DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date JUL 10 2000

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From (Acting) Division Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplement, HFS-820

Subject 75-Day Premarket Notification for New Dietary Ingredients

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	ProenOthera™
Firm:	Humanetics Corporation
Date Received by FDA:	April 27, 2000
90-Day Date:	July 25, 2000

In accordance with the requirements of section 413(a) 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 July 25, 2000.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT 73

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

JUL 10 2000

Ronald J. Zenk
President and CEO
Humanetics Corporation
18894 Lake Drive East
Chanhassen, Minnesota 55317

Dear Mr. Zenk:

This is in response to your letter to the Food and Drug Administration (FDA) dated April 27, 2000, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)). Your letter notified FDA of your intent to market a dietary supplement product containing the new dietary ingredient ProenOthera™, an extract from the seeds of the Evening Primrose *(Oenothera biennis)*. This new dietary ingredient notification is a resubmission as the first request was received on February 5, 1999, followed by a rejection letter sent on April 19, 1999.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient 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 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 ingredients do not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that the new dietary ingredient stated above will reasonably be expected to be safe. The information in your submission does not meet the requirements of 21 CFR 190.6(b)(3) because the actual description of the dietary supplement product is not specified exactly, instead noted generically as tablet, capsule or liquid. Your submission specifies two (2) dosage levels (50 mg and 200 mg) of the new dietary ingredient in a generic dietary supplement product. The dosage level for the new dietary ingredient needs clarification. In addition to these two (2) deficiencies (the description and dosage level of the new

dietary ingredient in the dietary supplement product), the conditions of use for the dietary supplement product that will marketed are not specified (see 21 CFR 190.6(b)(3)(i)).

Your submission contains evidence of history of use and other information that you assert is an adequate basis to conclude that the type of dietary supplement product containing the new dietary ingredient will reasonably be expected to be safe. Some of our concerns are identical to those concerns that were addressed in our letter to you dated April 19, 1999. For instance, you have indicated that the polyphenolic components, such as flavonoids, flavonoid oligomers, hydrolysable and non-hydrolysable tannins, ellagitannins, and gallotannis that comprise ProenOthera™ are widespread in common human foodstuffs. You also state that due to the complexity of the extract's composition, it is not "practical to chemically identify each component of the extract." Because the composition of the extract comprising ProenOthera™ is complex, you have taken a threefold approach to establish the safety of the new dietary ingredient ProenOthera™. Our examination of the information you submitted to establish the safety of ProenOthera™, however reveals that the information in the submission is inadequate to make such a determination (see 21 CFR 190.6(b)(4)). We describe below why we have concluded that the information you have submitted does not establish that a dietary supplement containing ProenOthera™ would be reasonably expected to be safe.

First, you state that history of use of various parts of the *Oneothera biennis* plant (e.g., leaves, shoots, roots) and its seeds in humans provides a basis to conclude your proposed product is safe. You state that *Oneothera biennis* was historically used as a food or medicine by the North American Indians and Europeans. However, significant differences in how the plants and their extracts were used appear to exist between the traditional food or medicinal uses of *Oenothera biennis* and the use of your proposed dietary supplement ProenOthera™. For example, the references that you provide that describe the traditional uses contain cautions about the use of this plant (e.g., "use with extreme caution," "use at your own risk," and "use with guidance of a medicine man"). Other evidence states that the historical use was either brief or for intermittent periods of time for specific health conditions (e.g., "piles," "skin diseases," or "cough and asthma") and not for chronic or long time use. In addition, many of the suggested treatments described in the references are for dermal exposure (e.g., "poultice," "wash," "ointment or dermal rub") and not oral exposure. Taken together, the information describing the historical usage of *Oenothera biennis* make it difficult to compare traditional food or medicinal use of *Oenothera biennis* and the dietary supplement ProenOthera™ and preclude this information from being a valid basis to conclude that your dietary supplement is reasonably expected to be safe.

You also asserted that the contemporary use of evening primrose-based products as dietary supplements in other countries provides a basis to conclude that your product is safe. However, no information is provided about post – market adverse effect reporting or surveillance programs that would establish the safety of these products. Moreover, the listing of one such product, Procell, on the Australian Register of Therapeutic Goods only

appears to reflect its compliance with product ingredient specifications and approved therapeutic claims, not as indicative of any assessment of the safety of this product.

