New Dietary Ingredient Notification
For
Saccharomyces Boulardii

Submitted By

Biocodex, Inc.
300 North Mill Street
P.O. Box 387
Creswell, Oregon 97426

January 28, 2005

Submitted To

Susan WALKER, M.D.,
Division of Dietary Supplements Programs (HFS – 810)
Office of Nutritional Products, Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

From: **Biocodex, Inc.**
300 North Mill Street
P.O. Box 387
Creswell, Oregon 97426

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5100 Paint Branch Parkway
College Park, Maryland 20740

Re: New Dietary Ingredient Notification

Date: January 28, 2005

Dear Dr. Walker:

Biocodex, Inc. is hereby submitting a New Dietary Ingredient (NDI) notification under 21 CFR § 190.6 for Lyophilised *Saccharomyces Boulardii* ("*S. boulardii*"), the dietary ingredient in our dietary supplement, Florastor®.

By way of background, this is the second NDI notification that we have submitted to the FDA. We submitted an NDI notification on March 16, 2004. On March 18, 2004, Vickey Lutwak from your office informed us by email that our notification had not been prepared according to the requirements in 21 CFR § 190.6. Specifically, we had failed to provide English translations of scientific publications containing evidence of the safety of using *S. boulardii* as recommended in Florastor® dietary supplements.

In this NDI notification for *S. boulardii* we provide all of the information required under 21 CFR § 190.6. We appreciate the helpful information provided by your office to assist us in preparing this notification.

1. Name and address of distributor and/or manufacturer

Distributor:	**Manufacturer:**
Biocodex, Inc. 300 North Mill Street P.O. Box 387 Creswell, Oregon 97426	Biocodex 1 Avenue Blaise Pascal 60000 Beauvais, France

2. Name of new dietary ingredient

Lyophilised *Saccharomyces boulardii*

3. Description of the dietary supplement that contains the new dietary ingredient

Description of dietary ingredient

S. boulardii is non-pathogenic yeast in the dietary supplement, Florastor®. *S. boulardii* is a probiotic that has been used widely in over 50 countries to prevent and relieve the symptoms of diarrhea. *S. boulardii* is not digested and absorbed in the gut and does not exert its effect systemically. Instead, *S. boulardii* acts locally in the lumen of the gut. During its passage through the intestine, *S. boulardii* mimics the physiological effects of the digestive flora.

Description of dietary supplement

Florastor® will be sold in the U.S. as a capsule (10 or 50 capsules/bottle) or a sachet (10 sachets/box), each containing live, freeze-dried lyophilized *S. boulardii* cells in powdered form.

Level of new dietary ingredient in the dietary supplement

Each capsule or sachet of Florastor® contains 250 mg (5 billion live freeze dried lyophilized cells) of *S. boulardii*.

Recommended conditions of use

The package labeling instructs consumers to take one capsule or sachet in the morning and one in the evening for a total of 2 units/day (500 mg/day).

4. Evidence that the new dietary ingredient can reasonably be expected to be safe when used as recommended

History of use

S. boulardii has been used extensively and safely in over 50 countries to relieve and prevent the symptoms of diarrhea. Biocodex Laboratories has manufactured and sold products containing *S. boulardii* (Ultra-levure™, Floratil™, Perenterol™) for over 40 years. *S. Boulardii* containing products have been approved for sale by over 50 countries worldwide, including 11 members of the European Union, as either a dietary supplement or an over the counter (OTC) drug.

S. boulardii has a well-established record of safe use by people of all ages (infants, children and adults), ethnicities and cultures. No serious side effects have been attributed to the use of *S. Boulardii* when used as recommended.

Scientific Publications

In addition to an extensive history of safe use worldwide, *S. boulardii* has been extensively clinically tested in rigorous scientific studies, many of which were randomized, double blind, placebo controlled studies.

We have enclosed copies of twelve (12) scientific studies in which *S. boulardii*, manufactured by Biocodex, was tested as a therapeutic agent to treat or prevent various forms of diarrhea, including antibiotic-associated diarrhea, clostridium difficile-associated diarrhea, acute diarrhea, diarrhea associated with tube feeding, AIDS related diarrhea and travelers' diarrhea. Complete and accurate English translations of articles that were originally published in a foreign language have been provided. The complete citations of these twelve scientific publications and three revieew articles are provided in the bibliography attached as **Appendix I**.

The key results regarding safety and efficacy that were reported in these 12 scientific publications are provided in Table 1, attached as **Appendix II**. The numbers of the references in Table 1 correspond to the numbers in the bibliography in Appendix I. The references are grouped according to the patient population targeted in the study.

