

CITIZEN PETITION

OF THE

**AMERICAN DIETETIC ASSOCIATION, THE OBESITY SOCIETY,
SHAPING AMERICA'S HEALTH, AND GLAXOSMITHKLINE
CONSUMER HEALTHCARE**

REQUESTING

THE FOOD AND DRUG ADMINISTRATION

TO

**DETERMINE THAT CLAIMS THAT DIETARY SUPPLEMENTS
PROMOTE, ASSIST, OR OTHERWISE HELP IN WEIGHT LOSS ARE
DISEASE CLAIMS UNDER SECTION 403(R)(6) OF THE FEDERAL
FOOD, DRUG AND COSMETIC ACT**

APRIL 17, 2008

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April 17, 2008

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I. ACTION REQUESTED

On behalf of the American Dietetic Association, The Obesity Society, Shaping America's Health, and GlaxoSmithKline Consumer Healthcare, LP ("GSK") (hereafter "petitioners"),¹ the undersigned submit this petition under the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301 et seq., to request the Commissioner of Food and Drugs to determine that dietary supplements bearing claims that they promote, assist, or otherwise help in weight loss are "disease claims" under Section 403(r)(6) of the FDCA. 21 U.S.C. § 343(r)(6). Specifically, petitioners request FDA to treat weight loss claims as disease claims because such statements purport to prevent or treat an abnormal or unhealthy condition that, while not itself a disease, is a significant risk factor for disease.² As set forth herein, this action is necessary in light of new information that was not available to FDA when it initially promulgated regulations implementing Section 403(r)(6) in 2000. 21 C.F.R. § 101.93(g)(2).

In support of this action, petitioners present extensive scientific evidence and consumer survey data that has been developed during the past decade. This new information conclusively establishes three critical facts. First, the condition of being overweight is a significant risk factor for several serious diseases, including diabetes, cardiovascular disease, and cancer.³ Second,

¹ The American Dietetic Association -- the nation's largest organization of food and nutrition professionals -- serves the public by promoting optimal nutrition, health and well-being. The Obesity Society is the leading scientific society dedicated to the study of obesity and it is committed to keeping the medical community and public informed of new advances. Shaping America's Health (SAH) was founded by the American Diabetes Association to reverse the obesity trends and overweight issues facing individuals, families, and communities. The mission of SAH is to prevent and treat excess weight and obesity, and to facilitate a better understanding of weight management. GSK has provided unrestricted grants to the American Dietetic Association, The Obesity Society, and SAH in support of the missions of these organizations. Any correspondence from FDA relating to this petition should be sent to Bruce Manheim, Ropes & Gray LLP, 700 12th Street, N.W., Washington, D.C. 20005.

² For the purposes of this request, petitioners intend that the term "weight loss claims" be construed broadly and, at a minimum, include the following types of statements: weight loss/burning fat/cellulite reduction; accelerated metabolism/energy burning; appetite reduction or increases satiety; blocks fat/accelerates transit; increases fat oxidation or reduces fat synthesis; blocks carbohydrates/enhances glucose metabolism; or blocks dietary fat absorption.

³ In the discussion that follows throughout the petition, the terms "normal weight," "overweight," and "obese," refer, respectively, to individuals with a Body Mass Index ("BMI") of 18.5-24.9, 25.0-29.9, and 30.0 and greater.

many Americans understand the health risks of being overweight and they rely on dietary supplements to lose weight. Third, there is little, if any, evidence, indicating that dietary supplements marketed for weight loss actually work. As a result of these three facts, many Americans are being thwarted in their efforts to lose weight, and reduce the risk of disease, by ineffective weight loss supplements. In fact, the Federal Trade Commission recently reported that more consumers are defrauded by weight loss products than any other product it evaluated.

The FDA could substantially address this problem by taking the actions in this petition. If FDA were to treat weight loss claims as disease claims, then manufacturers of weight loss supplements would be required to obtain FDA review of their claims *before* rushing to market. The FDA has established procedures allowing for consideration of certain types of "qualified health claims" for dietary supplements. To the extent that any manufacturer of a weight loss supplement seeks to avail itself of the health claims process, however, FDA may only review claims that the risk of developing a disease could be reduced through the intake of a substance in the supplement. The FDA may not review statements about a supplement where weight loss is the "pivot" of the health claim.

