (Soft and Hard) <sup>8</sup>	0.010	7	0.0031	
911 - 916	Other Sugar Products <sup>9</sup>		15	0	
	<b>Beverages Non-Alcoholic</b>				
	Coffee	0	254	0	
923	Teas	0.010	128	0.05664	
925	Regular Fruit Drinks and Ades	0.010	82	0.0363	

**Table 4-5b Estimated Intake of Immunel™ colostr whey nonprotein fraction in selected food categories (Cont'd)**

<b>Food Coding Scheme- USDA/ARS/BHNRC Food Surveys Research Group</b>	<b>Food Category</b>	<b>Immunel ™ Use Level (g/8-oz. serving)</b>	<b>Food Intake (g/d)</b>	<b>Immunel ™ Intake (g/day)</b>	<b>CSFII</b>
	<b>Beverages Non-Alcoholic</b>				
9252-9255, 9256	Low Cal. Fruit Drinks and Ades	0.010	18	0.00796	
924	Regular Carbonated Soft Drinks	0.010	267	0.118	
924	Low Cal. Carbonated Drinks	0.010	74	0.03274	
	<b>Total Mean Intake (grams)</b>			<b>0.31775</b>	
	<b>90th Percentile</b>			<b>0.6355</b>	

<sup>1</sup>Includes dietetic bars

<sup>2</sup>Includes tomatoes and lettuce products

<sup>3</sup>Includes citrus juices with pulp

<sup>4</sup>Includes low-fat ice creams etc.

<sup>5</sup>Includes only skim milk products

<sup>6</sup>Includes processed egg products

<sup>7</sup>Includes only tofu and similar products

<sup>8</sup>Includes chewing gum

<sup>9</sup>Includes jams, jellies, etc.

**Table 4-6a Tegricel™ colostrated whey protein concentrate--USDA major food categories and corresponding categories from 21 CFR 170.3 (n)**

USDA Food Category <sup>1</sup>	Categories listed in 170.3 (n) <sup>2</sup>	Total exposure estimated for major food categories
Total Vegetables	36	0.0618 g
Fruits and Fruit Preparations	16, 35	0.1933 g
Milk Products	31	0.2470 g
Beverages Non-Alcoholic	92	0.4426 g
Ready -to-Eat Cereals	571-574, 578	0.075 g
Snack Foods	54	0.053 g
Candy (Soft and Hard)	917-918	0.031 g

<sup>1</sup>Major food categories are those used in USDA's Continuing Survey of Food Intake by Individuals (Enns, *et al.*, 1997).

<sup>2</sup>Column 2 contains the number assigned to the various food categories as listed in 21 CFR § 170.3 (n), which are contained within those reported by Enns, *et al.* (1997).

**Table 4-6b Immunel™ colostrated low molecular weight whey protein fraction--USDA major food categories and corresponding categories from 21 CFR 170.3 (n)**

USDA Food Category <sup>1</sup>	Categories listed in 170.3 (n) <sup>2</sup>	Total exposure estimated for major food categories
Total Vegetables	36	0.00618 g
Fruits and Fruit Preparations	16, 35	0.01933 g
Milk Products	31	0.01514 g
Beverages Non-Alcoholic	92	0.2516 g
Ready -to-Eat Cereals	571-574, 578	0.0075 g
Snack Foods	54	0.0053 g
Candy (Soft and Hard)	917-918	0.0031 g

<sup>1</sup>Major food categories are those used in USDA's Continuing Survey of Food Intake by Individuals (Enns, *et al.*, 1997).

<sup>2</sup>Column 2 contains the number assigned to the various food categories as listed in 21 CFR § 170.3 (n), which are contained within those reported by Enns, *et al.* (1997).

## 5.0 SAFETY

### 5.1 Overview

Colostrum from ruminating mammals such as cows, goats, and sheep is likely to have been present in the human diet and consumed in the same way as milk for thousands of years, starting with domestication of ruminants some 40,000 years ago (Cordain, 1999). Some ethnic groups and persons in Eastern Europe and India continue to consume colostrum regularly (Solomons, 2002). In industrialized countries, however, the amount of colostrum present in the human diet as a by-product of bovine milk<sup>1</sup> (and products thereof) might be lower due to differences in livestock breeding practices, which often involve collection (and storage) of colostrum specifically for the purposes of hand-feeding offspring that have been separated from the mother. Consequently, whole colostrum *per se* has not been historically used in foods in its concentrated form, but rather as a by-product of milk (Yalcin, 2006 and Krissansen, 2007). Likewise, Sterling Technology's bovine colostrum isolates Tegrice<sup>TM</sup> and Immune<sup>TM</sup> have not been consumed as such.