The maximum daily dose of *S. boulardii* used in eight (8) of the studies exceeded the recommended daily dose for Florastor® (500 mg/day) and ranged as high as 3000 mg/day (Ref. #11). The last column (far right) presents conclusory comments made in the articles regarding the safety of *S. boulardii*. None of the references reported any serious side effects. In fact, several articles reported that the tolerability of *S. boulardii* was excellent.

Summary

Both an extensive history of commercial use and rigorous scientific tests have shown that *S. boulardii*is safe when used at the recommended dose in Florastor® (500 mg/day) or even much higher doses (tested up to 3000 mg/day).

Please do not hesitate to contact me if you have any questions about the information provided in this NDI notification or if you need any additional information.

Best regards,

Nicolas Coudurier
General Manager
Biocodex, Inc.
ncoudurier@biocodexusa.com

Appendix I
Saccharomyces Boulardii Bibliography

Scientific Publications

1. McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Moyer KA, Melcher SA, Bowen KE, and Cox JL. Prevention of β-lactam associated diarrhea by *Saccharomyces boulardii* compared with placebo. The American Journal of Gastroenterology, 90 (3): 439-448 (1995).

2. Surawicz CM, Elmer GW, Speelman P, McFarland LV, Chinn J, and Van Belle G. Prevention of antibiotic-associated diarrhea by *Saccharomyces boulardii*: A prospective study. Gastroenterology, 96 (4): 981-988 (1989).

3. Adam J, Barret A, Barret-Bellet C, *et. al.* Controlled double blind clinical trials of Ultra-levure: Multi-center study involving 25 physicians and 388 cases. Médecine et Chirurgie Digestives, 5 (6): 401-406 (1976).

4. McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Noyer KA, Melcher SA, Bowen KE, Cox JL, Noorani Z, Harrington G, Rubin M, and Greenwald D. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for Clostridium difficile disease. JAMA, 271: (24) 1913-1918 (1994).

5. Buts JP, Corthier G, and Delmee M. *Saccharomyces boulardii* for *Clostridium difficile*-associated enteropathies in infants. Journal of Pediatric Gastroenterology and Nutrition, 16: 419-425 (1993).

6. Hecker H. Results of a multicentre postmarketing surveillance study: Perenterol treatment in small children with diarrhea. Kinder- und Jungendmedizin, 2: 48 – 49 (2001).

7. Hoechter W, Chase D, and Hagenhoff G. *Saccharomyces boulardii*in acute adult diarrhea. Münchener Medizinische Wochenschrift, 132 (12): 188-192 (1990).

8. Chapoy P. Treatment of infantile acute diarrhea: Controlled trial of *Saccharomyces boulardii*. Annales de Pédiatrie, 32 (6): 561-563 (1985).

9. Cetina-Sauri G, Sierra Basto G. Therapeutic evaluation of *Saccharomyces boulardi* in children with acute diarrhea. Annales de Pédiatrie, 41 (6): 397-400 (1994). English translation of original article: Trib. Med. (56(2): 111-115 (1989).

10. Bleichner G, Blehaut H, Mentec H, and Moyse D. *Saccharomyces boulardii* prevents diarrhea in critically ill tube-fed patients. Intensive Care Medicine, 23: 517-523 (1997).

11. Saint-Marc T, Blehaut H, Musial C, and Touraine JL. AIDs-related diarrhea: A double blind trial of *Saccharomyces boulardii*. Semaine des Hôpitaux, 71 (23-24): 735-741 (1995).

12. Kollaritsch R, Holst R, Grobara P, and Wiedermann G. Prophylaxis of traveler's diarrhea with *Saccharomyces boulardii*. Fortschritte der Medizin, 111 (9): 152-156 (1993).

Review Articles

13. Davidson GP and Butler RN. Probiotics in pediatric gastrointestinal disorders. Current Opinion in Pediatrics, 12 (5): 477-481 (2000).

14. Elmer GW. Probiotics: "Living drugs." Am. J. Health-Syst. Pharm., 58 (12): 1101-1109 (2001).

15. McFarland LV and Bernasconi P. *Saccharomyces boulardii*: A review of an innovative biotherapeutic agent. Microbial Ecology in Health and Disease, 6: 157-171 (1993).

Appendix II

Table 1. Summary of scientific publications included in this Notification of a New Dietary Ingredient reporting safety and effectiveness of *Saccharomyces. Boulardii* (S.B.) in clinical trials. (Reference numbers correspond to bibliography in Appendix I.)

