



**Memorandum**

Date:     =    FEB 25 2004    

From: Interdisciplinary Scientist/Pharmacist , Division of Dietary Supplement Programs  
, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification:  
**Lactobacillus F19 (Lactobacillus paracasei subsp. paracasei strain F19)**

Firm: **Medipharm USA**

Date Received by FDA: **9/02/03**

90-Day Date: **12/03/03**

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Victoria Whisk  
for Gloria Chang

95S-0316

RPT209



Mark L. Richards  
Managing Director  
Medipharm USA  
10215 Dennis Drive  
Des Moines, Iowa 50322

NOV 14 2003

Dear Mr. Richards:

This is to inform you that the notification dated August 28, 2003, you submitted to pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on September 2, 2003. Your notification concerns the substance, *Lactobacillus paracasei* subsp. *paracasei* strain F19 which you refer to as "Lactobacillus F19" that you intend to market as a new dietary ingredient.

According to your notification, Lactobacillus F19 is recommended as a probiotic supplement for individuals who choose to maintain a diverse intestinal tract microflora. You recommend that manufacturers add a sufficient number of bacteria such that each serving delivers "a conservative"  $1 \times 10^9$  colony forming units (CFU) of Lactobacillus F19 on a daily basis.

This letter addresses your proposed use of Lactobacillus F19 as a new dietary ingredient in dietary supplements. Your notification indicates that Lactobacillus F19 may be added to conventional food products. The addition of certain ingredients used in dietary supplements to conventional foods could cause the food to be adulterated if the substance is not used in accordance with an approved food additive regulation or is not generally recognized as safe for the intended use. If you have any questions about the addition of Lactobacillus F19 to conventional food products that would be marketed in the United States, you should contact the staff in the Office of Food Additive Safety (OFAS), 5100 Paint Branch Parkway, College Park, Maryland 20740. You can also reach OFAS by telephone at (202) 418-3100.

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for

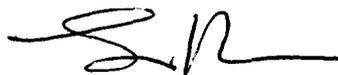
introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

Please note that acceptance of this notification for filing is a procedural matter, and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. FDA is not precluded from taking action in the future against any dietary supplement containing your new dietary ingredient if it is found to be unsafe, adulterated, or misbranded.

Your notification will be kept confidential for 90 days after the filing date of September 2, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any further questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

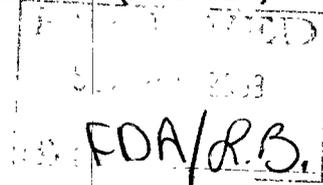


Susan J. Walker, M.D.  
Division Director  
Division of Dietary Supplement Programs  
Office of Nutritional Products, Labeling  
and Dietary Supplements  
Center for Food Safety  
and Applied Nutrition

# medipharm

August 28, 2003

Division of Standards and Labeling Regulations  
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-2371



FDA personnel:

Please find enclosed an original and two copies of our Pre-Market Notification for a New Dietary Ingredient, in accordance with 21CFR190.6 of the Code of Federal Regulations. Feel free to contact me at your earliest convenience should you require additional information.

Sincerely,

Mark L. Richards  
Managing Director  
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10215 Dennis Dr.  
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August 28, 2003

Division of Standards and Labeling Regulations  
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
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FOA/23

FDA personnel:

In accordance with 21CFR190.6 of the Code of Federal Regulations, Medipharm is submitting this premarket notification for a new dietary ingredient in order to manufacture and distribute *Lactobacillus paracasei* subsp. *paracasei* strain F19 (herein referred to as Lactobacillus F19) as a new dietary ingredient. We understand that Medipharm will not market this probiotic bacterial culture for a period of at least 75 days, pursuant to the requirements of the code above.

**Company Name and Complete Address of New Ingredient Manufacturer:**

Medipharm USA  
10215 Dennis Dr.  
Des Moines, IA 50022

**Name of New Dietary Ingredient:**

*Lactobacillus paracasei* subsp. *paracasei*

**Description of New Dietary Ingredient:**

**Organism Identification:** *Lactobacillus paracasei* subsp. *paracasei* is a Gram-positive, non-spore-forming, rod-shaped bacterium that was first validly published in the scientific literature by Collins et al. in 1989. As a member of the genus *Lactobacillus*, it has been classified in Volume II of The Genera of Lactic Acid Bacteria (Hammes and Vogel, 1995) as a facultatively heterofermentative lactobacillus, almost exclusively fermenting hexose sugars to lactic acid by the Embden-Meyerhof-Parnas pathway. The characteristic G + C content of the organism's DNA ranges from 45 to 47 mol %. The organism has been isolated from a variety of commercially available cheeses, from human gastrointestinal tracts (oral cavity, small intestine, and colon), in human sewage, and from silages.