Sterling Technology has not performed any nonclinical safety tests of Tegrice<sup>TM</sup> and Immune<sup>TM</sup>, relying on the available historical and scientific evidence supporting the safety of the source material, bovine colostrum, and other substances derived from mature cow's milk. A representative subset of these data is discussed subsequently.

### 5.2 Nonclinical Safety

Davis *et al.* (2007) examined the safety of colostrum from grass-fed cows (NZMP Colostrum Powder Low Protein, Fonterra Cooperative Group Ltd., New Zealand) when administered in the diet to weanling (4- to 6-week-old) Lewis rats for 90 days. The study was conducted at the Wellington Medical School, New Zealand, using OECD<sup>2</sup> guidelines. Animals were assigned to one of 3 groups (1 control, 2 test) consisting of 10 rats per sex. All animals received normal rat chow (10% skim milk powder) and drinking water *ad libitum*. However, the test groups received either 3% or 10% of their daily food intake (w/w) as bovine colostrum for 90 days. Food intake was monitored every two days and animals were observed at least 3 times each week; body weights were measured weekly. At the end of the study, animals were euthanized with carbon dioxide. Blood samples were collected for serum chemistry (carbohydrate metabolism, liver function, kidney function), including insulin-like growth factor (IGF-1), and hematological analyses. All animals underwent examination for gross changes, and, in accordance with OECD

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<sup>1</sup> Per 21 CFR § 131.110, milk is described as "...the lacteal secretion, practically free from colostrum, obtained by the complete milking of one or more healthy cows..."

<sup>2</sup> OECD: Organization for Economic Cooperation and Development.

guideline 408, the following organs and tissues were processed for histological examination: brain, spinal cord, pituitary, thyroid, parathyroid, thymus, esophagus, salivary glands, stomach, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, and lungs, aorta, gonads, uterus, ovaries, female mammary gland, prostate, testes, epididymides, and urinary bladder. In addition, femurs, soleus and EDL muscles were collected and used for bone mineral density/content, bone biomechanics, and muscle nitrogen content.

Mean daily colostrum consumption among males was approximately 0.75 g/rat/day for the 3% group and 2.28 g/rat/day for the 10% group; among females, it was 0.51 g/rat/day and 1.52 g/rat/day for the 3% and 10% group, respectively. Colostrum supplementation produced no signs of toxicity or gross behavioral changes. There were no statistically-significant differences between colostrum-fed animals and the control group in body weight, food consumption, clinical signs, hematological parameters, or muscle nitrogen levels. Most serum chemistry parameters were likewise unaffected by colostrum supplementation; the only statistically-significant effects were lower cholesterol in rats receiving 10% colostrum ( $p < 0.025$ ), and higher (33%) triglyceride concentration in rats receiving 3% colostrum ( $p < 0.005$ ) but not those receiving 10% colostrum. No gross anatomical changes, skeletal variations, histopathological findings, or changes in bone-related parameters were observed as a result of colostrum supplementation. Serum IGF-1 levels were slightly, but significantly ( $p < 0.01$ ), lower among 3% males and higher ( $p < 0.02$ ) among 10% females; the absence of a dose-response relationship and other physiological/histological effects would suggest these findings are not of toxicological concern. The authors concluded that these and previous findings indicate that colostrum consumption would not be expected to be associated with any adverse effects in normal healthy subjects.

### **5.3 Clinical Safety**

No studies were identified in the published scientific literature that specifically evaluated the safety of bovine colostrum in humans. In some studies (see section 6.2), subjects receiving bovine colostrum experienced mild gastrointestinal discomfort.

### **5.4 At-risk Populations**

Individuals allergic to milk might have an allergic response to bovine colostrum. Lefranc-Millot *et al.* (1996), for example, observed IgE cross-reactivity with colostrum IgG in a serological study of individuals with milk allergy.