Moreover, FDA is only authorized to allow certain types of qualified health claims for a supplement where there is some credible scientific evidence that supports the claim. Yet, there is no credible scientific evidence that would support any type of a claim accompanying a weight loss supplement. Indeed, during the past decade, several independent scientific teams have uniformly concluded that there is little, if any, evidence to support the efficacy of supplements marketed for weight loss. And, there is no evidence that the use of such supplements would reduce the risk of a particular disease. As a result, by taking the actions requested in this petition, FDA would protect millions of Americans who are currently relying on unproven and ineffective dietary supplements to lose weight.

The actions requested in this petition are fully consistent with, and required by, longstanding regulatory precedent. During the past decade, FDA has repeatedly determined that claims to reduce risk factors such as high cholesterol levels, high blood glucose, or high blood pressure are disease claims. Given the close link between an increased risk of disease and the condition of overweight, FDA must reach the same conclusion about weight loss claims. In this context, petitioners note that, consistent with FDA's earlier conclusions, this petition would not preclude manufacturers from making fully substantiated claims that their products "help to maintain weight that is already within the normal range." This petition also would not apply to conventional foods that may assist the general population in controlling weight.⁴

The finding requested by petitioners also would not conflict with FDA's determination in 2000 that weight loss claims are not disease claims because the condition of being overweight is

⁴ The agency's nutrient content claim regulations authorize qualifying foods to be promoted using descriptors such as "low calorie," "diet," and similar terms. Claims addressing particular "dietary needs" relating to overweight are regulated as "special dietary use" claims and are allowed for foods that comply with 21 C.F.R. § 105.66. Significantly, such special dietary use claims are permitted for foods only to the extent that such products supply particular dietary needs. Needs relating to weight control may reasonably be characterized as "dietary" only if they relate to the traditional role of diet in reducing body weight (i.e., through control of caloric intake or other diet-based measures, as opposed to a pharmacologic mode of action).

not a disease. Petitioners are not asking FDA to conclude that the state of being overweight is a disease. Rather, in light of the new and much stronger evidence that has emerged since 2000 about the risks of being overweight, petitioners are requesting FDA to restrict weight loss claims because they purport to treat an unhealthy condition that is a risk factor for disease – not the disease itself. The FDA did not consider this question in 2000. The agency's earlier finding about weight loss claims under one factor in its regulations by no means precludes a determination that such claims are disease claims under different and separate criteria in the regulations.

II. STATEMENT OF GROUNDS

A. SCIENTIFIC REPORTS FROM THE PAST DECADE CONFIRM THAT THE CONDITION OF OVERWEIGHT IS A SIGNIFICANT RISK FACTOR FOR SERIOUS CHRONIC DISEASES

Recent estimates indicate that at least one third of American adults are overweight and the numbers are growing each year.⁵ At the same time, the number of children and adolescents who are overweight has risen dramatically in the past several years.⁶ This trend is quite troubling because, as the number of Americans who are overweight increases each year, so does the number of individuals who are at increased risk of developing serious chronic diseases. Indeed, a substantial body of scientific evidence published during the past decade confirms that being "overweight" – as opposed to being obese – is an independent and significant risk factor for such diseases and other medical conditions. In light of these studies, which are summarized below, both the National Institutes of Health ("NIH") and the Centers for Disease Control and Prevention ("CDC") have expressly recognized and highlighted these risks.⁷

The health risks of being overweight are often discussed in conjunction with obesity and, as a result, until relatively recently they have been overshadowed by that disease. In the past several years, however, there has been new and significant research conducted into the independent health risks associated with overweight regardless of whether an individual eventually proceeds from the overweight category to the obese category. One of the first major government documents to focus on these risks was a report issued by NIH in September 1998.⁸

⁵ Centers for Disease Control and Prevention, National Center for Health Statistics. Prevalence of overweight and obesity among adults: United States, 2003-2004. (Accessed January 3, 2008, at http://www.cdc.gov/nchs/products/pubs/pubd/hestats/overweight/overwght_adult_03.htm) (reporting that 66.3% are overweight or obese and 32.2% are obese). Although there has been no significant change in obesity prevalence since 2003-2004, obesity rates have increased substantially since the 1980s. *See* Ogden C, et al. Obesity among adults in the United States: no change since 2003-2004. Washington, DC: Centers for Disease Control and Prevention, November 2007. (Accessed January 3, 2008, at <http://www.cdc.gov/nchs/data/databriefs/db01.pdf>).

