Note: The majority of studies cited in this document are hyper-linked to corresponding abstracts on the internet. Please see the references section at the end of this document in electronic format for easiest access. An electronic copy of this document can be obtained at www.pharmanexusa.com

Responses to Common Technical Questions Concerning the Pharmanex® BioPhotonic Scanner

Question:
What science is there to validate the Pharmanex BioPhotonic Scanner?

RESPONSE:
The Pharmanex BioPhotonic Scanner is backed by science.
The use of Raman spectroscopy for biological measurements is an established scientific discipline backed by years of research. The Pharmanex BioPhotonic Scanner is a patented application of Raman spectroscopy for the measurement of carotenoid antioxidant nutrients in living tissue for the improvement of nutrition. The use of biophotonics to assess biological molecules in living tissue is a distinct scientific discipline, and the Pharmanex BioPhotonic Scanner is an instrument that is based on this scientific discipline.

The use of Raman spectroscopy for the assessment of human tissue carotenoids has been validated by at least eight peer-reviewed studies conducted by third party entities unrelated to Pharmanex or the supplementation industry. (Bernstein, 1998, 2002; Ermakov, 2004a, 2004b; Gellermann, 2004, 2002; Hata, 2000; Zhao, 2003). Raman spectroscopy is an established and accepted detection method; a Medline search for the term *raman spectroscopy* yields over 4,400 articles. Most importantly, validation of Raman spectroscopy is recognized through the award of Nobel Prize to Sir CV Raman for its discovery in 1930.

Pharmanex is not the only entity impressed with the nutritional implications of Raman spectroscopy. In 2003 the National Cancer Institute (a division of the National Institutes of Health) awarded researchers at Yale University a $1 million grant to conduct a study using Raman detection of carotenoids as an objective measure of fruit and vegetable intake. Most large-scale nutritional studies rely on diet recall surveys, which are subject to errors of reporting fruit and vegetable consumption. The study will be completed in 2006 (Mayne *et al*, 2003; YCC News Release, 2003).

Importantly, Pharmanex has validated the use of Raman spectroscopy for the measurement of carotenoids in four studies including a large-scale clinical screening study with 1,375 subjects that confirmed a correlation between antioxidant status and lifestyle parameters (Smidt, 2003). A second study established efficacy of LifePak® to improve the antioxidant status of subjects over a 12-week period (Smidt, 2002), and a third study established a highly significant correlation ($r=0.78$, $p < 0.001$) between serum carotenoid levels and skin carotenoid levels as assessed by the Pharmanex BioPhotonic scanner (Smidt, 2004a). A fourth study was presented at the 45th Annual Meeting of the American College of Nutrition in Long Beach, California. The 372-subject clinical study re-confirmed the excellent correlation between skin Scanner scores and blood carotenoids, the currently accepted gold standard in research. In addition, the study demonstrated that the Pharmanex® BioPhotonic Scanner measurement has less variability than blood carotenoids (measured by the conventional HPLC method). A fifth study was presented by Dr. James Rippe at the National Meeting of the American College of Sports Medicine in June 2004 (Indianapolis, IN). This study confirmed that in overweight and obese individuals the level of adipose tissue accumulation negatively influenced skin carotenoid levels, and thus antioxidant status. More studies are ongoing, and after peer review, will be published in scientific journals.

The Pharmanex BioPhotonic Scanner is consistently well received by experts in all areas of science. Pharmanex Scientists have presented the science behind LifePak® and the BioPhotonic scanner at a number of scientific meetings. In February 2003, Pharmanex scientists joined with Dr. James Rippe and the inventor of the biophotonic scanner, Dr. Werner Gellermann in a presentation at the New York Academy of Sciences. In February 2003 and 2004, Pharmanex Scientists attended scientific meetings on antioxidants organized by the Oxygen Club of California in Cadiz, Spain, and Santa Barbara, California. Dr. Lester

Packer (the "father of antioxidants") is the founder and honorary president of the Oxygen Club and chaired these meetings. Dr. Carsten Smidt presented a scanner study at the Santa Barbara meeting. In April 2003 and 2004, Dr. Carsten Smidt attended the Federation of American Societies for Experimental Biology (FASEB) meetings in San Diego and Washington DC, and presented the results of two different scanner studies. The FASEB meeting is attended by more than 10,000 scientists from around the world, but only a small percentage are selected to present. In January of 2004, Dr. Carsten Smidt attended and presented the scanner/serum correlation study at the prestigious Gordon Research Conference on Carotenoids in Ventura, California. Dr. Smidt also scanned 60 of the top antioxidant researchers in the world at this conference. In all instances the Pharmanex BioPhotonic Scanner has been very well received by the scientific community.

Question:
If the BioPhotonic Scanner measures only carotenoids, how can it be used to infer the status of other nutrients?

