Vol 12

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

MAR 31 1998

Date

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

98 MAR 31 P3:13

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	Galacto-oligosaccharides
Firm:	EM Industries, Inc.
Date Received by FDA:	March 19, 1998
90-day Date:	May 31, 1998

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after May 31, 1998.

Robert J. Moore

Robert J. Moore, Ph.D.

95S-0316

RPT 24

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

MAR 20 1998

Ms. Anne Gochman
Manager, Regulatory Affairs
EM Industries, Inc.
7 Skyline Drive
Hawthorne, New York 10532

Dear Mr. Gochman:

This letter acknowledges receipt by the Food and Drug Administration (FDA) on March 19, 1998 of your notification, dated March 9, 1998, pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act), providing notice of your intent to introduce, or deliver for introduction into interstate commerce, the new dietary ingredient "galacto-oligosaccharides."

The date that the agency received your notification submitted under 21 U.S.C. 350b(a), March 19, 1998, is the filing date for the notification. In accordance with the requirements of 21 U.S.C. 350b, for 75 days after the filing date, EM Industries, Inc. shall not introduce, or deliver for introduction, into interstate commerce any dietary supplement that contains either of these new dietary ingredients, ademetionine and katsuobushi oligopeptide.

Please contact us if you have questions concerning this matter.

Sincerely,

Robert J. Moore, Ph.D.
Senior Regulatory Scientist
Division of Programs and Enforcement Policy
Office of Special Nutritionals

cc:
HFS-456 (file)
f/t:rjm:HFS-456:3/20/98:57852.ack:disc27

EM INDUSTRIES, INC.

7 Skyline Drive
Hawthorne, New York 10532
Phone: (914) 592-4660
Fax: (914) 592-9469

March 9, 1998

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

Re: New Dietary Ingredient Notification Pursuant to 21 CFR § 190.6 Requirement for Premarket Notification - for Galacto-oligosaccharide Powder and Liquid Supplements containing Galacto-oligosaccharides

Dear Sir or Madam:

I am writing on behalf of EM Industries, Inc. located at 7 Skyline Drive, Hawthorne, New York 10532 ("EM"). EM is the exclusive distributor of Elix'or products for Borculo Whey Products, the manufacturer. With this letter, we are providing notification pursuant to 21 CFR § 190.6 for a new dietary ingredient which EM will market after 75 days of your receipt of this notification.

This notice should be maintained as Confidential Business Information at least until 90 days after the filing date of the notification, pursuant to 21 CFR § 190.65 (e). This letter has 51 appendices in total. A complete index of these is also enclosed.

The food supplement which is the subject of this notification is natural galacto-oligosaccharides. This ingredient will be sold in a mixture under the brand name Elix'or, and will, hereafter, be referred to as Elix'or. The subject product of this notice may also be referred to as "OLIGO" in this letter and appendices. Other names have previously been employed for internal use. These other names may also have been used in the various appendices. Appendix 50 includes an explanation thereof. Elix'or is prepared from food quality lactose using an enzymatic process by which the lactose carbohydrate chain is extended in such a way that di,tri,tetra and penta saccharides, as well as others are formed. Elix'or can be sold as a syrup or powder.

Description of Product and Safety

The enzyme used to manufacture this food supplement is a beta galactosidase. The enzyme is obtained from a natural, non-pathogenic micro-organism. This micro-organism, Bacillus ciculans ATCC 4516, is considered safe for use in preparation of food supplements (appendix 47). The beta gluconases obtained from the micro-organism are also used in Europe and elsewhere in the production of beer, wine and soft drinks.

The galacto-oligosaccharides in Elix'or are completely soluble, indigestible sugars. They have an effect similar to that of dietary fibre. In this respect, the product is comparable to the many food supplement products already on the market that contain fructo-oligosaccharides.

The safety of the product Elix'or is demonstrated in Appendices 5-8,14,17,19,20,22,26,28,29. The safety of the enzyme and the end product Elix'or is demonstrated in Appendices 38 and 39-46. Appendix 38 reports of sub-chronic oral toxicity tests in

rats. The report concludes that when up to 20% Elix'or (referred to as "Oligo" in the study) was consumed in the food, there was no evidence of toxicity. This amount is equivalent to the intake of 14.5 g/kg body weight per day for male rats (16.4 g per kg body weight per day for female rats).

