SECTION SIX

The history of use or other evidence of safety establishing that the dietary ingredient zinc carnosine when used under the conditions recommended or suggested in the labeling of dietary supplement products will reasonably be expected to be safe and which is the basis on which the distributor of zinc carnosine has determined that the use of zinc carnosine is reasonably expected to be safe. See 21 CFR § 190.6(b)(4).

INTRODUCTION

Zinc carnosine has been clinically evaluated in Japan for both safety and efficacy as a novel antiulcer agent. In the Japanese studies zinc carnosine is identified as Z-103 and/or polaprezinc. While zinc carnosine has been clinically evaluated in Japan for a therapeutic indication, this submission to the Food and Drug Administration (FDA) will only rely on the safety data in the enclosed clinical and scientific Japanese studies. In marketing zinc carnosine in the United States (U.S.) the distributor's intended use of the dietary ingredient is specifically for use in dietary supplement products as a new source of zinc and at a level of use of 75 mg per day. The dietary ingredient zinc carnosine will not be marketed by the distributor with any claims inconsistent with its status as a dietary ingredient for inclusion in lawfully marketed dietary supplement products.

The recommended level of use of 75 mg per day of zinc carnosine will result in a dietary use of 17-18 mg of zinc and 57 to 58 mg of L-carnosine. Zinc functions as a component of various enzymes in the maintenance of structural integrity of proteins and has a wide range of biological roles. Of identified biological systems, zinc has catalytic, structural or regulatory roles in more than 200 zinc metalloenzymes. Physiologically, zinc is needed for growth and development and may have both antioxidant and immunomodulatory activity. Zinc supplementation is reported to help restore impaired immune function in those with zinc deficiency. The recommended dietary allowance (RDA) for zinc for adults is 8 mg per day for women and 11 mg per day for men. The tolerable upper intake level for adults is 40 mg per day, a value based on reduction in erythrocyte copper-zinc superoxide dismutase activity. See copy of Dietary Reference Intakes chart for zinc from Institute of Medicine, Food and Nutrition Board report on micronutrients as attachment 6(A).

L-carnosine, the other component of zinc carnosine, is a small molecule composed of the amino acids histidine and B-alanine. It is found in relatively high concentrations in several body tissues - most notably in the skeletal muscle, heart muscle, and in the brain.\(^2\) The exact biological role of carnosine is not completely known but it does possess antioxidant properties. Carnosine has been considered as a water soluble counterpart to Vitamin E in protecting membranes from oxidative damage.

L-carnosine has been included in some dietary supplement products currently being marketed in the U.S. at a level of use from 20-50 mg. See attachment 6(B) Twinlab Phos Fuel180 capsules and Endura High Magnesium Energy and Rehydration Drink. Therefore, both components of the dietary ingredient zinc carnosine have had a long use in the U.S. food supply and, at the level of recommended use of 75 mg, are at a very safe level of use for consumption as a dietary ingredient of zinc for use in dietary supplement products.

A full discussion of the scientific and clinical documentation providing a basis for the safety of zinc carnosine is provided in the expert review of Robert A. DiSilvestro, Ph.D. which is enclosed as Section 6(C). His curriculum vitae is enclosed as Section 6(D) and the scientific articles referenced by Dr. DiSilvestro are included as exhibits 6(E)(1) - 6(E)(26) as follows:

**Review Articles**


Studies in Cell Cultures and Other Studies In Vitro


Studies In Vivo-Nonhuman Species


6(E)(14) High levels of dietary carnosine are associated with increased concentrations of carnosine and histidine in rat soleus muscle Journal of Nutrition 131:287-90, 2001.


Series of papers translated from Japanese


Other Human Clinical Studies