

ATTACHMENT 4



ATTACHMENT 4

SALES IN OTHER COUNTRIES

Pages 132-142 redacted

ADDENDUM
Florastor (*Saccharomyces boulardii*) :

Time and Extent Application (TEA)

-COMPLEMENT FOR COUNTRIES FROM AFRICA & ASIA-

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2. LIST OF ALL COUNTRIES WHERE THE CONDITION IS MARKETED

See Attachment 2 (page 53).

**INFORMATION IN ACCORDANCE WITH PARAGRAPHS (C)(2)(I)
THROUGH (C)(2)(V) OF 21 CFR 330.14 SUBPART B.**

List of countries where supply is equivalent to OTC sale for which information in accordance with paragraphs (c)(2)(i) through (c)(2)(v) of 21 CFR 330.14 Subpart B is supplied :

AFRICA

Ivory Coast

Morocco

Senegal

South Africa

ASIA

India

Korea

These countries have been selected to supplement data included in original TEA with data from representative African and Asian countries in order to be totally reflective of the US population with regards to ethnic/ racial demographic considerations.

2(i) HOW THE CONDITION HAS BEEN MARKETED

TABLE 1 : Details on marketing regulation in additional countries selected for inclusion in the TEA.

Country	Drug sold in any general store	Sales of the drug restricted to pharmacies	Personal involvement of the pharmacist is required for delivering the drug
<i>AFRICA</i>			
IVORY COAST	no	yes	no
MOROCCO	no	yes	no
SENEGAL	no	yes	no
SOUTH AFRICA	yes	no	no
<i>ASIA</i>			
INDIA	no	yes	no
KOREA	no	yes	yes

**2(ii) CUMULATIVE NUMBER OF DOSAGE UNITS SOLD AND ESTIMATE OF POTENTIAL
CONSUMER EXPOSURE TO OTC SALES**

Table 2 : See on following page 5

Pages 5-9 redacted

**2(III) DESCRIPTION OF POPULATION DEMOGRAPHICS TO ENSURE THAT USE CAN BE
EXTRAPOLATED TO U.S. POPULATION**

Information relating to population demographics in the additional selected countries in Africa and Asia are provided in the following tables.

As discussed in the original TEA application dated December 2003, the sponsor is not aware on any population demographic factors such as racial/ethnic group that impacts upon either the safety or efficacy of *S. boulardii*. All available data support the fact that no population demographic factors as racial / ethnic group should impact upon either the safety or efficacy of *S. boulardii* when used in the USA.

DESCRIPTION OF THE POPULATION DEMOGRAPHICS

Sources Providing Information for Individual Countries

The following information sources have been identified that provide racial/ethnic demographic information for individual countries.

Source of Information	Country: Senegal										
Ministry of the environment of Senegal. http://ns.cse.sn	<p>The population in 2002 has been estimated to 9,855 million. There are mainly 5 ethnical groups that constitute the population:</p> <ul style="list-style-type: none"> • The <u>Wolof</u> is by far the largest ethnic group and comprises 42% of the population • The <u>Peul</u>, also known as Fulani, Fulbe or Fula, form 24% of the population • The <u>Serer</u> make up about 15-17% of the present population. • The <u>Diola</u> form 9% of the population. • The <u>Mandinka</u> (Mandingue, Malinke) represent 4%. <p>Other smaller ethnic groups include the <u>Lebou</u>, the <u>Soninke</u>, and the <u>Bassari</u>.</p>										
Source of Information	Country: South Africa										
<p>Statistics South Africa, Census 2001 (http://www.statssa.gov.za/SpecialProjects/Census2001/Census2001.htm)</p>	<table> <tr> <td>Black African</td> <td>35 416 166 (79.0%)</td> </tr> <tr> <td>Coloured</td> <td>3 994 505 (8.9%)</td> </tr> <tr> <td>Indian or Asian</td> <td>1 115 467 (2.5%)</td> </tr> <tr> <td>White</td> <td>4 293 640 (9.6%)</td> </tr> <tr> <td>Total</td> <td>44 819 778</td> </tr> </table>	Black African	35 416 166 (79.0%)	Coloured	3 994 505 (8.9%)	Indian or Asian	1 115 467 (2.5%)	White	4 293 640 (9.6%)	Total	44 819 778
Black African	35 416 166 (79.0%)										
Coloured	3 994 505 (8.9%)										
Indian or Asian	1 115 467 (2.5%)										
White	4 293 640 (9.6%)										
Total	44 819 778										

Sources Providing Information for Several Countries

The following information sources have been identified that provide racial/ ethnic demographic information for several countries. Where available, the data for the U.S.A from these sources is included below for comparative information.