Appendix 39 reports on human tolerance of galacto-oligosaccharides. The preparation of oligosaccharides in this tolerance study was "OLIGO" from which mono-and disaccharides (in particular lactose) had been removed. Up to 15g of galacto-oligosaccharides per day with an otherwise normal diet eaten by the test subject is tolerated well without any noticeable side-effects.

Galacto-oligosaccharides of the same type as Elix'or have been used as food ingredients in Japan for a number of years. 4,200 tones of galacto-oligosaccharides were produced in Japan in 1993. Foods that contain galacto-oligosaccharides include:

- Snow Brand F-plus, a baby food produced by Snow Brand
- Fiber & Oligo, a soft drink produced by Wakodo
- Be-feel, a dairy drink produced by Yakult
- C100, Seni & Oligo, a drink produced by Takeda (Appendix 26)
- Umer, a fermented dairy product, produced by Coberco/Netherlands

Galacto-oligosaccharides, therefore, already have a considerable history of safe use.

Conditions of Use

As the studies attached to the notice will indicate, studies have been performed in which 7.5, 15 and 25 grams of galacto-oligosaccharides were taken daily to the subjects evenly spread over the day. No adverse effects of the abdomen or other areas have been found in any of the test groups apart from slightly increased flatulence during the first few days of administration in the highest dose, 25 gram/day. Appendix 39

The efficacy of Elix'or has been shown in many studies. (See Appendices 1-49). The effect seems to be somewhat more pronounced in the test subjects consuming 15 grams per day. Therefore, based on the studies attached to this notice, we advise individuals to use approximately 7.5 to 15 grams of the ingredient galacto-oligosaccharides a day evenly spread over the course of the day. This means that between 16.5 and 33 grams of Elix'or syrup and

between 12.5 and 25 grams of Elix'or powder could be used for optimum effect. Elix'or will be sold as either a powder or syrup which may be added to beverages such as orange juice. The powder or syrup may also be manufactured into dietary supplement tablets or gel-capsules.

For the manufacture of Elix'or from lactose, a naturally occurring enzyme called B-galactosidase is used. This enzyme, derived from a non-pathogenic microorganism, is stimulated under specific conditions to catalyze the reaction converting lactose into galacto-oligosaccharides following the general process as indicated in Figure 1 below. The overall process for the manufacture of Elix'or is shown in Figure 2.

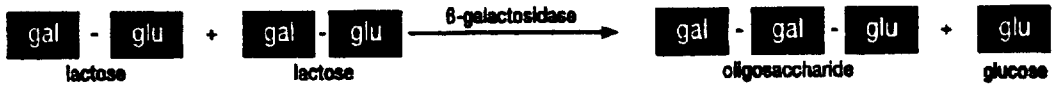


Figure 1.

A range of galacto-oligosaccharides varying in chain length are formed with the overall composition as shown in Table 1 below.

Chainlength $(Gal)_nGlc$		percentage of total galactooligosaccharides
Disaccharides *)	(n=1)	33
Trisaccharides	(n=2)	39
Tetrasaccharides	(n=3)	18
Pentasaccharides	(n=4)	7
Hexa-, Hepta- and Octasaccharides	(n=5,6,7)	3

*) other than lactose

Table 1.

Two of the trisaccharide present in Elix'or have been reported to occur in breast milk at levels of 3 mg/1 Appendices, 2,3,12.

Figure 2 , the overall process for the manufacture of Elix'or.