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**Research and Development of Lactobacillus F19 as a Probiotic:** Lactobacillus F19 was isolated from human colonic biopsies and selected as a candidate for a human probiotic, based on the results of a variety of screening criteria. The bacterium had the ability to survive the pH ranges characteristic of the stomach, it could bind to a variety of mucin sources, and grew in the presence of bile (Ljungh et al, 2002).

Once identified as a tentative suitable probiotic, media and procedures were developed in order to optimize cell growth and accurately identify the organism (Björneholm et al, 2002). In addition, genetic stability of the organism was assessed, in order to ensure that when the organism was grown on an industrial scale, freeze dried, and incorporated in a food matrix, the genetic material of the bacterium was not altered. Morelli and Campominosi (2002) reported that the plasmid profile of Lactobacillus F19 grown in an industrial setting was unaltered when compared to the profile of the same strain analyzed in the same laboratory six years earlier.

**Attributes of Lactobacillus F19 in Functional Foods:** One of the most practical ways to administer probiotics is through the manufacturing of functional foods. When probiotics are added to human foods, such products should not adversely affect the organoleptic properties of the finished products. A number of foods containing Lactobacillus F19 were evaluated by Ohlson et al (2002). Lactobacillus F19 was relatively stable in 3 % fat milk for 7 days, and had excellent survivability in yogurt, fermented milk, fruit-flavored drinkable yogurt, and a fruit juice (pH of 3.7) after 14 days. In addition, the organism enhanced the sensory characteristics of yogurts. The bacterium was able to withstand elevated temperatures associated with manufacturing processes. F19 did not decrease in number when exposed to 60°C for 15 seconds.

**Control of Lactobacillus F19 in Dairy Processing Plants:** Ohlson et al also evaluated the control measures necessary for production plant personnel to contain Lactobacillus F19 and prevent cross-contamination of other dairy plant products. The bacterium is sensitive to normal pasteurization (15 seconds at 72°C). It was also susceptible to normal plant disinfectants, including quaternary ammonium compounds, ethanol, peracetic acid, and amphoteric tensides, when used according to directions provided by disinfectant manufacturers.

**Types of Lactobacillus F19 Products to be Marketed:** Lactobacillus F19 is a probiotic culture and will be marketed as a base or stock culture, in a freeze-dried-powder form. Because of the intended usages of the product, Medipharm intends to market base cultures with concentrations ranging from 20 to 100 billion (2 to 10 x 10<sup>10</sup>)cfu/g, in order to conform to a variety of manufacturing needs.

**Recommended Products That Will Include Lactobacillus F19:** Because F19 has been shown to survive in a variety of food products (Ohlson et al, 2002) and in gelatin capsules (Sullivan et al, 2002; Crittenden et al, 2002), Medipharm intends

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to recommend that F19 be added to milk, yogurts, fermented milk, cottage cheese, ricotta or other pasty cheeses (Quarg), fruit juices (all are examples of functional food applications). Also, because *Lactobacillus paracasei* subsp. *paracasei* has been found as a normal bacterial species in commercial cheeses (Cheddar cheese, Gardiner et al, 1998; traditional Greek cheeses, Mama et al, 2002; Caciocavallo Silano cheese, Corsetti et al, 2001), *Lactobacillus* F19 will be recommended for cheeses as well. Low-fat ice cream has also been used as a functional food and Haynes and Playne (2002) have shown that *L. paracasei* subsp. *paracasei* has excellent viability for up to 12 months in ice cream. Thus, these types of dairy products will also be recommended as a potential administration vehicle for F19 supplementation. Lastly, F19 can be used to manufacture gelatin capsule or foil packet probiotic powders, as a daily human probiotic. Medipharm is currently marketing Synbiotic 2000 in the European Union as a safe, human probiotic powder.

**Recommended Usage of Lactobacillus F19:** The F19 organism has been administered between  $4 \times 10^8$  and  $1.5 \times 10^{11}$  cfu per person per day in numerous research studies, with the latter amount administered continuously for 12 weeks. These amounts produced no adverse side effects when supplemented to all ages of humans. Therefore, Medipharm is recommending manufacturers of functional foods or human probiotic supplements add a sufficient number of bacteria such that each serving delivers "a conservative"  $1 \times 10^9$  cfu of *Lactobacillus* F19 on a daily basis. In that way, people consuming 15 times the normal serving of a functional food are still within researched supplementation rates.