RESPONSE:
Serum carotenoids correlate to overall antioxidant status
Carotenoid molecules are not regenerated like other antioxidants, and are degraded in the process of neutralizing free radicals or reactive oxygen species. A typical carotenoid molecule like lycopene or β-carotene is able to sustain more than 20 free radical hits by lipid radicals before it becomes completely destroyed (Tsuchiya, 1994). Lycopene and β-carotene are just two examples of antioxidants among hundreds of antioxidants that make up the *antioxidant network.* Carotenoids act sacrificially to protect other members of the antioxidant network (such as vitamins E and C) from having to sustain free radical hits; in this way carotenoids will support the entire antioxidant network consequently reducing the danger from oxidative stress (Packer, 1994; Packer and Coleman, 1999). Conversely, high levels of oxidative stress (e.g., with smoking) adversely affect the antioxidant network, and the resulting increased free radical activity leads to a depletion or reduction in tissue carotenoids (Smidt and Shieh, 2003; Gollnick and Siebenwirth, 2002, Dietrich, 2003).

A recent study conducted by Svilaas *et al.* established carotenoids as a reliable indicator of other dietary antioxidants. Svilaas and his colleagues assessed antioxidant intake from diets of more than 2,670 adults, and evaluated blood serum antioxidants of 61 individuals for seven consecutive days. Svilaas *et al.* found the ability of carotenoids to predict serum levels of other antioxidants was stronger than the predictive ability of alpha, beta, delta, and gamma-tocopherols as well as glutathione (Svilaas, 2004). Carotenoids are not only convenient biomarkers because they are accurate predictors of overall antioxidant status, but also they are Raman active and can be detected without the concerns of blood samples (Bernstein, 1998, 2002; Gellermann 2002a; Zhao, 2003, Ermakov, 2004b). Furthermore, carotenoids are delivered to tissues by the same mechanism as other fat-soluble antioxidants. This shared LDL delivery mode is the proposed mechanism to explain the correlation between tissue carotenoids and other fat-soluble antioxidants in multiple studies (Lasheras et al., 2002; Steinberg & Chait, 1998).

Serum carotenoids correlate to skin carotenoids
Skin carotenoids analyzed by HPLC were shown to correlate significantly to serum carotenoid levels (Peng, 1995). The significant correlation between skin biopsy-levels of carotenoids and serum carotenoid levels eliminates the need for routine skin removal. A recent study of 104 participants showed a highly significant correlation between serum total carotenoids and skin carotenoids as assessed by Raman Spectroscopy ($r = 0.78$, $p < 0.001$) (Smidt, 2004). A second study confirmed the correlation of the n=104; this second study included 372 participants. Three separate correlation plots were produced and all showed highly significant correlations (range .78 –.82, $p<.0001$) between total serum carotenoid level and Raman spectroscopy-derived skin carotenoid scores (Zidichouski, 2004). These data bridge the findings of Svilaas, and Peng, to validate Raman Spectroscopy as a method to assess skin carotenoid status as an indication of broad-spectrum antioxidant status, without the inconvenience of skin and blood samples.

Carotenoids accepted as indicator of fruit and vegetable intake
Carotenoids include more than 50 antioxidants widely distributed among fruits and vegetables. When ingested from dietary sources, the presence of carotenoids in living tissue is an indicator for the presence of

other important nutrients common to those dietary sources (Svilaas, 2004). Based on this correlation, the National Cancer Institute awarded a $1 million research-grant to Yale scientists to conduct a study using the Raman-detection of carotenoids as an objective measure of fruit and vegetable intake (Mayne *et al*, 2003; YCC News Release, 2003). The correlation between carotenoids and other nutrients applies to nutritional supplements only to the degree they deliver optimal amounts of all essential and generally beneficial nutrients. For this reason, LifePak® is formulated as a broad-spectrum multivitamin, mineral, antioxidant supplement, which contains nutrients in amounts similar to a diet rich in fruits and vegetables.

Question:
What aspects of health are positively affected by proper carotenoid nutrition?

RESPONSE:
Carotenoids have been shown in countless studies to support many areas of health
The scanner is not intended to diagnose, mitigate, treat, or cure any disease. Nonetheless, convincing evidence suggests that certain carotenoids have been linked to health benefits including reduced risk of age-related macular degeneration, cataracts, cardiovascular disease, and prostate cancer. A review article written by Pharmanex scientists will appear in the peer-reviewed journal *Current Trends in Nutraceutical Research*. The article includes a review of the role of carotenoids in human health and is summarized below (Smidt and Burke, 2004).

Eye Health
A number of studies support the protective role of carotenoids in the prevention of age-related eye diseases. For example, reduced risks of cataracts (Brown *et al.,* 1999; Chasan-Taber *et al.,* 1999) and age-related macular degeneration (Seddon, 1994; Bone, 2000, 2001, 2003; Landrum, 1997, 1996; Elless, 2000; Bernstein, 2002, Richer, 1999; Hammond, 1997) have been associated with high intakes of vegetables rich in the carotenoids lutein and zeaxanthin.