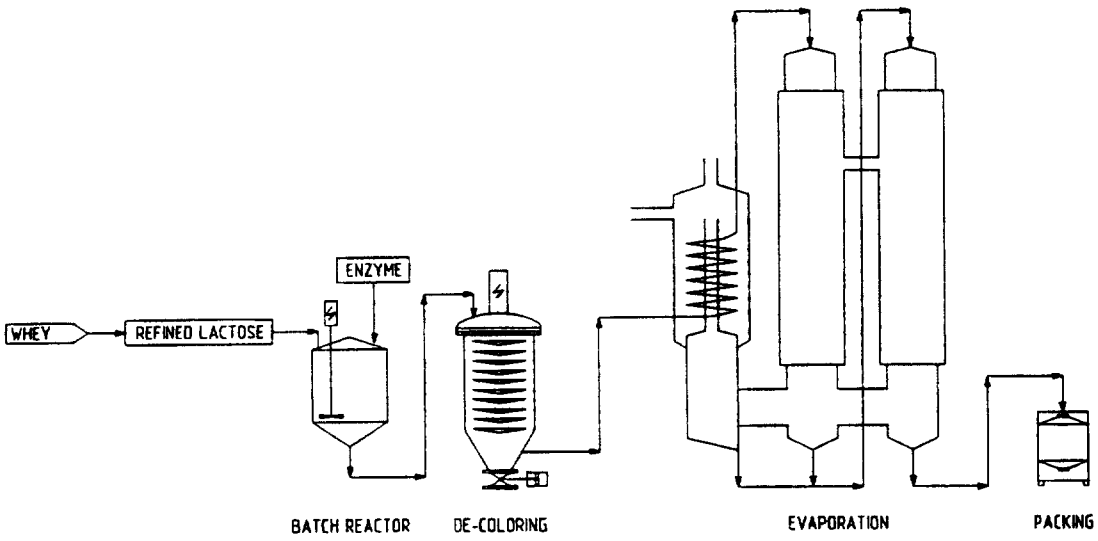


Figure 2.

Use as a Dietary Supplement

The effects of galacto-oligosaccharides on human health can be related first by direct effects of the product and second by indirect effects which are connected with the stimulation of growth and activity of commensal bifidobacteria in the host's gut. The latter is called the bifidogenic effect.

In the last 15 years it has been proven that a well balanced microflora in the human gut can improve health in several ways Appendix 1. Galacto-oligosaccharides promote the growth of bifidobacteria and lactobacilli while suppressing other less favorable bacteria.

At least 500 different micro-organisms are present in the human colon at counts of up to 10^{14}. This very complex cocktail of micro-organisms can be divided into positive bacteria like lactobacilli and bifidobacteria present in combined counts of 10^{10}/g faeces and negative bacteria like enterobacteriaceae and streptococci with typically lower counts of up to 10^{8}/g faeces

Appendices 2,3,5-8,17,22,24,25,29,32,51. These micro-organisms are in direct contact with the host through the colonic cell wall.

Elix'or can be used to supplement the diet in two ways:

1. The dietary fibre action.

Research has clearly demonstrated the non-digestibility of the galacto-oligosaccharides in Elix'or in the upper intestinal tract. In vivo studies with pigs which were cannulated at the end of their ileum, showed that the galacto-oligosaccharides in Elix'or passed the small intestine almost completely intact. This was confirmed with in vitro studies in which galacto-oligosaccharides from Elix'or were incubated with homogenates of human small intestinal mucosa to simulate the human upper digestive tract. No significant breakdown occurred. Appendix 48

Fig. 3, The liberation of galactose form Elix'or galacto-oligsacharides and lactose by human intestinal enzymes, shows the effect of human intestinal enzymes on Elix'or galacto-oligosaccharides in comparison with lactose.

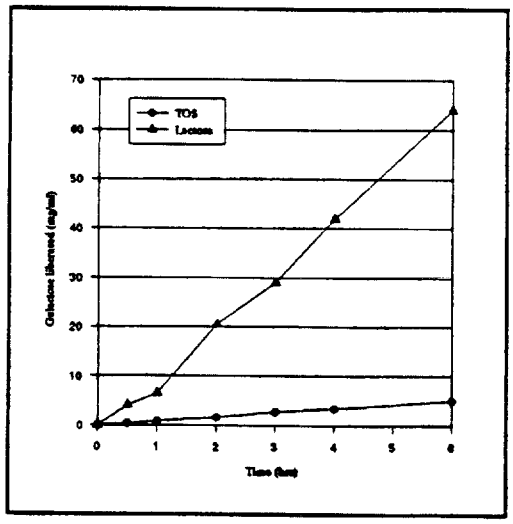


Figure 3.

Based on these experiments Elix'or can be considered a soluble dietary fibre which reaches the colon undigested, where it is fermented by the resident microflora. It was found, in a study with elderly patients suffering from constipation that administering trigalacto-oligosaccharides significantly reduced their degree of constipation Appendix 51.

2. Enhanced absorption of nutritionally important minerals.

Results from experiments with rats fed galacto-oligosaccharides and pigs fed Elix'or show significant increases in mineral absorption. Of particular interest is the improvement of absorption of magnesium (Mg) iron (Fe) and zinc (Zn) demonstrated in studies with pigs, Appendix 14 and improvement of calcium absorption (Ca) demonstrated in studies with rats Appendices 19,20,34 and 37. This is yet to be verified with human studies.