⁶ Ogden CL, et al. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 2006;295:1549-55 (reporting that in 2003-2004, 17.1% of U.S. children and adolescents were overweight). (Exh. 1).

⁷ *See* National Institute of Diabetes and Digestive and Kidney Diseases. Do you know the health risks of being overweight? (Accessed January 3, 2008, at http://win.niddk.nih.gov/publications/health_risks.htm); Centers for Disease Control and Prevention. Overweight and obesity. (Accessed January 3, 2008, at <http://www.cdc.gov/nccdphp/dnpa/obesity/>).

⁸ Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the Evidence Report. Washington, DC: National Institutes of Health, September 1998. (NIH Publication No. 98-4083). (Exh. 2).

Since publication of that report, a wealth of scientific and epidemiological studies has been published establishing that overweight is a risk factor for several serious diseases, including type 2 diabetes, cardiovascular disease, certain types of cancer, and obesity.⁹ These studies are briefly summarized below for each of these diseases.¹⁰

Moreover, petitioners are attaching an expert report from five top scientists in the field.¹¹ To ensure that the scientific bases underlying this petition are principled and sound, GSK convened a panel of these researchers and clinicians in May 2006 to evaluate the relationship between being overweight and the risk of developing serious chronic diseases. Specifically, the expert panel examined the available epidemiological evidence in the scientific literature on the health risks of being overweight, with a specific focus on the relationship between BMI and type 2 diabetes, cardiovascular disease, cancer, and morbidity. Their report was limited to an examination of these relationships. The individuals serving on this panel included: George Blackburn, M.D., Ph.D., Harvard Medical School; Madelyn Fernstrom, Ph.D., University of Pittsburgh Medical Center; John Foreyt, Ph.D., Baylor College of Medicine; Arthur Frank, M.D., George Washington University; and Anne Wolf, M.S., R.D., University of Virginia School of Medicine. As can be seen from their report included in the addendum to this petition, these scientists confirmed that there is strong relationship between the state of being overweight and an increased risk of disease.

1. Numerous Epidemiological Studies from the Past Decade Establish the Condition of Overweight as a Significant Risk Factor for Diabetes, Cardiovascular Disease, Cancer, and Obesity

a. Diabetes

In the United States, 18.2 million people (6.3% of the population) have diabetes and, each year, 1.3 million new cases are diagnosed in people 20 years of age or older. Complications of diabetes can include, among other things, heart disease, stroke, high blood pressure, blindness, and kidney disease.¹² The link between type 2 diabetes and weight gain is well established; almost 90% of those with type 2 diabetes are overweight or obese. The association between the risk for diabetes and weight gain in women was documented in the 1990 publication of the

⁹ The risk of increased morbidity from being overweight is distinguishable from the risk of increased mortality, which is more difficult to determine. *Compare* Adams KF, Schatzkin A, Haris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006;355:763-78 and Jee SH, Sull JW, Park J, Lee S, Ohrr H, Guallar E, Samet JM. Body-mass index and mortality in Korean men and women. *N Engl J Med* 2006;355:779-87 with Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *JAMA* 2005;293:1861-7.

¹⁰ Being overweight increases the risk of other diseases, including gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, fatty liver disease, and psoriasis. *See* National Institute of Diabetes and Digestive and Kidney Diseases. Do you know the health risks of being overweight? (Accessed January 3, 2008, at http://win.niddk.nih.gov/publications/health_risks.htm). These are not reviewed here.

¹¹ Blackburn G, Fernstrom M, Foreyt J, Frank A, Wolf A. Impact of overweight on morbidity and mortality: report submitted to GlaxoSmithKline Consumer Healthcare. November 1, 2007. (Exh. 3).

¹² American Diabetes Association. (Accessed January 3, 2008, at www.diabetes.org).

Nurses' Health Study.¹³ A later study using data from the Nurses' Health Study reported similar results: the risk of diabetes increased with BMIs greater than 22.¹⁴ For those with a BMI in the overweight range, the risk of diabetes was up to ten times greater relative to those with a BMI of 22 or less.