Because Tegrigel™ colostrum whey protein concentrate and Immunel™ colostrum low molecular weight whey protein fraction may contain proteins to which persons with milk sensitivity may react, the statement “Contains milk products” will be included on the product label.

## 6.0 SUPPORTING EVIDENCE

### 6.1 Experimental Animal Studies

Sterling Technology, Inc. sponsored a study to test the effects of colostrum-derived protein food supplements in gnotobiotic pigs. The study was conducted under South Dakota CITE Grant #219. In this study, the research team tested the ability of colostrum derivatives to protect animals from the consequences of infection with pathogenic organisms. The effects of colostrum whey fractions with molecular weights greater than 50 kDa and as well as low molecular weight fractions were examined. The studies indicated that both colostrum whey fractions were able to kill several bacterial pathogens of economic importance. Piglets supplemented with 10% bovine colostrum whey for 14 days were challenged with pathogenic *E. coli* on Day 2 of the experiment. All animals being supplemented were found to have better antibody response to antigens, and had a shorter, less severe course of the disease. The researchers also reported that calves supplemented with bovine colostrum whey had fewer problems with scouring, and as shown especially in veal calves, had improved uptake and utilization of iron and improved levels of hemoglobin and hematocrit. No adverse reactions were reported in the test animals (Hurley unpublished 1994 study).

### 6.2 Clinical Studies

There are numerous reports in the published literature of human studies examining the effects of bovine colostrum on a variety of conditions; there are also various review articles. Solomons (2002), for example, reviewed the evidence supporting an association between bovine colostrum intake and response against various pathogens. Kelly (2003), on the other hand, has reviewed the evidence supporting the beneficial effects of bovine colostrum supplementation in improving a variety of conditions such as athletic performance, body composition, and gastrointestinal disturbances. Table 6-1 provides an overview of a subset of studies reviewed by Kelly (2003). While these were not safety studies *per se*, they provide further supporting evidence of the overall safety of bovine colostrum and derivatives thereof (*i.e.*, Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immunel<sup>TM</sup> colostrum low molecular weight whey protein fraction). Adverse effects reported by some study subjects receiving bovine colostrum included mild gastrointestinal discomfort (Rump *et al.*, 1992; Plettenberg *et al.*, 1993).

Marnila and Korhonen (2011) reviewed various human studies evaluating the efficacy of bovine whey or colostrum preparations in treating various conditions (*i.e.*, diarrhea, hypercholesterolemia, upper respiratory tract infections). The treatment regimens included oral administration of bovine IgG at up to 0.5 g/kg bw/day to infants and children (equivalent to 30 g/day in a 60-kg person) for 6 months, and 60 g of colostrum protein administered orally to adults for 8 weeks. The authors indicate that clinical studies of hyperimmune milks show no adverse health effects from such products.

### **6.3 Marketed Products**

As previously mentioned, whole colostrum *per se* has not been historically used as a food or food ingredient in its concentrated form. However, an online search through [www.amazon.com](http://www.amazon.com) revealed that more than 100 products containing substances derived from bovine colostrum are presently marketed as nutritional supplements. Table 6-2 lists some of these products.

**Table 6-1 Subset of human studies reviewed by Kelly (2003) that examined the use of bovine colostrum for specific conditions**