Indirect Effects

Several researchers in the fields of pre-probiotics have reported on the relation between colonic microflora and health.

Mitsuoka, Appendix 1, describes the importance of a well balanced colonic flora for the well-being of the human body. Under ordinary conditions this microflora is very stable and is not influenced significantly by the diet. However, under abnormal conditions such as emotional stress, consumption of antibiotics, cancer etc. this can change dramatically. Researchers have shown that there is a significant difference in the microflora of the

colon between breastfed infants and bottle fed ones. The breastfed babies have higher counts of bifidobacteria and lactobacilli and lower counts of pathogens like clostridia, Appendices 2-3. The difference is attributed to the presence of bifidogenic factors in human milk like galacto-oligosaccharides, such as the fucosyl type galacto-oligosaccharides, and also the Elix'or trigalacto-oligosaccharides Appendices 4,13.

Galacto-oligosaccharides promote the growth of bifidobacteria and lactobacilli in preference to pathogens. These beneficial bacteria then prevent colonization by the pathogens. They produce short chain fatty acids (SCFA) which increase acidity. The combined effect of the presence of SCFA and the low pH create unfavorable conditions for the growth of pathogens. Furthermore, butyric acid, one of the SCFA formed, is a source of energy for the mucosal cells of the colon cell wall which helps to keep the colonic wall in good condition. Bifidobacteria and lactobacilli produce bacteriocins against pathogens Appendix 12. Furthermore, they compete with the pathogens for the nutrients which reach to

colon. This phenomenon of a stable microflora is called colonial resistance; the adapted gutflora prevents colonization by pathogens Appendix 10.

A well established effect of an increase in bifidobacteria and lactobacilli in the gut is the higher tolerance to lactase deficient people.

Another possible benefit of the presence of bifidobacteria and lactobacilli, is the stimulation of the immune system through interaction of the bacteria with the gut wall Appendices 9,10. This phenomenon, however, requires further investigation.

Other effects possibly related to increased counts of lactobacilli and bifidobacteria are a hypo-cholesterolemic effect Appendix 10 and the inhibition of carcinogenesis Appendices 10,11. Direct links between these effects and Elix'or have not been published yet.

A number of in vivo studies have been carried out proving the bifidogenic effect of galacto-oligosaccharides in humans, Appendices 5,6,7,8.

Borculo Whey Products has done research in vitro with several relevant micro-organisms: pathogens as well as bifidobacteria and lactobacilli isolated from human faeces. The results illustrate the very selective stimulation of positive bacteria using galacto-oligosaccharides, the pathogens tested did not show any growth at all. See Table 2, on the bifidogenic effect of galacto-oligosacharides in vitro.

Strains	Number of strains tested	bifidogenic effect
Positive bacteria :		
Bifidobacterium longum	2	+++
Bifidobacterium infantis	3	++
Bifidobacterium breve	2	+++
Bifidobacterium adolescentis	1	+++
Bifidobacterium bifidum	3	++
Lactobacillus acidophilus	2	+++
Pathogens :		
Clostridium perfringens	1	-
Clostridium sporogenes	1	-
Clostridium paraputrificium	1	-
Clostridium difficile	1	-
Escherichia coli	2	-
Enterococcus faecalis	1	-
Klebsiella pneumoniae	1	-

Table 2.

A research program of tests with human volunteers to demonstrate the bifidogenic effect and related health effects of Elix'or in vivo is in progress. Results are not yet available.

Elix'or is a prebiotic food ingredient. As it is nondigestible it reaches the colon, where it selectively stimulates beneficial commensal gut microorganisms like bifidobacteria and lactobacilli in their growth and activity, thus improving the host's health.

Tolerance

A daily consumption of approximately 40 grams Elix'or as part of the every day diet with a normal dietary fibre content (Dutch conditions) does not produce unpleasant side effects.

However, consumption of considerably higher amounts may lead to flatulence and may eventually have a laxative effect, Appendix 39.