Since January 2000, several studies have been published that further establish and highlight the risk that individuals who are overweight have of developing type 2 diabetes. For example, in a study published in the *New England Journal of Medicine* in 2001, Hu et al. examined 16 years of follow-up data from the Nurses' Health Study and found that the relative risk ("RR") of developing the disease was 7.59.¹⁵ That same year, Field et al. also published a report assessing the risk of developing diabetes in overweight individuals.¹⁶ That study was based on an analysis of data from two prospective cohort studies – the Nurses' Health Study with women and the Health Professionals Follow-up Study involving men. In both cohorts, these investigators found that the risk of developing diabetes increased progressively with increasing levels of BMI. Among both women and men, those who were overweight were significantly more likely to develop diabetes (RR, 4.6 for women; RR, 3.5 for men) than their same-sex, normal weight peers.

Two additional studies published in the last three years further demonstrate that the risk of diabetes increases progressively with increasing weight. One of these reports – the San Antonio Heart Study – involved a prospective, population-based study of Mexican Americans and non-Hispanic whites.¹⁷ Among Mexican Americans, those who were overweight had a risk of diabetes that was 2.7 times greater than those of normal weight; for overweight, non-Hispanic whites, the risk of diabetes was four times greater than for those of normal weight. That study was followed up by a report published in 2004 by St-Onge et al. examining the association between BMI and risk of the metabolic syndrome (a constellation of diabetes, hypertension, and dyslipidemia risk factors) among individuals in the normal weight and slightly overweight range.¹⁸ On the basis of a review of NHANES III data, the authors corroborated the link between increasing BMI and the risk of metabolic syndrome.

b. Cardiovascular Disease

With over one million new cases in the United States each year, cardiovascular disease currently plagues more than 80 million Americans who suffer from stroke, atherosclerosis,

¹³ Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 1990;132:501-13. (Exh. 4).

¹⁴ Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995;122:481-6. (Exh. 5).

¹⁵ Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes in women. *N Engl J Med* 2001;345:790-7. (Exh. 6).

¹⁶ Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 2001;161:1581-6. (Exh. 7).

¹⁷ Burke JP, Williams K, Venkat Narayan KM, Leibson C, Haffner SM, Stern MP. A population perspective on diabetes prevention: whom should we target for preventing weight gain? *Diabetes Care* 2003;26:1999-2004. (Exh. 8).

¹⁸ St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. *Diabetes Care* 2004;27:2222-8. (Exh. 9).

coronary heart disease, hypertension, congestive heart failure, and other forms of the disease.¹⁹ The association between weight gain and the risk for cardiovascular heart disease was reported in the mid-1990s by Willett et al.²⁰ They found that the risk of coronary heart disease in women increased consistently with increasing BMI, and that women with BMIs within the overweight range had twice the risk of coronary heart disease as those in the normal weight range (RR, 2.06). Even women with BMIs on the higher end of normal weight range (23-24.9) were found to be at increased risk compared to those with a BMI of less than 21 (RR, 1.46). In a separate paper, the same findings of risk were reported for men – overweight men had a relative risk of coronary heart disease of 1.49 compared to men with a BMI of less than 23.²¹

Additional studies have fully established overweight as a significant risk factor for cardiovascular disease.²² For example, in 2001, Field et al. reported that individuals who are overweight are significantly more likely than their normal weight peers to develop hypertension, hypercholesterolemia, and heart disease (women: RR, 1.7, 1.1, and 1.4, respectively; men: RR, 1.7, 1.3, and 1.5, respectively).²³ A year later, Wilson et al. also demonstrated that the risk of hypertension, hypercholesterolemia, and cardiovascular disease increased among overweight men and women.²⁴ In comparison to those of normal weight, the risk of hypertension, hypercholesterolemia, and cardiovascular disease in overweight individuals was consistently higher than for those of normal weight (women: RR, 1.75, 1.35 and 1.20, respectively; men: RR, 1.46, 1.19 and 1.21, respectively). These findings were further confirmed in 2004 on the basis of a review of NHANES III data.²⁵ The odds of developing hypertension and hypercholesterolemia once again were shown to be significantly greater for overweight individuals (women: OR, 1.92 and 2.26; men: OR, 1.75 and 1.57).²⁶ Most recently, a study demonstrated that higher BMI during childhood is associated with an increased risk of coronary heart disease in adulthood.²⁷

¹⁹ American Heart Association; American Stroke Association. Heart disease and stroke statistics: 2008 update at-a-glance. Dallas, TX: American Heart Association, 2008. (Exh. 10).