<b>ENDPOINT EVALUATED</b>	<b>NUMBER OF SUBJECTS ENROLLED</b>	<b>TEST SUBSTANCE/DURATION</b>	<b>ADVERSE EFFECTS ASSOCIATED WITH BOVINE COLOSTRUM</b>	<b>REFERENCE</b>
Body composition and athletic performance	18 male & 17 female elite field hockey players	60 g whey protein concentrate (placebo) or bovine colostrum for 8 weeks	Not mentioned	Hofman <i>et al.</i> (2002)
Body composition	22 subjects (men & women) already performing resistance exercise training	20 g whey protein concentrate (placebo) or bovine colostrum powder for 8 weeks	Not mentioned	Antonio <i>et al.</i> (2001)
Athletic performance	13 female elite rowers (6 in test group)	60 g whey protein concentrate (placebo) or bovine colostrum for 9 weeks	Not mentioned	Brinkworth <i>et al.</i> (2002)
Serum and muscle IGF-I levels	9 male track athletes	25 mL bovine colostrum mixed with 100 mL milk whey or 125 mL bovine colostrum beverage for 8 days	Not mentioned	Mero <i>et al.</i> (1997)
Immunodeficiency-related diarrhea	29 subjects	10 g bovine colostrum concentrated for Ig for 10 days	None	Stephan <i>et al.</i> (1990)
Immunodeficiency-related diarrhea	25 subjects	10 g bovine colostrum concentrated for Ig for 10 days	Minor gastrointestinal complaints, including flatulence and nausea	Plettenberg <i>et al.</i> (1993)
Chronic diarrhea	37 subjects	10 g bovine colostrum for 10 days	Minor gastrointestinal complaints, including flatulence and nausea	Rump <i>et al.</i> (1992)
NSAID-induced GI dysfunction	7 males	125 mL bovine colostrum or whey (placebo) 3 times daily for 7 days	Not mentioned	Playford <i>et al.</i> (2001)
NSAID-induced GI dysfunction	15 subjects	125 mL bovine colostrum or whey (placebo) for 7 days	Not mentioned	Playford <i>et al.</i> (2001)
Surgery	40 persons undergoing stomach or pancreatic surgery	14 g bovine colostrum or placebo beverage beginning 3 days before surgery	None	Bolke <i>et al.</i> (2002a)
Surgery	60 persons undergoing coronary bypass surgery.	42 g bovine colostrum or placebo beginning 2 days prior to surgery	Not mentioned	Bolke <i>et al.</i> (2002b)

000058

**Table 6-2 List of marketed colostrum-derived nutritional supplement products**

<b>Manufacturer</b>	<b>Number of Products</b>
21st Century	1
4life	3
Allergy Research Group	8
BioActive NUTRIENTS	1
BIONUTRICALS	1
BulkColostrum.com	1
Childlife	3
DaVinci	3
Designs for Health	1
Doctors Choice, Naturally	1
Ecological Formulas	2
Epicuren	5
Flying Basset	1
Genceutic Naturals	1
Global Health Trax	1
Good'n Natural	1
Immulox	1
Immune Tree	4
Jarrow	3
Kal	14
KRK SUPPLEMENTS	2
Life Time	1
Naturade	3
Nature's Sunshine	2
New Life	3
Now Foods	11
Nutricology	2
Olympian Labs	3
ONUMMI 8	1
Ortho Molecular Products	2
PMG ALL NATURAL	1
PowerNutra	1
Progressive Labs	1
Proper Nutrition	5
Pure Source	1
Roex	3
Sanar Naturals	1
Sedona Labs	8
SeQuel	2
Source Naturals	6
Surthrival	2
Swanson Premium	1
Swanson Ultra	1
Symbiotics	58
Total Body Research Labs	5
TriMedica	5
Vitamin Shoppe	2

## 7.0 SUMMARY AND CONCLUSION

Sterling Technology, Inc. (Sterling Technology) has developed two products, marketed under the names Tegrice<sup>TM</sup> and Immune<sup>TM</sup>, that are derived from bovine whole colostrum whey through methods typically used in cheese-making, along with ultrafiltration to separate the whey proteins from the nonprotein constituents. Tegrice<sup>TM</sup> contains the majority of the proteins. Immune<sup>TM</sup> is a by-product of Tegrice<sup>TM</sup>, containing low molecular weight proteins and nonprotein components.

With assistance from an Expert Panel specifically convened for the purpose of reviewing information in the present document regarding safety, specifications, manufacturing, proposed uses, *etc.*, Sterling Technology has sought affirmation that the use of Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction is generally recognized as safe (GRAS) through scientific procedures, and exempt from the premarket approval requirements for food additives. Tegrice<sup>TM</sup> and Immune<sup>TM</sup> would be used in foods for the general human population at levels up to 1 g/serving and 100 mg/serving, respectively.

Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction are produced through conventional GMP food industry processes to meet rigid established specifications. To assess safety, Sterling Technology has relied on the available historical and scientific evidence supporting the safety of the source material, bovine colostrum, and other substances derived from mature cow's milk.