Low Energy Value

As the galacto-oligosaccharides of Elix'or are not hydrolysed and absorbed in the small intestine, they are low caloric sugars. Their energy contribution comes from the fermentation by the gut microflora. The caloric value of the galacto-oligosaccharides is 2 keal/g (cf. sugar: 4 kcal/g). Taking into account the carbohydrate composition of Elix'or, the overall caloric value is:

Elix'or on dry matter:	2.8 kcal/g (11.7 kj/g)
Elix'or syrup:	2.1 kcal/g (8.8 kj/g)

Low cariogenicity

The galacto-oligosaccharides of Elix'or have low cariogenicity. In vitro studies have shown that predominant micro-organisms of the oral microflora cannot easily produce acid and dental plaque from galacto-oligosaccharides. Tests were performed with Streptococcus mutans amongst others. [Appendix 49]

Sweetness

The relative sweetness was determined for two concentrations of syrup, the results of which are shown in table 3 below.

Elix'or® (wt% dry solids)	relative sweetness
10	0.32
15	0.34

$$\text{Relative Sweetness} = \frac{\text{Sucrose concentration}}{\textit{Elix'or}^{®}\text{ concentration of equiv. sweetness}}$$

Table 3.

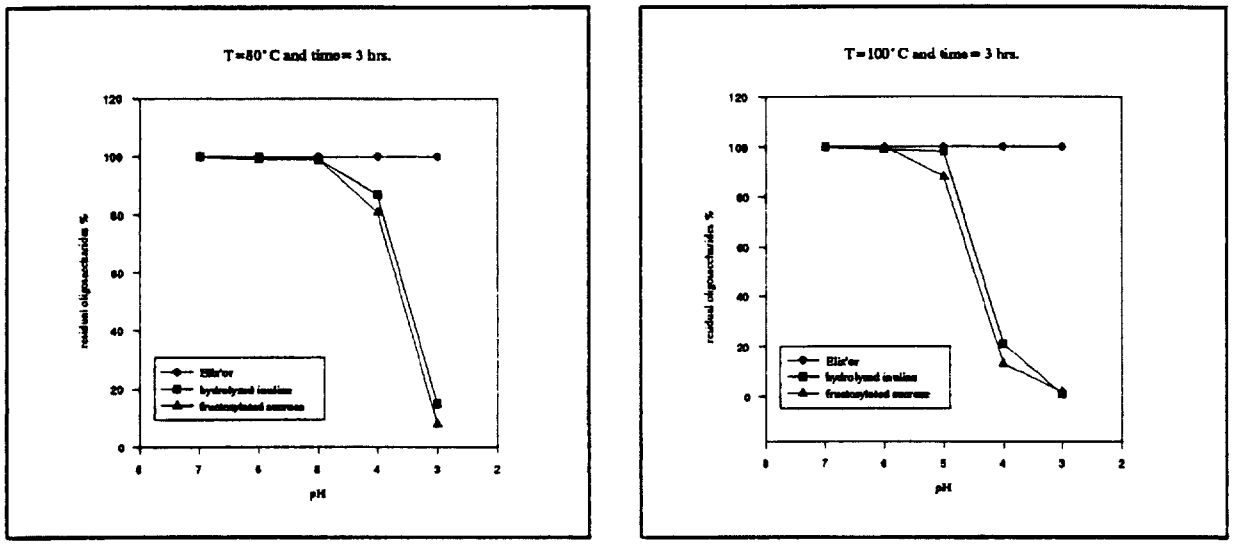
Elix'or is available as a 75 wt% syrup and a powder. The syrup is a slightly yellowish clear liquid with an agreeable, slightly sweet taste. The powder is white with a sweet taste.

Physical Characteristics

The chemical and physical characteristics are discussed below.

Heat Stability

The galacto-oligosaccharides in Elix'or are very stable under the severe conditions of low pH and high temperatures as indicated in Figures 4a-c.


T=80°C and time= 3 hrs.
T=100°C and time= 3 hrs.
T=120°C and time= 30 min.
pH

Figures 4a-c.

Storage Stability

Elix'or syrup at a pH of 3.6 was analyzed for breakdown of galacto-oligosaccharides with time at 30°C. Fig. 5 shows that the total amount of galacto-oligosaccharides does not change under these storage conditions. Furthermore, the composition of the galacto-oligosaccharides fraction remains unaltered during storage, as can be seen from the chromatogram shown in Figures 5 and 6.

Figure 5, the storage stability of Elix'or syrup as a function of time at 15 and 30°C.