In your second approach to establish the safety of ProenOthera™, you asserted that the chemicals present in this dietary supplement are comparable to those present in the typical diet. A list quantifying some of the major chemical components contained in ProenOthera™ along with examples of the levels of these chemicals in some food or beverages or herbal supplements was presented. Based on the data, your submission states that a typical diet provides about 78% of the amount of the representative substances in ProenOthera™. However, no assessment is given of the safety of the aggregate exposure to these polyphenolic components from typical dietary exposure in addition to the amount associated with dietary supplement exposure. The chemical composition of this type of plant extract and the foods and beverages described in the submission may vary considerably. This makes assessment of their toxicity or safety difficult and a lack of information or great uncertainty in the available information can not be interpreted to evidence lack of potential toxicity or to establish that a substance is safe. Moreover, several of the dietary items used for comparison to ProenOthera™ may not be associated with daily dietary exposure (e.g., "red wine," "raspberry juice," peony root") for most people, which limits the relevance as a basis for assessing the safety of these substances for daily use. Also literature values for the level of polyphenolic chemicals in foods varies widely (see Rommel, A., Red raspberry phenolic: Influence of processing, variety, and environmental factors, In: Phenolic Compounds in Foods and their Effects on Health, Edited by C-T Ho, CY Lee, M-T Huang, ACS Symposium Series 506: 259-286, 1992 versus Daniel, E.M. et. Al., Extraction, stability, and quantification of ellagic acid in various fruits and nuts, J. Food Composition and Analysis, 2: 338-349, 1989).

Your third approach was to provide information from human and animal studies to establish the safety of ProenOthera™. You stated that two human clinical trials using selected polyphenolic compounds found in ProenOthera™ have been performed. But neither of these studies provided information adequate to establish the safety of ProenOthera™. One study was an epidemiological study that was designed to assess the safety of the substances in ProenOthera™. The other study is, however, only a reference to studies that may have been conducted, but it contained no data or references that would enable you to provide a basis for determining whether ProenOthera™ was safe.

Your submission also provided data from two (2) 28-day animal studies. You stated that this information is evidence of the safety of chronic exposure to ProenOthera™. We disagree that these studies provide a basis to conclude that ProenOthera™ is safe. First, studies of a 28-day duration period are of limited utility to assess the effects of chronic exposure to a substance. Second, differences in some outcome measurements were seen in experimental animals in the control and treatment groups. However, the submission does not explain why these findings are not problematic. For example, a dose-related decrease in the liver enzymes alanine aminotransferase (ALT) and aspartate

aminotransferase (AST) was reported in both female and male rats in both studies. Both studies also reported an increase in blood urea and a decrease in total serum protein in female rats and a dose-related decrease in creatine phosphokinase (CK) and sorbitol dehydrogenase (SDH) in male rats. ProenOthera™ also induced significant decreases in potassium (K) in both females and males in both studies.

Changes in several hematology parameters, such as statistical increases in hematocrit (HCT), hemoglobin (HB), red blood cell count (RBC) and white blood count (WBC) and non-significant trends in platelet and lymphocyte numbers, were also seen in male rats treated for 28-days with exposure to ProenOthera™ in 3, 30, and 90 mg/kg/day dosages. Although not statistically significant, a similar pattern of effects on these measures was seen in ProenOthera™-treated female rats. The nature or significance of the effects of ProenOthera™ on the blood chemistries and hematologic measures were not addressed or explained in your submission. Given the large variability in data and small sample size of the animal groups, these findings raise questions about the safety of long-term consumption of ProenOthera™ that need further clarification and explanation.

The submission also contains data of the histopathological analysis of tissues from the experiments that exposed rats to 90 mg and 300 mg ProenOthera™/kg bw/day. But, no indication of the experimental group to which each animal belonged was provided making the assessment of the histopathological findings and distinguishing treatment effects difficult. Autolysis of the gastrointestinal tract (jejunum, ileum and cecum) was reported in a number of individual rats. The data seem to suggest that this pathology appeared to occur more often in ProenOthera™-treated rats than in the control rats. This finding suggests that further assessment of this and other histopathological findings is needed because some polyphenols have been found to alter the status and processes of the digestive tract. For example, tannins have been demonstrated to damage the mucosal lining of the gastrointestinal tract (see Mitjavila, S., et. at., Tannic acid and oxidized tannic acid on the functional state of rat intestinal epithelium, J Nutr 107:2113, 1977; Deshpande, S. S., et. al., Chemistry and safety of plant polyphenols, Advances in Experimental Medicine and Biology, 177: 457-496, 1984) and to bind both dietary proteins and endogenous proteins to form insoluble tannin-protein complexes.