Colostrum from ruminating mammals such as cows, goats, and sheep is likely to have been present in the human diet and consumed in the same way as milk for thousands of years. In recent years, bovine colostrum has become a primary ingredient of hundreds of dietary supplements. In a nonclinical safety study, rats receiving 10% of their daily food intake (w/w) as bovine colostrum for 90 days did not exhibit any signs of toxicity. Adverse effects reported by human subjects receiving bovine colostrum concentrates during clinical studies have generally been limited to mild gastrointestinal discomfort. To address any potential issues in individuals allergic to milk, the statement "Contains milk products" will be included on the product label.

The available evidence suggests there is a consensus among qualified experts that the use of Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction as described entails a reasonable certainty of no harm and is GRAS as shown through scientific procedures.

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**APPENDIX 1: RESULTS OF HEAVY METALS ANALYSES OF BOVINE  
COLOSTRUM WHEY USED TO PRODUCE TEGRICEL™  
COLOSTRAL WHEY PROTEIN CONCENTRATE AND  
IMMUNEL™ COLOSTRAL WHEY NONPROTEIN  
FRACTION**



Report Number  
11-122-2183

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**REPORT OF ANALYSIS**

For: (17774) STERLING TECHNOLOGY  
(605)692-5552

Mail to: **STERLING TECHNOLOGY  
DEREK KJELDEN  
133 32ND AVE S  
BROOKINGS SD 57006-**

Date Reported: 05/02/11  
Date Received: 04/25/11

**SAMPLE ANALYSIS**

Lab number: 1840957

Analysis	Level Found	Units	Detection Limit	Method	Analyst-Date	Verified-Date
Sample ID: 0125811						
Mercury (total)	n.d.	ppm	0.02	COLD VAPOR	akj-05/02	kkh-05/02
Lead (total)	n.d.	ppm	0.10	ICP-MS	trh-05/02	kkh-05/02
Cadmium (total)	n.d.	ppm	0.05	ICP-MS	trh-05/02	kkh-05/02
Arsenic (total)	n.d.	ppm	0.50	ICP-MS	trh-05/02	kkh-05/02
Total Heavy Metals	n.d.	ppm	10.0	ICP/ICP-MS	akj-05/02	kkh-05/02
Melamine	n.d.	ppm	1	LC/MS/MS	mjh-04/27	jcp-04/27
Sample ID: 0125711						
Mercury (total)	n.d.	ppm	0.02	COLD VAPOR	akj-05/02	kkh-05/02
Lead (total)	n.d.	ppm	0.10	ICP-MS	trh-05/02	kkh-05/02
Cadmium (total)	n.d.	ppm	0.05	ICP-MS	trh-05/02	kkh-05/02
Arsenic (total)	n.d.	ppm	0.50	ICP-MS	trh-05/02	kkh-05/02
Total Heavy Metals	n.d.	ppm	10.0	ICP/ICP-MS	akj-05/02	kkh-05/02
Melamine	n.d.	ppm	1	LC/MS/MS	mjh-04/27	jcp-04/27

**Notes:**

n.d. - Not Detected.  
Total heavy metals are the sum of :Arsenic, lead, cadmium, tin, copper, silver, molybdenum, mercury, antimony, and bismuth.

For questions contact  
(b) (6)

Sue Ann Seitz  
Client Service Representative  
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000064



Report Number  
11-013-2212

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**REPORT OF ANALYSIS**

For: (17774) STERLING TECHNOLOGY  
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**Mail to:** STERLING TECHNOLOGY  
DEREK KJELDEN  
133 32ND AVE S  
BROOKINGS SD 57008-