**Conditions of Use:** *Lactobacillus* F19-supplemented functional foods or human probiotic supplements will be recommended to individuals who choose to maintain a diverse intestinal tract microflora.

**Lactobacillus F19 Safety and Efficacy Research in Humans:** Effective probiotic bacterial cultures ideally should be able to colonize the G.I. tract in sufficient numbers greater than negative controls. In addition, the probiotic organism should be safe when fed to adults, but more importantly, infants and the elderly, where immune system function may be less effective than in healthy adults. Morelli et al (1998) reported that *Lactobacillus paracasei* represented the major population of *Lactobacilli* in newborn infants. Over a 6-month period, fecal samples were taken from 16 neonates and the workers identified the bacterial species present. Forty strains of *L. paracasei* were identified. Xanthopoulos et al (1999) corroborated these findings in a similar study. The researchers isolated six strains of *Lactobacillus paracasei* subsp. *paracasei* from fecal samples taken from four newborns.

Several studies have been conducted in humans using *Lactobacillus* F19. Sullivan et al (2002) published results of a study involving 77 infants (less than 2 years of age) and 30 elderly adults (greater than 65 years of age), supplemented with or without F19. Eight children from each group withdrew from the trial when they contracted

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viral infections or otitis media. Two additional infants were removed from the placebo group when they developed severe gastrointestinal symptoms. Thus, 61 infants completed the study.

Thirty-one infants supplemented with a placebo (control group) had an average age of 13.6 months with an age standard deviation of 2.0 months. Thirty children in the treatment group received  $2 \times 10^{10}$  colony forming units (cfu) per day ( $1 \times 10^{10}$  cfu twice daily) and the group had an average age of 12.5 months with an age standard deviation of 1.4 months. The infants were supplemented with treatment or control capsules for 3 weeks, and the experiment was terminated after fecal samples were taken 5 weeks from day 0.

Thirty elderly participants completed the study conducted with adults. Thirteen people in the treatment group had an average age of 75.5 years with an age standard deviation of 5.2 years. The placebo group had an average age of 77.8 years of age with an age standard deviation of 7.2 years. Treatment adults were administered 150 mL of a fermented milk product twice daily for 12 weeks. *Lactobacillus* F19 was added at a rate of  $3.5 \times 10^8$  cfu/mL of fermented milk, for a total daily administration of F19 at  $1.05 \times 10^{11}$  cfu/day. The experiment was terminated at 20 weeks from day 0, when the last fecal samples were taken.

Fecal samples were obtained from the participants and transported to the laboratory anaerobically and one of the criteria of response for assessment of intestinal tract colonization was numbers of *Lactobacillus* F19 per g of feces. Results presented by Sullivan et al (2002) indicated that the F19 organism significantly increased in the treatment infants and elderly participants, based on more than 4 log increases in the numbers of *Lactobacillus* F19 per g of feces. Two weeks after the last administration of the F19 treatment capsules, 20 % of the infants still hosted significant numbers of F19 in their fecal samples. Four weeks after the last F19 administration to the elderly participants, nearly 8 % of the adults retained a significant numbers of F19 per g of feces.

The authors concluded that the *Lactobacillus* F19 was well-tolerated by children and elderly adults, with no adverse symptoms noted in individuals receiving F19. It performed as an ideal probiotic, increasing in number during probiotic supplementation. The authors also reported a transient increase in *Lactobacillus* spp. other than F19 in the elderly participants.

In an additional report, Crittenden et al (2002) reported findings from two studies conducted in Finland. In one trial, five healthy adults consumed 200 mL of a fermented milk product containing  $1 \times 10^8$  cfu of F19 per g of milk product, twice daily, for 12 days ( $4 \times 10^{10}$  cfu per day). Biopsies of the colonic mucosa and enumeration of F19 per g of feces were the criteria of response. In the second

study, five healthy adults and four milk-hypersensitive adults were supplemented with two, daily, 200 mL volumes of fermented milk containing  $1 \times 10^6$  cfu of F19

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per mL ( $4 \times 10^8$  cfu of F19 per day) for 1 week. Details of the results of the studies are presented in Crittenden et al (2002). The authors concluded that no adverse side effects were reported when F19 was consumed by healthy adults. They point out that in addition, a portion of the participants in the Sullivan et al (2002) studies were seropositive for *Helicobacter pylori*. Because milk-hypersensitive adults in the Finnish study and the *H. pylori* seropositive adults in the Crittenden study were supplemented with F19, it was concluded that F19 was safe even in individuals suffering from "mild illnesses".