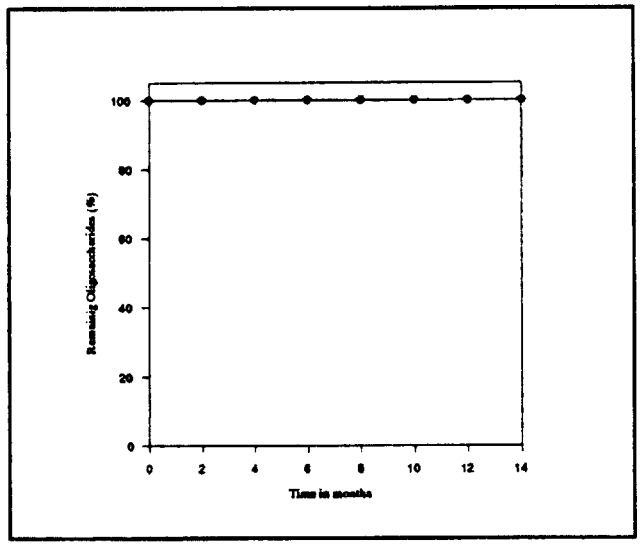


Figure 5.

Figure 6, the storage stability of Elix'or during storage.

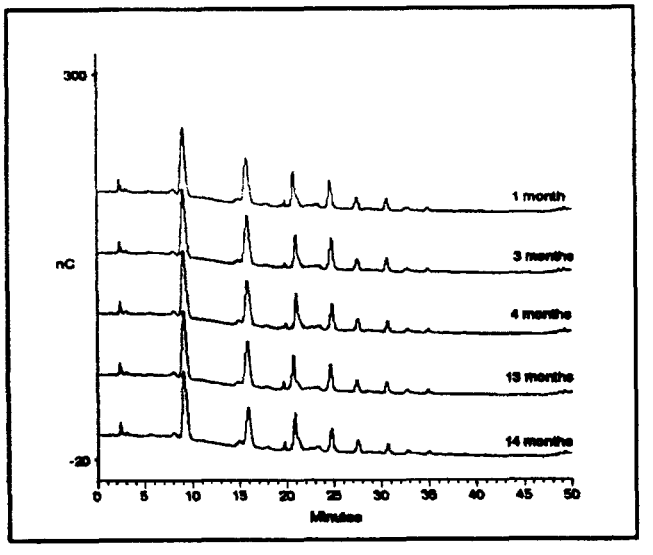


Figure 6.

A solution of Elix'or containing 10 wt% solids was analyzed for color formation in a 1 wt% glycine buffer by heating it for 10 minutes at 120 °C. The results are depicted in Figure 7, the

degree of coloring of Elix'or as a function of pH at 120° C relative to the color at pH 7 (=100%) (Extinction measurements at 450 nm).

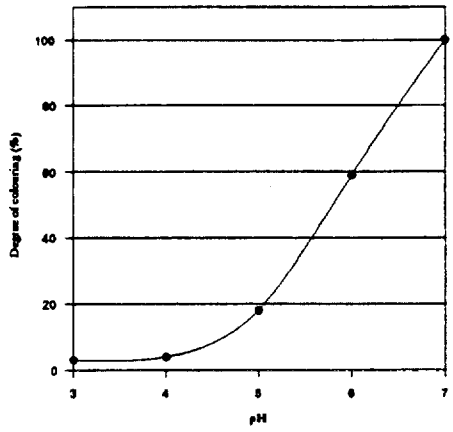


Figure 7.

Water Activity

The water activity as a function of Elix'or dry solids of the syrup is shown in Figure 8 below. Elix'or is supplied as a 75 wt% solids syrup, ensuring very high microbial stability.

Figure 8, water activity of Elix'or as a function of dry solids percentage of the syrup.

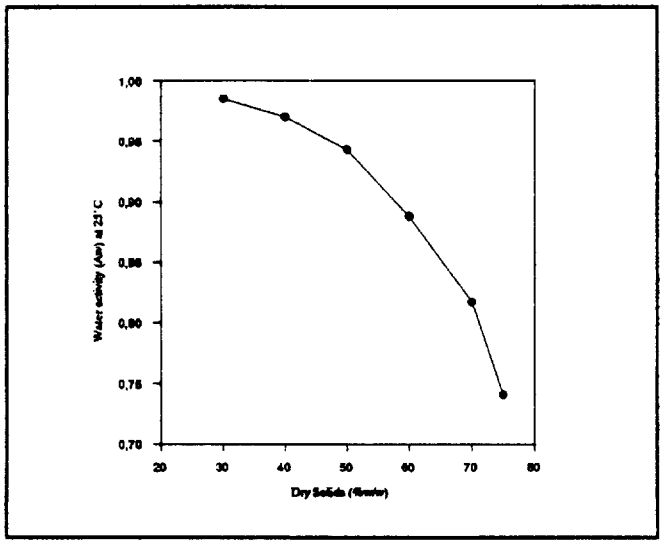


Figure 8.