Date Reported: 01/13/11  
Date Received: 01/07/11

**SAMPLE ANALYSIS**

Lab number: 1799425

Analysis	Level Found	Units	Detection Limit	Method	Analyst-Date	Verified-Date
Sample ID: 0123610						
Mercury (total)	n.d.	ppm	0.02	COLD VAPOR	mlm-01/12	kkh-01/12
Lead (total)	n.d.	ppm	0.10	ICP-MS	akj-01/12	kkh-01/12
Cadmium (total)	n.d.	ppm	0.05	ICP-MS	akj-01/12	kkh-01/12
Arsenic (total)	n.d.	ppm	0.50	ICP-MS	akj-01/12	kkh-01/12
Total Heavy Metals	n.d.	ppm	10.0	ICP/ICP-MS	akj-01/12	kkh-01/12
Melamine	n.d.	ppm	1	LC/MS/MS	mjh-01/13	jcp-01/13
Sample ID: 0123810						
Mercury (total)	n.d.	ppm	0.02	COLD VAPOR	mlm-01/12	kkh-01/12
Lead (total)	n.d.	ppm	0.10	ICP-MS	akj-01/12	kkh-01/12
Cadmium (total)	n.d.	ppm	0.05	ICP-MS	akj-01/12	kkh-01/12
Arsenic (total)	n.d.	ppm	0.50	ICP-MS	akj-01/12	kkh-01/12
Total Heavy Metals	n.d.	ppm	10.0	ICP/ICP-MS	akj-01/12	kkh-01/12
Melamine	n.d.	ppm	1	LC/MS/MS	mjh-01/13	jcp-01/13

**Notes:**

n.d. - Not Detected.  
Total heavy metals are the sum of :Arsenic, lead, cadmium, tin, copper, silver, molybdenum, mercury, antimony, and bismuth.

For questions contact

(b) (6)

Sue Ann Seitz  
Client Service Representative  
sueann@midwestlabs.com (402)829-9892

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000065

**Ramos-Valle, Moraima**

**From:** Katherine Vega Intertek [katherine.vega@intertek.com]  
**Sent:** Wednesday, May 16, 2012 1:09 PM  
**To:** Ramos-Valle, Moraima  
**Subject:** Sterling Technology GRAS Notice  
**Attachments:** 16May2012GRASRevisionsLetter.pdf; SterlingTechRevisedGRASClaim.pdf;  
 16May2012SterlingGRASpp52&58.pdf

Dear Ms. Ramos,

We are very grateful for your consideration and most helpful (and prompt!) feedback.

Attached are the following documents, some of which are intended to replace various pages of the submitted GRAS notice:

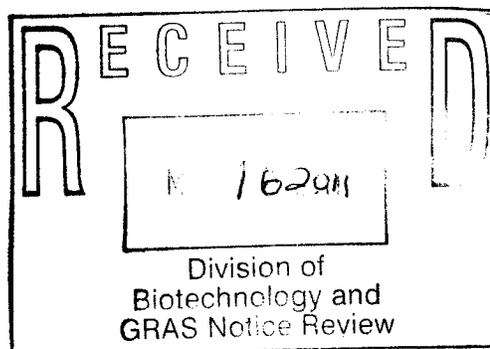
- (1) Signed letter from myself, acting as agent of Sterling Technology;
- (2) Revised GRAS Exemption Claim (pages 2 and 3); and
- (3) Revised pages 52 and 58.

I hope these changes eliminate any ambiguity regarding Sterling Technology's as the entity that made the GRAS determination based on *scientific procedures*. Please feel free to contact me with any questions or other feedback you might have.

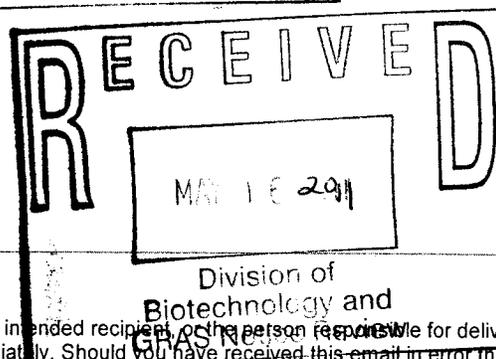
Best regards,

Katherine

Katherine Vega, Ph.D.  
 Scientific & Regulatory Consultant  
 Intertek Cantox  
 1011 US Highway 22, Suite 200  
 Bridgewater, NJ 08807  
 USA  
 Tel: 908-429-9202  
 Fax: 908-429-9260  
 Email: [kvega@cantox.com](mailto:kvega@cantox.com)



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5/16/2012

**Intertek**

**CANTOX**

HEALTH SCIENCES INTERNATIONAL  
1011 US Highway 22, Suite 200,  
Bridgewater, New Jersey 08807-2950  
Phone: 908-429-9202  
Fax: 908-429-9260