Finally, the data from the second animal study provided, which exposed male and female rats to 300 mg ProenOthera™/kg bw/day, are questionable for drawing meaningful conclusions because it appears that an appropriate control group was not included with the treatment group. An examination of the findings for the experiment shows that the control data (mean, maximum, minimum, SEM) for the second experiment are identical for a number of clinical measurements to those in the first animal experiment, suggesting that no control animals were run in the second experiment and the control data from the first experiment were used for comparison. This is not a valid experimental procedure.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that ProenOthera™, when used under the conditions

recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(b) as a dietary supplement that contains the new dietary ingredient specified for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under 21 U.S.C 331(a) and (v).

Please contact us if you have any questions concerning this matter.

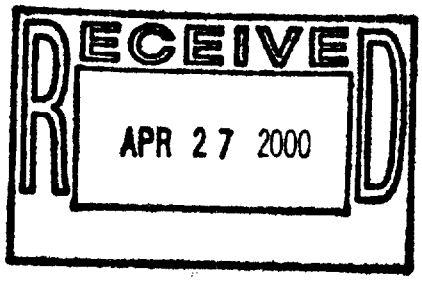
Sincerely yours,

Virginia L. Williams

for Felicia B. Satchell
(Acting) Division Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements

HUMANETICS

April 26, 2000



Robert Moore, Ph.D.
Office of Nutritional Products,
Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

Re: ProenOthera™

Dear Dr. Moore:

This new dietary ingredient premarket notification is being filed on behalf of Humanetics, Inc., which will be the distributor of this new dietary ingredient. Please refer to Humanetics' prior filing with respect to this ingredient and the Administration's April 19, 1999 response to that submission.

The name of the new dietary ingredient is ProenOthera™. This ingredient is an extract from the seeds of the Evening Primrose, *Oenothera biennis*.

ProenOthera™ is intended for use in dietary supplements in liquid, capsule or tablet form. It is recommended for use at a level of 50 mg. up to four times per day or for use in a single daily dose of 200 mg. ← 4 x 50 mg

Enclosed herewith is a document setting forth the basis for concluding this new dietary ingredient will reasonably be expected to be safe.

Sincerely yours,

Ronald J. Zenk
President and CEO

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Humanetics Corporation 18894 Lake Drive East Chanhassen, Minnesota 55317 612-937-7660 fax 612-937-7667 www.humaneticscorp.com

NEW ZEALAND PHARMACEUTICALS LIMITED

ProenOthera™

Basis for concluding this new dietary ingredient will reasonably be expected to be safe.

PROENOTHERA™

BASIS FOR CONCLUDING THIS NEW DIETARY INGREDIENT WILL REASONABLY BE EXPECTED TO BE SAFE

Background

ProenOthera™ is an extract from the seeds of the Evening Primrose, *Oenothera biennis,* a native plant species of North America. ProenOthera™ is a natural extract that has not been chemically modified. It is a mixture of polar compounds of which several groups predominate.[1,2]

Owing to a growing understanding of the association between free radicals and some biological systems, there has been intense interest in safe and functional natural compounds that will supplement the antioxidants already part of the diet.[3] For example, pine bark extracts (eg, Pycnogenol®) and grape seed extracts (eg, Activin®) are sold in the USA and in many countries as dietary supplements.

The compounds comprising ProenOthera™ are widespread in nature.[4] The major groups are tannin-derived polyphenolic compounds including flavonoids, flavonoid oligomers, hydrolysable and non-hydrolysable tannins, ellagitannins and gallotannins. Carbohydrates make up the balance of the mass.

The major components of ProenOthera™ are found in edible seeds, fruit, vegetables and many traditional herbal medicines.[5,6,7,8,9] The range of components found in ProenOthera™ is similar to that found in other tannin or polyphenolic extracts derived from vegetable sources, for example pine bark and grape seed extracts.

Over 2000 varieties of flavonoids are known and many of them are present in the human diet. Preparations from plants that contain flavonoids as the principal physiologically functional constituents have been made for centuries to benefit human health.[10]

Recently, trials have confirmed that modest quantities of orally ingested tannins may be nutritionally useful in the human body.[1,11]

Safety Assessments

ProenOthera is a chemically unmodified extract of the seeds of *Oenothera biennis.* The composition of this extract, as with many natural extracts of this nature, is complex, and it is not practical to chemically identify each component of the extract. Our approach to confirming the safety of ProenOthera™ has therefore been threefold. We have:

- established the prior and present existence of *Oenothera biennis* in the human diet.
- identified certain chemical species present in ProenOthera,™ and shown that these species are present in foods or herbal products used in the world today, and compared the levels with those in ProenOthera.™
- carried out trials on rats to assess potential toxic effects and estimated a tolerable upper intake level based on these results.