²⁰ Willett WC, Manson JE, Stampfer MJ, Colditz GA, Rosner B, Speizer FE, Hennekens CH. Weight, weight change, and coronary heart disease in women. *JAMA* 1995;273:461-5. (Exh. 11).

²¹ Rimm EB, Stampfer JM, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older U.S. men. *Am J Epidemiol* 1995;141:1117-27. (Exh. 12).

²² Anderson JW, Konz EC. Obesity and disease management: effects of weight loss on comorbid conditions. *Obes Res* 2001;9(Suppl 4):326S-34S. (Exh. 13); Eckel RH, Krauss RM. American Heart Association call to action: obesity as a major risk factor for coronary heart disease. *Circulation* 1998;97:2099-100. (Exh. 14); Krauss RM, Winston M, Fletcher BJ, Grundy SM. Obesity: impact on cardiovascular disease. *Circulation* 1998;98:1472-6. (Exh. 15).

²³ Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 2001;161:1581-6. (Exh. 7).

²⁴ Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* 2002;162:1867-72. (Exh. 16).

²⁵ Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004;79:379-84. (Exh. 17).

²⁶ Moreover, in a more recent paper evaluating the association of bodyweight with coronary artery disease, the authors found that the better outcomes for those who were overweight and mildly obese could be explained by the lack of discriminatory power of BMI to differentiate between body fat and lean mass. That suggests that a different measure might further demonstrate that those who are overweight (like those who are obese) run an increased risk of a cardiovascular event. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG,

c. Cancer

Approximately 1.2 million new cases of cancer are diagnosed each year.²⁸ During the past decade, several case-control and prospective cohort studies have been published which document the risk that overweight individuals have of developing certain types of cancers. One report, which was published in *Lancet Oncology* in 2002, shows that the risk of cancer increases with increasing BMI.²⁹ Another review undertaken by the International Agency for Research on Cancer summarized the links between overweight, obesity, and cancer risk based on a comprehensive evaluation of epidemiological studies published in the scientific literature. That report, which appeared in *Nature* in 2004, concluded that those who are overweight are at increased risk of developing several types of cancer, including colon cancer (RR, 1.5 for men, 1.2 for women), postmenopausal breast cancer in women (RR, 1.3), endometrial cancer (RR, 2.0), kidney cancer (RR, 1.5), esophageal adenocarcinoma (RR, 2.0), pancreatic cancer (RR, 1.3), gallbladder cancer (RR, 1.5), and gastric cardiac adenocarcinoma (RR, 1.5).³⁰ These results were, just recently, corroborated by the American Institute for Cancer Research.³¹

The association between overweight and an increased risk of mortality from cancer was further established based on data from a prospective study of a large cohort of U.S. adults ("Cancer Prevention Study II").³² In that study, which was published in the *New England Journal of Medicine* in 2003, the authors reported that overweight women had a significantly elevated risk of death from all types of cancers (RR, 1.08). They also documented an increased risk for certain types of cancer, including colorectal cancer (RR, 1.10), breast cancer (RR, 1.34), uterine cancer (RR, 1.50), ovarian cancer (RR, 1.15), kidney cancer (RR, 1.33), and non-Hodgkin's lymphoma (RR, 1.22). Overweight men were also found to have significantly elevated risks of colorectal cancer (RR, 1.20), pancreatic cancer (RR, 1.13), prostate cancer (RR, 1.08), kidney cancer (RR, 1.18), multiple myeloma (RR, 1.18), and leukemia (RR, 1.14). On the basis of these findings, the authors of this study estimated that more than 90,000 cancer-related deaths could be prevented each year if all adults had a BMI of less than 25 throughout their lives.

Mookadam F, Lopez-Jiminez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368:666-78. (Exh. 18).

²⁷ Baker JL, Olsen LW, Sorensen, TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med* 2007;357:2329-37. (Exh. 19).