Source of Information	Country Information						
	U.S.A.	India	South Korea	Senegal	Morocco	Ivory Coast	South Africa
U.S. State Department: country background notes http://www.state.gov/r/pa/ei/bgn/ Accessed 29 March 2004	Data not presented	Indo-Aryan 72%, Dravidian 25%, Mongoloid 2%, others (1/ 2004)	Korean; small Chinese minority (3/ 2004)	Wolof 43%; Fulani (Peulh) and Toucouleur 23%; Serer 15%; Diola, Mandingo, and others 19% (6/ 2003)	Arab-Berber 99% (11/ 2003)	More than 60 ethnic groups, classified into five principal divisions: Akan, Krou, Mande, Northern Mande, Senoufo/Lobi. The Baoules, in the Akan comprise the largest-single subgroup (15-20% of the population). The Betes, the Senoufos in, and the Malinkes are the next largest groups, (10-15% each of the population): 0/ 2003	black 77.8%; white 10.2%; colored 8.7%; Asian (Indian) 2.5%; other 0.8.5% (6/ 2003)

Source of Information	Country Information						
	U.S.A.	India	South Korea	Senegal	Morocco	Ivory Coast	South Africa
The CIA World Fact Book 2002 http://www.cia.gov/cia/publications/factbook/fields/2075.html This entry provides a rank ordering of ethnic groups starting with the largest and normally includes the percent of total population. Accessed 29 March 2004	white 77.1%, black 12.9%, Asian 4.2%, Amerindian and Alaska native 1.5%, native Hawaiian and other Pacific islander 0.3%, other 4% (2000)	Indo-Aryan 72%, Dravidian 25%, Mongoloid and other 3% (2000)	homogeneous (except for about 20,000 Chinese)	Wolof 43.3%, Pular 23.8%, Serer 14.7%, Jola 3.7%, Mandinka 3%, Soninke 1.1%, European and Lebanese 1% other 9.4%	Arab-Berber 99.1% other 0.7% Jewish 0.2%	Akan 42.1% Voltaiques or Gur 17.6% Northern Mandes 16.5% Krous 11% Southern Mandes 10% other 2.8% (includes 130,000 Lebanese and 20,000 French) (1998)	black 75.2%, white 13.6%, Colored 8.6%, Indian 2.6%

Source of Information	Country Information						
	U.S.A.	India	South Korea	Senegal	Morocco	Ivory Coast	South Africa
Map Zones http://www.mapzones.com Accessed 29 March 2004	80%White 12%Black 3%Asian and Pacific Islanders 5%Other including Native Americans and many other groups	72% Indo-Aryans 25% Dravidians 3% Other including Mongoloids	99.9%Korean 0.1%Other mostly Chinese	Wolof 36% Fulani 17% Serer 17% Toucouleur 9% Diola 9% Mandingo 9% European and Lebanese 1% other 2%	Data not presented	Data not presented	75.2%Black African including Zulu, Xhosa, Tswana, and Sotho 13.6%White including Afrikaners and British 8.6%Coloured (mixed race) 2.6%Asian mostly Indians

Source of Information	Country Information						
	U.S.A.	India	Korea	Senegal	Morocco	Ivory Coast	South Africa
InfoPlease Almanac: Ethnicity and Race by Countries http://www.infoplease.com/ipa/A0855617.html Accessed March 29, 2004	White. 75.1%; Black:12.3%, American Indian and Alaska Native: 0.9%; Asian:3.6%; Native Hawaiian and Other Pacific Islander: 0 1%; Other race.5.5%; Hispanic origin: 12.5%	Indo-Aryan 72% Dravidian 25% Mongoloid and other 3% (2000)	South Korea homogeneous (except for about 20,000 Chinese)	Wolof 36%, Fulani 17%, Serer 17%, Toucouleur 9%, Diola 9%, Mandingo 9%, European and Lebanese 1%, other 2%	Arab-Berber 99.1% other 0.7% Jewish 0.2%	Akan 42.1% Voltaiques (Gur) 17.6% Northern Mandes 16.5% Krous 11% Southern Mandes 10% other 2.8% (includes 130,000 Lebanese and 20,000 French)	black 75.2% white 13.6% Colored 8.6% Indian 2.6%