May 16, 2012

Moraima Ramos  
Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835

Dear Ms. Ramos:

Per our discussion yesterday, as authorized agent, I am submitting on behalf of Sterling Technology, Inc the enclosed revised pages (changes: p.2, 1<sup>st</sup> full paragraph; p.3, next to last paragraph; p.52, 2<sup>nd</sup> full paragraph; and p.58, 3<sup>rd</sup> paragraph) of the GRAS notice recently submitted for the use of two substances (to be marketed as Tegrice<sup>®</sup> and Immunel<sup>®</sup>) derived from bovine colostrum. The changes are intended to clarify that: (1) the GRAS determination was made by Sterling Technology; and (2) the basis of this determination was scientific principles, not history of use *per se*<sup>1</sup>.

Please feel free to contact me with any other questions you might have regarding this submission. My contact information is provided below. Thank you for your consideration.

Sincerely,

(b) (6)

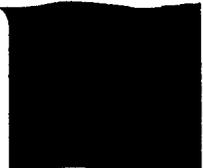
Katherine Vega, PhD  
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Bridgewater, NJ 08827  
E-mail: [Katherine.Vega@Intertek.com](mailto:Katherine.Vega@Intertek.com)  
Phone: (908) 429-9202  
FAX: (908) 429-9260

<sup>1</sup> Does not preclude consideration of the long-time presence of bovine milk and related substances in the human diet.

000067



133 32nd Avenue South  
 Brookings, SD 57006  
 800.522.3699  
 p: 605.692.5552  
 f: 605.692.9080  
 www.sterlingtechnology.com



**GRAS EXEMPTION CLAIM**

Sterling Technology, Inc. has determined that the use of two (2) substances derived from bovine colostrum, a whey protein concentrate (to be marketed as Tegrice<sup>TM</sup>) and a low molecular weight whey protein fraction (to be marketed as Immune<sup>TM</sup>), in foods as described herein is generally recognized as safe (GRAS) based on scientific procedures and is therefore exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act.

Sterling Technology Inc. Representative

Signature \_\_\_\_\_ (b) (6) \_\_\_\_\_

Date May 16, 2012

Dilip Patel, PhD  
 Director of R & D and Quality

<p><b>NAME AND ADDRESS OF NOTIFIER</b></p> <p>Sterling Technology, Inc.          133 32nd Ave.          Brookings, SD 57006</p>	<p>Contact Name: Dilip Patel, PhD          Phone: 605-692-5552          Fax: 605-692-9080          E-mail: dilip.patel@sterlingtechnology.com</p>
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**DESCRIPTION OF THE GRAS SUBSTANCE**

Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction are derived from bovine whole colostrum whey through methods typically used in cheese-making, along with ultrafiltration to separate the whey proteins from the nonprotein constituents. Tegrice<sup>TM</sup> contains the majority of the proteins. Immune<sup>TM</sup> is a by-product of Tegrice<sup>TM</sup> production, derived from the fraction (*i.e.*, filtrate) remaining after the colostrum whey is subjected to ultrafiltration; it contains primarily nonprotein components and small amounts of low-molecular weight (<500 Daltons) whey proteins. Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction are produced through conventional GMP food industry processes to meet rigid established specifications.

**INTENDED USE**

Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immune<sup>TM</sup> colostrum low molecular weight whey protein fraction are intended to be used in foods as direct additives in accordance with the physical or technical functional effects described in 21 CFR §170.3 (o) and under the conditions of current Good Manufacturing Practice (GMP). Uses do not include meat or poultry products.

## 5.0 SAFETY

### 5.1 Overview

Colostrum from ruminating mammals such as cows, goats, and sheep is likely to have been present in the human diet and consumed in the same way as milk for thousands of years, starting with domestication of ruminants some 40,000 years ago (Cordain, 1999). Some ethnic groups and persons in Eastern Europe and India continue to consume colostrum regularly (Solomons, 2002). In industrialized countries, however, the amount of colostrum present in the human diet as a by-product of bovine milk<sup>1</sup> (and products thereof) might be lower due to differences in livestock breeding practices, which often involve collection (and storage) of colostrum specifically for the purposes of hand-feeding offspring that have been separated from the mother. Consequently, whole colostrum *per se* has not been historically used in foods in its concentrated form, but rather as a by-product of milk (Yalcin, 2006 and Krissansen, 2007). Likewise, Sterling Technology's bovine colostrum isolates Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> have not been consumed as such.