These experiments provide clear evidence that the *Lactobacillus* F19 probiotic is safe in healthy humans from the age of 1 year to 85 years of age, and F19 is safe in humans with some underlying disorders.

### Supportive Research Studies in the Literature:

Björneholm, S., A., Eklöv, M. Saarela, and J. Mättö. 2002. Enumeration and identification of *Lactobacillus paracasei* subsp. *paracasei* F19. *Microbial Ecology in Health and Disease*. Suppl. 3:7-13.

Collins, M.D., B.A. Phillips, and P. Zanoni. 1989. Deoxyribonucleic acid homology studies of *Lactobacillus casei*, *Lactobacillus paracasei* sp. nov., subsp. *paracasei* and subsp. *tolerans*, and *Lactobacillus rhamnosus* sp. nov., comb. nov. *Int. J. Syst. Bacteriol.* 39:105-108.

Corsetti, A., M.R. Corbo, M. Albenzio, R. di Cagno, M. Gobbetti, and P.F. Fox. 2001. Microbiology and biochemistry of Caciocavallo Silano cheese. *Italian Journal of Food Science*. 13:297-309.

Crittenden, R., M. Saarela, J. Mättö, A.C. Ouwehand, S. Salminen, L. Peltö, E.E. Vaughan, W.M. de Vos, A. von Wright, R. Fondén, and T. Mattila-Sandholm. 2002. *Lactobacillus paracasei* subsp. *paracasei* F19: Survival, ecology and safety in the human intestinal tract- a survey of feeding studies within the PROBDEMO project. *Microbial Ecology in Health and Disease*. Suppl. 3:22-26.

Gardiner, G., R.P. Ross, J.K. Collins, G. Fitzgerald, and C. Stanton. 1998. Development of a probiotic Cheddar cheese containing human-derived *Lactobacillus paracasei* strains. *Appl. Environ. Microbiol.* 64:2192-2199.

Hammes, W.P., and R.F. Vogel. 1995. The genus *Lactobacillus*. In *The Lactic Acid Bacteria, Volume 2, The Genera of Lactic Acid Bacteria* (eds. Wood, B.J.B., and W.H. Holzapfel). Blackie Academic and Professional, New York, USA, pp. 10-54.

Haynes, I.N., and M.J. Playne. 2002. Survival of probiotic cultures in low-fat ice-cream. *Australian Journal of Dairy Technology*. 57:10-14.

Liungh, Å., J. Lan, and N. Yanagisawa. 2002. Isolation, selection and

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characteristics of *Lactobacillus paracasei* subsp. *paracasei* F19. *Microbial Ecology in Health and Disease*. Suppl. 3:4-6.

Mama, V., M. Hatzikamari, A. Lombardi, N. Tzanetakis, and E. Litopoulou-Tzanetakis. 2002. *Lactobacillus paracasei* subsp. *paracasei* heterogeneity: the diversity among strains isolated from traditional Greek cheeses. *Italian Journal of Food Science*. 14:351-362.

Morelli, L., and E. Campominosi. 2002. Genetic Stability of *Lactobacillus paracasei* subsp. *paracasei* F19. *Microbial Ecology in Health and Disease*. Suppl. 3:14-16.

Morelli, L., C. Cesena, C. de Haën, and L. Gozzini. 1998. Taxonomic *Lactobacillus* composition of feces from human newborns during the first few days. *Microbial Ecology*. 35:205-212.

Ohlson, K., S. Björneholm, R. Fondén, and U. Svensson. 2002. *Lactobacillus* F19-a probiotic strain suitable for consumer products. *Microbial Ecology in Health and Disease*. Suppl. 3:27-32.

Sullivan, Å., R. Bennet, M. Viitanen, A. Palmgren, and C.E. Nord. 2002. Influence of *Lactobacillus* F19 on intestinal microflora in children and elderly persons and impact on *Helicobacter pylori* infections. *Microbial Ecology in Health and Disease*. Suppl. 3:17-21.

Xanthopoulos, V., I. Ztaliou, N. Tzanetakis, and E. Litopoulou-Tzanetaki. 1999. Differentiation of *Lactobacillus* isolates from infant faeces by SDS-PAGE and rRNA-targeted oligonucleotide probes. *J. Appl. Microbiol.* 87:743-749.

Respectfully Submitted:

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



Title: Mark L. Richards, Managing Director, Medipharm USA

Date: \_\_\_\_\_

8-28-03

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