Source of Information	Country Information						
	U.S.A.	India	Korea	Senegal	Morocco	Ivory Coast	South Africa
Population Statistics: http://www.library.uu.nl/wesp/populstat/populhome.html Accessed 29 March 2004	Non-Hispanic white 75%; non- Hispanic black 12%; Hispanic 10%; Asian/Pacific islanders 3,3%; American Indian and Eskimo 0,7%	Indo-Aryan (Caucasoid) 72%; Dravidian (Aboriginal) 25; others (Mongoloid) 3	Korean 99,9%	Wolof 43%; Serer 15%; Fulani (Peul) 14%; Tukolor 9%; Diola 5%; Mandingo 4%; other 10%	Arab 65%; Berber 33%; other less than 1%	Akan 30-42%; Volta 11,7-16%, Malinke 16%; Mane Nord 11,4%; Krou 10,5- 15%; Mande Sud 7,7- 11%	black 77,6% (Zulu, Xhosa, Pedi, Sotho, Tswana); white 10,4%; coloured 8,7%; Asian 2,5%

Source of Information	Country Information						
	U.S.A.	India	South Korea	Senegal	Morocco	Ivory Coast	South Africa
Source Yahoo World Fact Book (http://education.yahoo.com/reference/factbook/po/popula.html)	white 83.5%, black 12.4%, Asian 3.3%, Amerindian 0.8% (1992)	Indo-Aryan 72%, Dravidian 25%, Mongoloid and other 3%	homogeneous (except for about 20,000 Chinese)	Wolof 43.3%, Pular 23.8%, Serer 14.7%, Jola 3.7%, Mandinka 3%, Soninke 1.1%, European and Lebanese 1%, other 9.4%	Arab-Berber 99.1%, other 0.7%, Jewish 0.2%	Baoule 23%, Bete 18%, Senoufou 15%, Malinke 11%, Agni, Africans from other countries (mostly Burkinabe and Malians, about 3 million), non-Africans 130,000 to 330,000 (French 30,000 and Lebanese 100,000 to 300,000)	black 75.2%, white 13.6%, Colored 8.6%, Indian 2.6%

2(IV) DIFFERENCES IN PATTERN OF USE

TABLE 4 : Pattern of use : Current approved OTC / Prescription dose and duration

Country	Dosage	Daily dose		How often the drug is to be used in the day	Duration of treatment
		Number of capsules	mg / day		
AFRICA					
IVORY COAST	50 mg capsule	4	200	Twice a day	Not specified
	250 mg sachet	2	500	Twice a day	
MOROCCO	250 mg capsule	1 to 2	250 - 500	One or twice a day	Not specified
SENEGAL	50 mg capsule	4	200	Twice a day	Not specified
	250 mg sachet	2	500	Twice a day	Not specified
SOUTH AFRICA	250 mg capsule	2	500	Twice a day	Not specified
	50 mg capsule	1 to 4	50 - 200	One or twice a day	Not specified
ASIA					
INDIA	250 mg capsule ⁽¹⁾	1 to 4	250 - 1000	Twice a day	Not specified
	sachet	2 to 4	500 - 100	Twice a day	
KOREA	250 mg capsule and sachet	2 to 4	500 - 1000	Twice a day	max. 30 days
	100 mg capsule	3 to 6	300 - 600	3 times a day	max. 30 days

⁽¹⁾ The drug "econorm" that is sold as sachets is, in addition, presented also as capsules from April 2004.

Explanatory comments regarding differences in pattern of use across countries :

There are differences from one country to another but globally daily doses are typically in the range of 250 (or 200 mg) to 500 mg. The dosage proposed for OTC use in the U.S. is consistent with the dosage range approved globally.

- Different capsule strengths i.e. 50 or 250 mg are marketed in different countries dependant upon local marketing strategy and preferences.
- The drug is usually taken twice a day.
- Duration of treatment is not specified in any country, except for Korea.

**2(V) COUNTRIES SYSTEM FOR IDENTIFYING ADVERSE EXPERIENCES.
PARTICULARLY THOSE WHICH OCCUR IN AN OTC SETTING**

Ivory Coast and Senegal

There is no official organisation for collecting information on side effects or adverse drug reactions.

Morocco

The pharmacovigilance system is run by the Moroccan Anti-poison Center located in the Hygiene National Institute part of Moroccan Ministry of Health. This center is also responsible for any toxicological events at both levels: individual and collective. Morocco has a decentralised system of pharmacovigilance. There are seven regional centres of pharmacovigilance who report regularly to the Anti-poison Centre. This system is responsible for all medicinal products: prescription drugs and over-the-counter drugs. In 1992 Moroccan Anti-poison Centre has been recognised as the 34th collaborative center of the W.H.O. Collaborating Centers for Pharmacovigilance.

Healthcare professionals (physicians, clinicians, pharmacists, nurses, dentists, pharmaceutical industry) and public submit adverse drug reaction report via phone call, mail to the regional centers or directly to the Moroccan Anti-poison Centre. An electronic ADR form to fill and submit is available on the Moroccan Anti-poison Centre website.