Ref #	Study	Age of Subjects (yrs)	# of Subjects	Daily Dose (mg/day)	Efficacy	Safety
	Antibiotic-associated diarrhea					
1	McFarland, et al. *The Am. J. Gastroenterol.* (1995)	18 -86	193	1000	S.B. was effective in decreasing incidence of diarrhea: S.B. group: 7/97 (7.2%) Placebo: 14/96 (14.96%)	No significant adverse events were reported among patients receiving S.B.
2	Surawicz, et al. *Gastroenterol* (1989)	18 – 100	180	250	S.B. was effective in decreasing incidence of diarrhea: S.B. group: 11/116 (9.5%) Placebo: 14/64 (21.8%)	No side effects were reported.
3	Adam, et al. *Médecine et Chirurgie Digestives* (1976)	≤ 16	388	250	S.B. was effective in decreasing incidence of diarrhea: S.B. group: 9/199 (4.52%) Placebo: 33/189 (17.5%)	No side effects were reported.
	Clostridium difficile-associated diarrhea (CDD)					
4	McFarland, et al. *JAMA* (1994)	Adults	124	1000	S.B. was effective in decreasing incidence of recurrence of CDD: S.B. group: 26.3% recurrence Placebo: 44.8% recurrence	Thirst (n = 5) Constipation (n = 8)
5	Buts, et al. *J. Ped. Gastroenterol.* (1993)	0.2 - 11	19	< 1yr: 500 1-4yr: 750 >4yr: 1000	S.B. eliminated diarrhea in 18/19 (95%) subjects.	No side effects were reported.

Ref #	Study	Age of Subjects (yrs)	# of Subjects	Daily Dose (mg/day)	Efficacy	Safety
	Acute diarrhea					
6	Hecker, *Kinder- und Jugendmedizin* (2001)	0 – 17	940	50-1500	Physicians' assessment of S.B. (Perenterol) in children: Efficacy: "very good" = 52%; "good" = 38% Tolerability: "very good" = 70%; "good" = 29%	1.7% experienced side effects (flatulence or allergic reactions). "The safety of using Perenterol [*S. boulardii*] even in small children, which had already been empirically shown during many years of extensive use …, was confirmed during the present study ***."
7	Hoechter, et al., *Munch. Med. Wschr.* (1990)	18-65	92	150 – 200	S.B. significantly decreased frequency of loose stools within 2 days: S.B. group: 17.2% reduction Placebo: 13.6% reduction	"No severe side effects were observed in any patient." One patient in each group (S.B. and placeo) reported constipation or vomiting.
8	Chapoy, et al. *Annal. de Ped.* (1985)	Infants	38	500	S.B. significantly decreased the frequency and weight of loose stools.	"No side effects were noted and the acceptability of treatment was excellent."
9	Cetina-Sauri and S. Basto, *Trib. Med.* (1989)	0.25 - 3	130	800	S.B. significantly decreased the number of loose stools within 1 – 4 days.	"The number of clinical cures was larger than in the placebo group … there were no side effects."
	Tube-fed patients					
10	Bleichner, et al., *Int. Care Med.* (1997) Multi-center, randomized, double blind, placebo controlled study.	≤ 18	128	2000	S.B. significantly reduced the percentage of days with diarrhea: S.B. group: 14.2% Placebo: 18.9%	"The tolerance of *S. boulardii* was good and no adverse effect was noted."

Ref #	Study	Age of Subjects (yrs)	# of Subjects	Daily Dose (mg/day)	Efficacy	Safety
	AIDS					
11	Saint-Marc, et al. *Semaine des Hôpitaux* (1995) Randomized, double blind, placebo controlled study.	≥ 18	36	1500-3000	A significantly higher percentage of subjects receiving S.B had diarrhea resolved within 1 week: S.B. group: 61% resolved Placebo: 12% resolved	"Tolerability was outstanding." "[T]olerability of *S. boulardii* was excellent in all patients, with a total absence of adverse effects ...." "No clinical or paraclinical adverse events have occurred in the patients followed for a longer time."
	Traveler's Diarrhea					
12	Kollaritsch, et al., *Fortschr. Med.* (1993) Randomized, double blind, placebo controlled study.	> 6	1016	250-1000	S.B. reduced the rate of diarrhea: S.B. group (n = 655): 28.7% Placebo (n = 361): 39.1%	"No severe side effects or disorders necessitating discontinuation of administration were reported. This may demonstrate that the safety profile of SB is excellent and thus represents a more or less ideal prophylactic agent."

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Publications