Moisture Retention

Elix'or syrup should be stored in an airtight container to prevent moisture loss. Fig. 9 illustrates the rate of moisture uptake at 34% and 75% relative humidity. It is important to store Elix'or in an airtight container to prevent moisture loss. These instructions will be provided on product labels.

Figure 9, change in total weight for Elix'or at RH of 34% and 75% as a function of time.

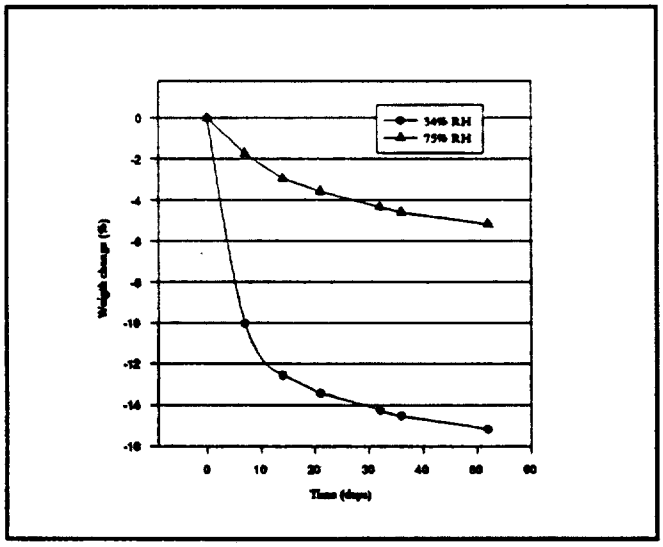


Figure 9.

The viscosity of Elix'or syrup is approximately 2500 cPs 25°C; 75% dry solids). The dependence of viscosity of the syrup on total at 10°C, 20°C and 40°C is shown in Figure 10. The effect of temperature on viscosity is shown in Figure 11.

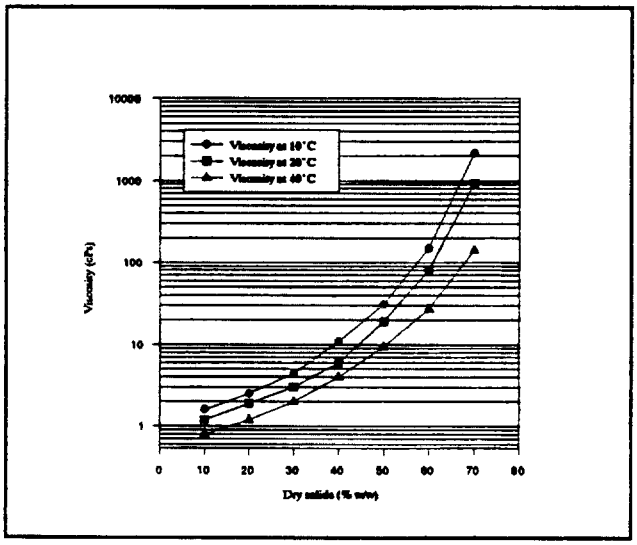


Figure 10.

Figure 11, the effect of temperature on viscosity.

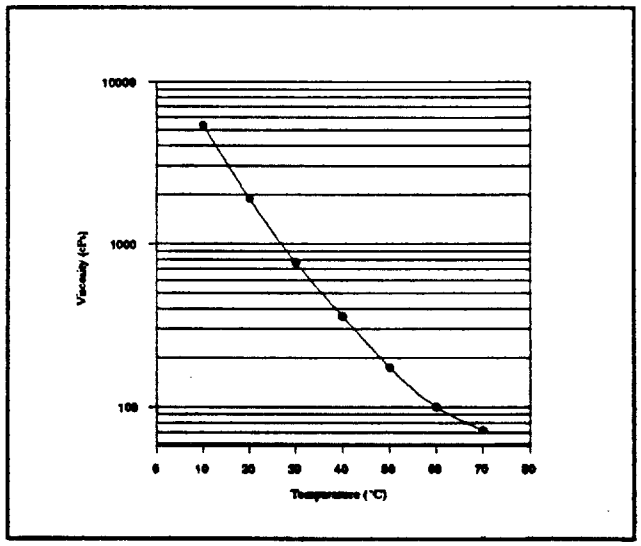


Figure 11.