²⁸ Centers for Disease Control and Prevention. NCHS Data on Cancer. (Accessed January 3, 2008, at <http://www.cdc.gov/nchs/data/factsheets/cancer.pdf>).

²⁹ Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. *Lancet Oncol* 2002;3:565-74. (Exh. 20).

³⁰ Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature* 2004;4:579-91. (Exh. 21).

³¹ World Cancer Research Fund; American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research, 2007. Chapter 6.1, Body composition, growth, and development: body fatness; p. 210-28. (Exh. 22). This report concluded that being overweight increases the risk of esophageal adenocarcinoma, pancreatic cancer, colorectal cancer, postmenopausal breast cancer, endometrial cancer, and kidney cancer. In addition, the evidence indicated a very probable association between being overweight and gallbladder cancer.

³² Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625-38. (Exh. 23).

d. Obesity

As mentioned at the outset, the proportion of Americans who are obese has increased at an alarming rate in recent years. Between 1980 and 2002, the prevalence of obesity among adults doubled in the United States and it is currently estimated at 32% of the population.³³ Individuals who are obese were at one time overweight, and research confirms that the progression from overweight to obesity is quite common. Thus, overweight is an independent risk factor for obesity. In a prospective, cohort study examining weight trends in over 9,000 young adults followed for 20 years, being mildly or moderately overweight at ages 20-22 was linked with a substantial incidence of obesity by ages 35-37.³⁴ For example, 41% of white, 47% of Hispanic, and 66% of black women who had a BMI of 24-25 at ages 20-22 became obese by ages 35-37. Among women who had a BMI of 26-27.9 at 20-22 years of age, approximately 80% became obese by ages 35-37, regardless of racial or ethnic group. Therefore, overweight individuals are also at increased risk of obesity as they age.

2. Recent Studies of Pathophysiological Mechanisms Also Confirm That Being Overweight Is a Significant Risk Factor for Disease

In addition to the epidemiological studies cited above, there have also been numerous investigations during the past decade of the cellular and molecular mechanisms associated with adipose tissue. These studies further confirm, and provide an underlying physiological basis for, the finding that overweight is a significant risk factor for various diseases. Until recently, fat tissue was thought of mainly as a passive storehouse of energy. During the recent past, however, major scientific strides have clarified the dynamic role that adipose tissue plays in the etiology and maintenance of chronic inflammation associated with type 2 diabetes, cardiovascular disease, and cancer.³⁵ Indeed, chronic low-grade inflammation has been directly implicated in the pathogenesis of both cancer and cardiovascular disease. As described briefly below, researchers believe that chronic inflammation associated with weight gain helps explain the link between overweight and an increased risk of disease.³⁶

³³ Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* 2002;288:1723-7. (Exh. 24); Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA* 2004;291:2847-50. (Exh. 25); Ogden CL, et al. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 2006;295:1549-55. (Exh. 1).

³⁴ McTigue KM, Garrett JM, Popkin BM. The natural history of the development of obesity in a cohort of young U.S. adults between 1981 and 1998. *Ann Intern Med* 2002;136:857-64. (Exh. 26).

³⁵ For example, investigators have found that adipose tissue secretes a large number of proteins – adipokines – that act in an autocrine, paracrine, or endocrine fashion to control various metabolic functions. See Greenberg A, Obin M. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr* 2006;83(Suppl):461S-5S. Fat cell production of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- α (TNF), and adipocytokines, such as adiponectin and leptin, are also important for many aspects of inflammation and immunity. See Tolg H, Moschen A. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nature* 2006;6:772-83; Van Gaal L, Mertens I. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006;444:875-80.

³⁶ Fogarty AW, Glancy C, Jones S, et al. A prospective study of weight change and systemic inflammation over 9 years. *Am J Clin Nutr* 2008;87:30-5.