Sterling Technology has not performed any nonclinical safety tests of Tegrice<sup>TM</sup> and Immunel<sup>TM</sup>, relying on the available evidence supporting the safety of the source material, bovine colostrum, and other substances derived from mature cow's milk. A representative subset of these data is discussed subsequently.

### 5.2 Nonclinical Safety

Davis *et al.* (2007) examined the safety of colostrum from grass-fed cows (NZMP Colostrum Powder Low Protein, Fonterra Cooperative Group Ltd., New Zealand) when administered in the diet to weanling (4- to 6-week-old) Lewis rats for 90 days. The study was conducted at the Wellington Medical School, New Zealand, using OECD<sup>2</sup> guidelines. Animals were assigned to one of 3 groups (1 control, 2 test) consisting of 10 rats per sex. All animals received normal rat chow (10% skim milk powder) and drinking water *ad libitum*. However, the test groups received either 3% or 10% of their daily food intake (w/w) as bovine colostrum for 90 days. Food intake was monitored every two days and animals were observed at least 3 times each week; body weights were measured weekly. At the end of the study, animals were euthanized with carbon dioxide. Blood samples were collected for serum chemistry (carbohydrate metabolism, liver function, kidney function), including insulin-like growth factor (IGF-1), and hematological analyses. All animals underwent examination for gross changes, and, in accordance with OECD

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<sup>1</sup> Per 21 CFR § 131.110, milk is described as "...the lacteal secretion, practically free from colostrum, obtained by the complete milking of one or more healthy cows..."

<sup>2</sup> OECD: Organization for Economic Cooperation and Development.

## 7.0 SUMMARY AND CONCLUSION

Sterling Technology, Inc. (Sterling Technology) has developed two products, marketed under the names Tegrice<sup>TM</sup> and Immunel<sup>TM</sup>, that are derived from bovine whole colostrum whey through methods typically used in cheese-making, along with ultrafiltration to separate the whey proteins from the nonprotein constituents. Tegrice<sup>TM</sup> contains the majority of the proteins. Immunel<sup>TM</sup> is a by-product of Tegrice<sup>TM</sup>, containing low molecular weight proteins and nonprotein components.

With assistance from an Expert Panel specifically convened for the purpose of reviewing information in the present document regarding safety, specifications, manufacturing, proposed uses, *etc.*, Sterling Technology has sought affirmation that the use of Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immunel<sup>TM</sup> colostrum low molecular weight whey protein fraction is generally recognized as safe (GRAS) through scientific procedures, and exempt from the premarket approval requirements for food additives. Tegrice<sup>TM</sup> and Immunel<sup>TM</sup> would be used in foods for the general human population at levels up to 1 g/serving and 100 mg/serving, respectively.

Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immunel<sup>TM</sup> colostrum low molecular weight whey protein fraction are produced through conventional GMP food industry processes to meet rigid established specifications. To assess safety, Sterling Technology has relied on the available evidence supporting the safety of the source material, bovine colostrum, and other substances derived from mature cow's milk.

Colostrum from ruminating mammals such as cows, goats, and sheep is likely to have been present in the human diet and consumed in the same way as milk for thousands of years. In recent years, bovine colostrum has become a primary ingredient of hundreds of dietary supplements. In a nonclinical safety study, rats receiving 10% of their daily food intake (w/w) as bovine colostrum for 90 days did not exhibit any signs of toxicity. Adverse effects reported by human subjects receiving bovine colostrum concentrates during clinical studies have generally been limited to mild gastrointestinal discomfort. To address any potential issues in individuals allergic to milk, the statement "Contains milk products" will be included on the product label.

The available evidence suggests there is a consensus among qualified experts that the use of Tegrice<sup>TM</sup> colostrum whey protein concentrate and Immunel<sup>TM</sup> colostrum low molecular weight whey protein fraction as described entails a reasonable certainty of no harm and is GRAS as shown through scientific procedures.

Submission End

000071