Freezing Point Depression

The freezing point as a function of dry solids of the syrup is depicted in Figure 12.

Figure 12, Shows the freezing point depression of Elix'or as a function of dry solids (wt%).

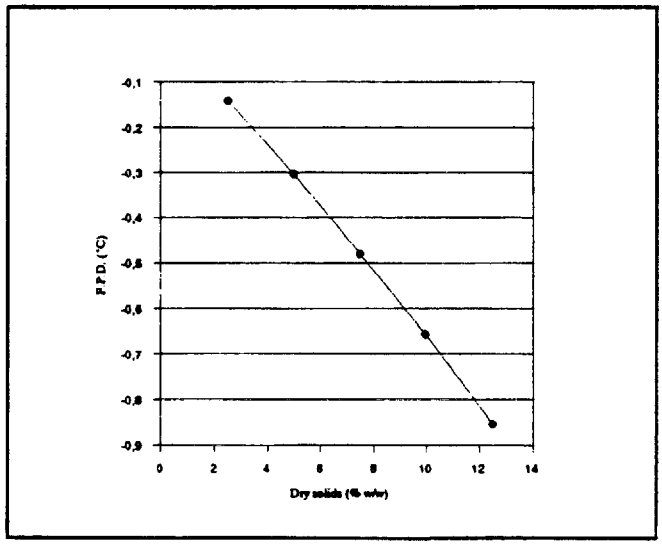


Figure 12.

Storage conditions for the Elix'or powder should be clean, dry, 10-20 degrees centigrade, 40-60 % relative humidity and away from the

strongly odorous materials. Storage conditions for the Elix'or syrup should be clean, dry and away from strongly odorous materials.

Shelflife

Instructions and expiration dates will be provided on product labels.

Appendix I

Specification

ELIX'OR SYRUP

Name	Elix'or
Product Code	259
Type	galacto-oligosaccharide syrup
Appearance	clear golden yellow syrup
Odor and taste	pleasant, slightly sweet

Physical/Chemical Properties	Average
Dry matter (w/w)	75 %
Galacto-oligosaccharides	60 % on DM

Lactose.anh	20	% on DM
Glucose.anh	19	% on DM
Galactose	1	% on DM
Protein (KjN *6.38)	0.03	%
Ash	0.15	%
pH	3.6	
Refraction	77	°Brix
Density	1.38	kg/l

Microbiological Data

Total plate count	(PCMA, 72 h, 30°C)	≤ 3000 / g
Enterobacteriaceae	(EE, 24 h, 30°C)	absent in 1 g
Salmonellae	(ELISA)	absent in 25 g
Yeasts	(OGGA, 96 h, 25°C)	≤ 50 / g
Moulds	(OGGA, 96 h, 25°C)	≤ 50 / g

Delivery in bag-in-box (25 kg) and octobox

Elix'or powder

Name:	Elix'or
Product Code	289
Type	Oligosaccharide powder
Appearance	White powder
Odor and taste	Pleasant, slightly sweet
Physical/chemical properties	Average

Dry matter (w/w)	95%
Galacto-oligasaccharides	60% on DM
Lactose.anh	20% on DM
Glucose.anh	19% on DM
Galactose	1% on DM
Protein (KjN*6.38)	0.03% on DM
Ash	0.15% on DM

Microbiological data

Total plate count	(PCMA, 72 h, 30°C)	≤ 3000/g
Enterobacteriaceae	(EE, 24 h, 30°C)	absent in 1 g
Salmonellae	(Elisa)	absent in 25 g
Yeast	(OGGA, 96 h, 25°C)	≤ 50/g
Moulds	(OOGA, 96 h, 25°C)	≤ 50/g

A complete list of Appendices referenced above is attached to this letter. Please call if there are any questions or comments, if necessary, we would welcome a meeting with you and members of your staff to review this notice or any additional questions you may have.

Anne Gochman

Anne Gochman
Manager, Regulatory Affairs

INDEX OF APPENDICES

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