Several studies over the past ten years of overweight individuals have shown a significant increase in systemic inflammation as indicated by increases in acute-phase-C-reactive protein ("CRP"), a marker for chronic inflammation.³⁷ For example, during a nine year period, a linear association was observed between an increase in weight and serum CRP, with a one kg increment in weight gain resulting in an additional increase in CRP of 0.09 mg/L.³⁸ In addition, a recent study of middle-aged men found that those who reported a weight increase averaging approximately 15 pounds over a 10 yr period expressed more oxidative injury and inflammation in skeletal muscle compared with subjects that maintained a stable body weight over the same time period.³⁹ Thus, even mild accretion of adipose tissue is associated with oxidative stress and inflammation in human muscle. On the other hand, recent studies suggest that the benefits of calorie-restriction can likely be attributed to reduced fat stores and an accompanying decrease in the concentration of fat-derived peptides, such as cytokines, complement factors and substrates.⁴⁰

The foregoing studies of the biochemistry involving inflammation and adipose issue have been further supplemented by imaging studies during the past decade. Computer tomography scans and magnetic resonance imaging now allow investigators to measure specific adipose tissue deposits in the human body. Utilizing these techniques, scientists have examined the relationship of these different types of adipose tissue, including abdominal subcutaneous adipose tissue and visceral adipose tissue, to insulin resistance, metabolic syndrome, and the development of type 2 diabetes and clinical cardiovascular events. These studies have found that changes in body composition – that is, the distribution of different types of adipose tissue and the ratio of fat free mass to fat mass – may significantly impact the risk of cardiovascular disease, type 2 diabetes and cancer in overweight individuals.⁴¹

Specifically, work in this area has focused primarily on central fat distribution and, in particular, visceral adiposity. Despite the smaller size of the visceral adipose tissue depot, which is found in the deeper tissues and around the organs, many investigations have demonstrated that visceral adipose tissue mass is significantly correlated with insulin resistance, type 2 diabetes, and cardiovascular events.⁴² Although there is some disagreement among investigators as to whether visceral adiposity or abdominal subcutaneous adiposity is the primary cause of the increased risk, there is no question that there is increasingly strong evidence that fat accumulated

³⁷ See, e.g., Visser M, Bouter L, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999;282:2131-5; Koenig W, Sund M, Frohlich M, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men. *Circulation* 1999;99:237-42.

³⁸ Fogarty AW, Glancy C, Jones S, et al. A prospective study of weight change and systemic inflammation over 9 years. *Am J Clin Nutr* 2008;87:30-5; see also Bogers RP, Bemelmans WJ, Hoogenveen RT. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300,000 persons. *Arch Intern Med* 2007;167:1720-8.

³⁹ de la Maza M, Olivares D, Hirsch S, et al. Weight increase and overweight are associated with DNA oxidative damage in skeletal muscle. *Clin Nutr* 2006;25:968-76.

⁴⁰ Barzilai N, Gupta G. Revisiting the role of fat mass in the life extension induced by caloric restriction. *J Gerontol A Biol Sci Med Sci* 1999;54:890-96.

⁴¹ Lebovitz H, Banerji M. Point: visceral adiposity is causally related to insulin resistance diabetes care. *Diabetes* 2005;28:2321-5.

⁴² *Id.*; see also references 9-11, 13, 14, 16, 19, and 20.

in the trunk should be considered harmful.⁴³ Even in non-obese subjects, abdominal fat accumulation is correlated with glucose intolerance, hyperlipemia, and hypertension.⁴⁴ Thus, in addition to the epidemiological studies summarized above, biochemical and imaging studies from the past decade further confirm the increased risk that results from being overweight.

B. OVERWEIGHT AMERICANS WHO SEEK TO REDUCE THEIR RISK OF DISEASE ARE BEING DIVERTED FROM EFFECTIVE WAYS TO LOSE WEIGHT BY EXAGGERATED AND UNSUBSTANTIATED CLAIMS ACCOMPANYING WEIGHT LOSS SUPPLEMENTS

1. Consumer Survey Data Confirm That Individuals Understand the Health Risks of Being Overweight and Many Use Dietary Supplements to Lose Weight

As the above-referenced scientific reports and studies have appeared over the past decade, the link between being overweight and an increased risk of developing a serious disease has become much more firmly planted in the public's mind. As the results from these studies have been published, there have been concomitant publications in the media, including the popular press, that have described the increased risks of being overweight, including diabetes,⁴⁵ cardiovascular disease,⁴⁶ cancer,⁴⁷ and other maladies.⁴⁸ At the same time, this information has likely been conveyed directly to overweight individuals during visits with their physicians. As a result, many Americans now understand the adverse health consequences and risks of disease that may result from being overweight.