Historical and present-day use of the Evening primrose plant and ProenOthera™

The Evening Primrose has a history of prior use and ProenOthera™ is a chemically unmodified extract of its seeds. It has been used as a traditional food[5,6] and as a medicine.[5,8,9] It was imported and cultivated in Europe for its edible leaves, shoots and roots.[6] The seedpods of certain varieties were consumed by North American Indians.[6] The seeds of *Oenothera biennis* were also used as a medicine by the Forest Potawatomi[8] and the whole plant has been used as a medicinal tea.[5,8] The oil extracted from evening primrose seeds is sold as a dietary supplement around the world.

Over 400,000 doses of ProenOthera™ have been sold in New Zealand and Australia as a dietary supplement since 1998. In August 1999, the retail antioxidant product Procell™, which contains ProenOthera™ as its active ingredient, was listed on the Australian Register of Therapeutic Goods by the Australian Therapeutic Goods Authority.[12] This procedure is equivalent of the FDA not making any comment on a premarketing notification of a new dietary supplement under the DSHEA.

Identified chemical species of ProenOthera

The mixture of compounds comprising ProenOthera™ is generally found in the normal human diet. The compounds are in dietary seeds, fruits and vegetables that contain phenolic compounds, including flavonoids, gallates, hydrolysable and non-hydrolysable tannins, and the oligomeric proanthocyanidins. Table 1 indicates the chemical species in ProenOthera that have been identified and the estimated intake of these species in other food. This table shows that the identified chemical species in ProenOthera are present in the diet today.

Most of the phenolic compounds found in the Evening Primrose (gallic acid, catechin, oligomeric proanthocyanidins and procyanidin B3) are also present in the widely used pine bark, grape seed and green tea extracts. These extracts have been used in the USA and many other countries for a number of years.

Other compounds in ProenOthera™ but not present in the products detailed above (ellagic acid and pentagalloylglucose), are present in a number of other widely consumed fruit[13] or herbal supplements.[14]

The level of ellagic acid has been quantified in 26 commercial fruits and nuts.[15] Raspberries and blackberries were both found to contain 1.5 mg/g ellagic acid per dry weight of the fruit, strawberries 0.63 mg/g, walnuts 0.59 mg/g, pecans 0.33 mg/g, and cranberries 0.12 mg/g. Taking the results from only strawberries, raspberries, blackberries, walnuts, pecans and cranberries, Daniel[14] estimates that each person in the US consumes 0.94 mg ellagic acid per day on an annualised basis. However, Rommel et al[19] shows that drinking a single glass of raspberry juice may result in the consumption of 7 mg of ellagic acid alone.

Pentagalloylglucose was identified as a major soluble gallotannin in 37 commercial medicinal herb samples of peony root.[16] Peony root is also listed in The Japanese Pharmacopoeia.[17] Powdered peony root, known to contain pentagalloylglucose, is used in a traditional Korean and Chinese soup; 10-20 g of powdered root together with pork, garlic, ginger, onions and tofu makes a four-person serving. The root is also taken as a medicinal tea; 3-5 g of powdered root in one serving per day.

Table 1: Identified components of ProenOthera™ and their presence in the diet.

Component	**Foods** *food or supplement*	*level in food*	*est. intake (portion size)*	**ProenOthera** *typical composition*	*in 200 mg ProenOthera*
Gallic acid	red wine	95 mg/l[18]	14 mg (150 ml)	1.2 %	2.4 mg
Ellagic acid	raspberry juice	5-50 ppm[19]	1-7 mg (150 ml)	1.9%	3.8 mg
Catechin	wine red wine	45 mg/l[18] 191 mg/l[18]	6.8 mg 29 mg (150 ml)	1.0%	2.0 mg
Procyanidin B3	wine	11 mg/l[18]	1.7 mg (150 ml)	2.1%	4.2 mg
Pentagalloylglucose	peony root	2.28 mg/g[16]	6.8 mg (3 g) 11 mg (5 g)	2.0 %	4.0 mg
Proanthocyanidins	grape seed extract	89%[20]	45 mg (50 mg)	70%	140 mg
	cereals & legumes	1-2%[21*]	1 g (50 g)		

* reported as condensed tannins or tannins.