Regional centers reports once a month any ADRs to Moroccan Anti-poison Centre. The applicant must report all serious suspected adverse drug reactions, within 24 hours.

South Africa

South Africa has a well developed system for reporting and collection of adverse drug reactions. In South Africa, all reportable adverse drug reactions associated with 'Over The Counter' (OTC) products are sent to the National Adverse Drug Event Monitoring Centre (NADEMC) within the Medicines Control Council (MCC).

The National Adverse Drug Event Monitoring Centre (NADEMC) is a special unit of the Medicines Control Council, Department of Health, based in the Division of Pharmacology, Department of Medicine. The Division of Pharmacology provides the unit with close links with medical and pharmacy practice which strengthens the work of the monitoring centre. The aim of the NADEMC is to monitor the safety of medicines used in South Africa. The main purpose of the centre is to identify as rapidly as possible serious, previously unrecognised reactions to drugs, and to establish the causal relationship between the drug and the reaction. The centre uses a system of voluntary reporting of suspected adverse reactions to drugs by the health professions. Doctors, dentists, pharmacists and other health care professionals are asked to report all suspected adverse drug events, irrespective of whether the event is

well recognised or previously unreported, potentially serious or clinically insignificant. Reports are not usually accepted directly from patients as a medical opinion on any adverse reaction is important. Patients who experience a suspected adverse reaction are advised to report this to a medical practitioner, dentist, pharmacist, nurse or other health professional who should then report to the NADEMC.

Reporting by Health Care Professionals can be carried out using the adverse reaction report form available from the NADEMC (Adverse Drug Reaction and Product Quality Problem Report Form). Alternatively in-house report forms can be used providing that all the necessary data elements are included on the form in a readable format. All unexpected adverse drug reactions (serious or non serious) must be reported within fifteen days of first noting.

The NADEMC serves as the national contributing centre to the World Health Organization programme on International Drug Monitoring in Uppsala, Sweden. When an ADR report form is received by the NADEMC, the data is entered into the Centre's Adverse Drug Reaction Information (ADRI) database and given a unique identification number. The reporter will receive an acknowledgement letter, which will quote the unique identification number of the report. ADR reports are evaluated by the NADEMC to assess the causal relationship between the medicine and the reported reaction. The data, together with data from other sources, are used to assist in the evaluation and monitoring of the post-marketing safety of medicines.

India

Active monitoring of adverse drug reactions in India has been in place since 1982.

India has a decentralised system of pharmacovigilance. The regional pharmacovigilance centers are located in PGI (Chandigarh), JIPMER (Pondicherry), KGMC (Lucknow), and Seth GS Medical College (Mumbai). These centres report ADRs to the National Pharmacovigilance Center. The National Pharmacovigilance Center is located in the Department of Pharmacology part of All India Institute of Medical Sciences, New Delhi. It is affiliated to WHO collaborating Centre for ADR Monitoring, Uppsala, Sweden.

Healthcare professionals (physicians, dentists, nurses, pharmacist) can report suspected adverse drug reactions by letter, phone, fax, email or by personal contact to any of the five adverse drug reaction monitoring centers. A postal ADRs Monitoring form can be used for reporting, this is available from the Central Drug Standards Control Organization (CDSCO), part of the Ministry of Health and Family Welfare. The submitted data will be collated and evaluated by the National Pharmacovigilance Center.

The National Pharmacovigilance Centre, AIIMS, New Delhi invites reports of all suspected adverse reactions to drugs and other medicinal substances, including herbal, traditional or alternative remedies. The Centre particularly requests reports of:

- All suspected reactions to new drugs especially drugs of current interest and/or uncommon, severe and life threatening reactions to older drugs.

- All suspected drug interactions resulting in ADRs.

- Reactions to other drugs which are suspected of significantly affecting a patient's management including reactions suspected of causing :
 - Death
 - Danger to life
 - Resulting in hospitalization
 - Prolongation of hospitalization
 - Absence from productive activity
 - Increased investigational or treatment costs
 - Birth defects

Korea

The Korean Food and Drug Administration (KFDA), is the regulatory authority of South Korea, which is responsible for all the affairs such as drug approval, safety control of pharmaceuticals/cosmetics/foods, and their safety/efficacy evaluation. The department responsible for pharmacovigilance in KFDA is the Pharmaceutical Safety Bureau, which is divided to 5 divisions, of which two divisions are mainly involved in pharmacovigilance: pharmaceutical safety division for AE/ADRs from clinical trials and pharmaceutical surveillance division for most AE/ADR monitoring. Most of AE/ADR reports are sent to pharmaceutical surveillance division except for those from clinical trials, which are sent to pharmaceutical safety division