Cardiovascular Health
The carotenoids lutein and lycopene have been shown separately to support multiple aspects of cardiovascular health. Studies show positive health implications of lutein including decreased risk of mortality from cardiovascular disease (Kouris-Blazos, 2002), decreased progression of pre-atherosclerotic conditions (Dwyer, 2001), and other cardioprotective effects (Olmedilla, 2001; Cardinault, 2003).

The cardioprotective effects of lycopene have also been shown in multiple studies including reduced risk of myocardial infarction (Kohlmeier, 1997), lower risk of cardiovascular disease (Sesso, 2004), reduced LDL oxidation (Agarwal, 1998), and reduced production of LDL cholesterol (Fuhrman *et al.,* 1997).

Cancer
Epidemiological studies have shown that high intakes of tomatoes and tomato products, rich in lycopene, as well as high blood levels of lycopene are significantly associated with decreased prostate cancer risk (Deming, 2002; Giles, 1997; Giovanucci, 1995, 2002; Lu, 2001; Vogt, 2002). The finding of Kucuk *et al.* suggests that lycopene supplementation may decrease prostate cancer growth (Kucuk *et al.,* 2001). These effects may be attributed to lycopene's antioxidant and DNA protective properties (Riso *et al.,* 1999; Porrini and Riso, 2000).

Carotenoids may also play a role in cancer prevention because they can enhance gap junctional communication (GJC) between cells. (Krutovskikh *et al.,* 1995; Yamasaki *et al.,* 1995; Yamasaki, 1995; Dahl *et al.,* 1995; Trosko, 2003). Lycopene and β-carotene have been shown to enhance GJC significantly, and these effects are not related to their known antioxidant properties (Sies and Stahl, 1997; Stahl *et al.,* 1997; Zhang *et al.,* 1991). Thus, carotenoids may act via two distinct mechanisms of action to protect from cancer: as antioxidants to prevent mutagenic DNA alterations, and as promoters of GJC.

Oxidative Stress correlates to skin carotenoid concentration
Many of the above diseases are known to be linked to oxidative stress. A population study of 1,375 subjects was conducted at the Pharmanex Research Institute and found that individuals with high oxidative stress

generally have low skin carotenoid levels as measured by Raman spectroscopy, independent of subjects' dietary carotenoid consumption. This correlation was demonstrated by using Urinary MDA test, a proven model for oxidative stress (Smidt and Shieh, 2003).

Question:
Are other methods of testing more accurate at assessing antioxidant status?

RESPONSE:
Raman spectroscopy has been shown to be more reliable than other methods and more suitable for routine measurements reduced probability of error
Before Raman detection of carotenoids, established methods of measuring antioxidant status included the analysis of blood, urine, or tissue samples. These tests are expensive, invasive (e.g. *skin biopsies; blood draw*), have a higher probability of error (multiple steps involved in sample preparation and quantification all increase the magnitude of the overall error). Moreover, it may take weeks to receive the results. Also, the accuracy of tests using blood/serum or urine is placed in question due to possible effects of recent meals as the timing that the biological sample is taken (blood or urine) influences the outcome. A recent clinical study showed that Raman measurement of carotenoids in humans skin (palm of hand) correlates very highly with total serum carotenoid levels quantified from fasted serum (Smidt, Gellermann, & Zidichouski, 2004). The BioPhotonic Scanner is a great way to measure carotenoid levels safely and non-invasively at the site of action with the added advantage that it is well suited for routine measurements in large populations. The ability to assess carotenoid status through Raman spectroscopy will lead to further advances in nutritional and biological measurement.

Question:
How do Pharmanex formulations address the issue of excessively high levels of antioxidants acting as pro-oxidants?

RESPONSE:
Pharmanex products contain nutrient amounts proven to be safe in clinical studies

The levels of all nutrients found in Pharmanex products are based on well documented epidemiological, clinical, pre-clinical and safety studies. LifePak® is formulated to provide optimal nutrition with substantiated levels of nutrients that will not induce a pro-oxidative state. Included in the comprehensive blend of antioxidants is a balanced carotenoid combination in amounts similar to those provided by diets high in fruits and vegetables: 7.5 mg β-carotene, 5 mg lycopene, 2 mg α-carotene and 2 mg lutein. Each ingredient in LifePak® is present in amounts that are documented to be safe for long-term supplementation. Further, LifePak is safe when taken in conjunction with a diet high in fruits and vegetables. The daily amounts of all vitamins and minerals are well below the No-Observed Adverse Effect Levels (NOAEL) established by the Council for Responsible Nutrition (CRN) in 1997 and the Upper Limits (UL) established by the Food and Nutrition Board of the National Research Council.

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