Proanthocyanidins, a heterogeneous group of vegetable tannins, are based structurally on flavan-3-ol constituent units, linked 4→6 or 4→8 (B-types); the doubly linked (A-types) representatives of this class of compounds being characterized by the introduction of an additional ether linkage, eg 2→7. Further structural variants include hydroxylation patterns, differences in stereochemistry and the presence of galloylated monomer units in the chains. Proanthocyanidins are also known as condensed tannins.[21]

Both cereals and legumes contain appreciable quantities of phenolic compounds (notably condensed tannins) and make a significant contribution to human diet.

Safety studies

In scientific studies,[†] selected polyphenolic compounds such as those found in ProenOthera™ have undergone human clinical trials.[22,23]

[†] In an earlier submission we quoted a book written about Pycnogenol®. A referenced statement says that chronic toxicity trials have been carried out on dogs which indicate that no adverse effects would be produced in man until 35,000 mg are taken for six months.

Extensive enquiries located the original authors but they failed to supply any references which could authenticate their claims or confirm whether or not any safety factors were taken into account when making their safety claim. Nor was it possible to gain any information on the nature of any adverse effects noted at higher doses.

In view of the above, no weight can be placed on the results reported in this reference. (However the long history of use of Pycnogenol in many countries including the USA suggests that if there were safety issues with Pycnogenol, they would have become apparent by now).

The chronic toxicity study carried out on ProenOthera (reported below) has shown that no adverse effects have been seen in rats fed 100 times the normal per kilo human dose for 1 month.

In order to determine the safety of chronic exposure to ProenOthera™ a 28 day rat feeding trial was undertaken.[24] This chronic toxicity study included full necropsy, blood analysis and histopathology of male and female rats fed zero (the control), one, ten and thirty equivalents of the recommended human dose of ProenOthera.™ All of the rats survived and there were no significant health problems identified.

A second 28-day rat feeding study with ProenOthera™, undertaken to determine the effects at 100 times the recommended human dose, showed that all of the rats survived and remained in good health.[25] The report shows *no observable adverse effects* in rats at feeding levels of 300 mg/kg. This is 100 times the recommended human dose of 3 mg/kg and on this basis it is reasonable to expect that ProenOthera is safe at levels of up to 200 mg per day.

ProenOthera™ was also tested for acute toxicity and proven not to be orally toxic to rats according to the Federal Hazardous Substances Act Regulations, (16 CFR 1500.3). This independent study by Consumer Product Testing Co (USA) subjected both male and female albino rats to a dose equivalent to five grams per kilogram body weight[26] (i.e. 1667 times the recommended human dose).

Dose Considerations

Health Authorities recognise the health benefits of fruit and vegetables and recommend eating at least five helpings per day of fruit and vegetables. For most people this recommendation will increase their intake of dietary tannins. It is estimated that the average American's intake of one group of polyphenolic compounds, the flavonoids, is up to 1 gram per day.[27] Dietary supplementation of fruit and vegetable polyphenolic compounds may be recommended to help maintain efficient bodily function. Supplementation of the daily diet with ProenOthera™ will be recommended at 50 mg from one to four times daily, or as a single dose of 200 mg. At the maximum recommended dose this represents 20% of the estimated daily intake of flavonoids.

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[3] Frankel, E.N. "Natural and biological antioxidants in foods and biological systems. Their mechanism of action, applications and implications." *Lipid Technology*, (July, 1995) 77-80.

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[5] Hamel, P.B. et al. "Cherokee plants." Sylva, N.C., Herald Pub. Co. 1975, p33.

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[14] Goto, H., et al., "Endothelium-dependent vasodilator effect of extract prepared from the roots of *Paeonia lactiflora* on isolated rat aorta." *Planta Medica*, **62** (1996) 536-43.

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[16] Chuang, Wu-Chang, et al. "A comparative study on commercial samples of the roots of *Paeonia vitchii* and *P. lactiflora*." *Planta Medica* **62** (1996) 347-351.

[17] The Japanese Pharmacopoeia, 13th Edition 1996, The Society of Japanese Pharmacopoeia (Publ.), Japan, pp 859-860.

[18] Sun, Baoshan et al. "Separation of Grape and Wine Proanthocyanidins According to their Degree of Polymerization." J. Agric. Food Chem. **46** (1998) 1390-1396.

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[20] Prieur, Corinne et al. "Oligomeric and polymeric procyanidins from grape seeds." Phytochemistry **36/3** (1994) 781-784.

[21] Deshpande, S. S. "Chemistry and Safety of Plant Polyphenols." *Advances in Experimental Medicine and Biology* **177** (1984) 457-495.

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[25] Study Number: AHSC 75587, Animal Health Services Centre, Massey University, 2000.

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