There are three major sources where drug safety information can be collected: clinical trials, post marketing surveillance (PMS) required by KFDA and spontaneous reports from routine medical practices. PMS is implemented to fulfill re-examination of a new pharmaceutical product (or new indication, preparation, etc) after its approval by KFDA with a certain minimum number of cases to be collected (3000 or 600) during a defined number of years (6 or 4 years). This particular regulation of PMS is very similar to the one in Japan, for reference. KFDA defines the period and the number of cases to be collected for re-examination requirement. The duration of the surveillance is either for 6 or 4 years from the date of a product approval.

- 6-year requirement: New molecular entity, a drug with different type of active ingredient or different combination of the ingredients from a drug already in the market, a drug with the same active ingredient to a product already in the market but with different route of administration.

- 4-year requirement: A drug with the same active ingredient and the same route of administration to a product already in the market but with additional indication apparently different from the one already in the market, others that KFDA acknowledged to require to implement re-examination.

The number of cases required to collect during the re-examination period is either 3000 or 600.

- 3000 cases: New molecular entity developed in Korea for the first time, new molecular entity under development outside Korea (one not approved in Korea), new molecular entity developed and approved outside Korea with its approval date not

longer than 3 years in the country where the product was developed, new molecular entity developed and approved outside Korea and its use only limited in the country where the product was developed.

- 600 cases: The others (those not under 3000 case-requirement)

In terms of the regulation, KFDA defines the methods of monitoring AE/ADRs in the following six categories:

- 1) Spontaneous or voluntary reporting system: requesting physicians or pharmacists to report AE/ADRs spontaneously after using a drug.
- 2) Mandatory or compulsory monitoring system: obligating physicians or hospital to report AE/ADRs after using a drug
- 3) Regulatory monitoring system: obligating pharmaceutical companies to collect and report AE/ADRs for their products
- 4) Intensive monitoring system: monitoring AE/ADRs by setting the patient group with AE/ADRs of a drug as a numerator and the patient group with the experience of the drug as a denominator by forming the monitoring team consisting of physicians, nurses, pharmacists, etc.
- 5) Recording linkage monitoring system: collecting and monitoring all the records of individual patients such as admission record, outpatient record, vaccination record, death certificate, etc.
- 6) Published information monitoring: collecting AE/ADRs through literature such as conference report, WHO reports including clinical data, safety bulletin from regulatory agencies of other countries, medical and pharmaceutical book and journals, etc.

As described above, most of AE/ADR reports go to pharmaceutical surveillance division. KFDA requires physicians, pharmacists, herb doctors and nurses to report any adverse event (AE) and/or adverse drug reaction (ADR) to KFDA within certain time frame indicated in the regulation. For AE/ADRs that are serious (SAE/SADRs), they should be reported within 15 days from the time that SAE/SADRs were noted by the one who reports them. The others are to be reported within 3 months, according to the temporary article of the regulation prepared by KFDA (to be officially announced soon). There is a standard form provided by KFDA for reporting AE/ADRs from post marketing surveillance and spontaneous AE/ADRs. The one from PMS contains the summary of reassessment information approved by KFDA and the details of AE/ADR information such as patient, description of AE/ADR, date of onset, causal relationship, etc. The form for spontaneous AE/ADR report does not include the summary of reassessment information, however.

The pharmacovigilance system in Korea can be viewed as a centralized system because the commissioner office (central office) has the organization (pharmaceutical surveillance division) to collect and monitor safety information in one database although they may be collected through regional offices. KFDA has a website for health care professionals and pharmaceutical companies to report AE/ADRs. They can also be reported via facsimile. No particular systems apply specifically to pharmacovigilance requirements for over-the-counter products by KFDA.

3. HOW LONG CONDITION HAS BEEN MARKETED IN EACH COUNTRY.
HOW LONG CURRENT LABELLING HAS BEEN APPROVED

TABLE 5 : Duration of marketing ; labelling

Country	How long the drug has been marketed	How long current labelling has been in use	It has been authorized accepted or approved by a regulatory body
<i>AFRICA</i>			
IVORY COAST	Around 40 years	7 years	no
MOROCCO	12 years	1 year	no
SENEGAL	Around 40 years	7 years	no
SOUTH AFRICA	250 mg 2 years	2 years	no
	50 mg more than 10 years	more than 10 years	yes
<i>ASIA</i>			
INDIA	6 years	6 years	yes
KOREA	Over 14 years	Over 14 years	yes