⁴³ See de Simon G, Devereux R, Kizer J, et al. Body composition and fat distribution influence systemic hemodynamics in the absence of obesity: the HyperGEN Study. *Am J Clin Nutr* 2005;81:757-61; Freedland E. Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: implications for controlling dietary carbohydrates: a review. *Nutr & Metab* 2004;1:1-12; Miles JM, Jensen MD. Counterpoint: visceral adiposity is not causally related to insulin resistance. *Diabetes Care* 2005;28:2326.

⁴⁴ Singh RB, Rastogi SS, Niaz MA, Postiglione A. Association of central obesity and insulin resistance with high prevalence of diabetes and cardiovascular disease in an elderly population with low fat intake and lower than normal prevalence of obesity: the Indian paradox. *Coron Artery Dis* 1998;9:559-65.

⁴⁵ See, e.g., Stein R. Fitness over thinness for hearts: but another study cites diabetes risk for overweight women. *Washington Post*. September 8, 2004:A03; Parker-Pope T. Another reason to lose weight: doctors struggle to convey risks of diabetes. *Wall Street Journal*. September 23, 2003:D1; Manning A. Overweight kids may be at risk for diabetes. *USA Today*. March 14, 2002:8D.

⁴⁶ See e.g., Nagourney E. Vital signs: at risk; weight as a formula for a stroke. *New York Times*. December 17, 2002:F8; Maugh TH II. The nation; slight weight gain found to increase heart failure risk; science: a study says that putting on as little as four pounds can be dangerous to health. *Los Angeles Times*. August 1, 2002:16; Okie S. Study links excess weight to risk of heart failure. *Washington Post*. August 1, 2002:A02.

⁴⁷ See e.g., Brody J. Personal health: another study finds a link between excess weight and cancer. *New York Times*. May 6, 2003:F7; Armstrong D. Obesity is linked to cancer deaths: study finds Americans raise their risk of dying by being too overweight. *Wall Street Journal*. April 24, 2003:D3; Hellmich N. Being overweight linked to dying of cancer. *USA Today*. April 24, 2003:1A; Fackelmann K. Breast cancer risk rises with weight gain. *USA Today*. April 9, 2002:8D.

⁴⁸ See e.g., Marchione M. Overweight kids at risk of fractures, study shows. *Washington Post*. November 22, 2005:A11; Extra body weight can be hard on the knees: overweight people are at a greater risk for cartilage damage, which may require surgery. *Los Angeles Times*. June 6, 2005:F8; Stein R. Study links excess weight to likelihood of Alzheimer's: risk increases in women overweight at 70. *Washington Post*. July 15, 2003:A01; Hellmich N. Extra weight shaves years off lives. *USA Today*. January 7, 2003:1A.

That was precisely the finding of an extensive consumer survey – "The Landmark Survey" – conducted by the Center for Survey and Research Analysis at the University of Connecticut in collaboration with the Center for Weight Loss at the University of Pennsylvania.⁴⁹ The results of that study were presented at the 2006 Annual Scientific Meeting of the North American Association for the Study of Obesity⁵⁰ and a paper summarizing these findings has been accepted in the publication, *Obesity*.⁵¹ In this study, more than 12,000 households were reached via telephone, and a sample of 3,500 adults completed an in-depth telephone interview about weight loss practices, including the use of dietary supplements for weight loss and a reduced risk of disease. The maximum expected sampling error associated with a sample of this size is 1.66 percentage points at a 95 percent confidence level.

The results were striking: overall, consumers who identified themselves as overweight believe that weight loss is directly related to improvement of their health and reducing the risk of disease. Specifically, of those surveyed who described themselves as "slightly overweight" or "very overweight" (n=1,707), the Landmark Survey found that:

92% of overweight individuals believe that losing weight will improve their health;

94% of overweight individuals believe that being overweight increases their risk of certain diseases;

94% of overweight individuals believe that an overweight person is more likely to develop chronic illnesses such as diabetes or high blood pressure compared to someone who is not overweight; and

83% of overweight individuals believe that being overweight negatively impacts other aspects of their health.

At the same time, of those who indicated that they had made at least one attempt to lose weight (n=1,582), the Landmark Study found that 43% stated that the most important benefit that they hoped to gain by losing weight was to improve their health. That compared with just 10% who indicated that they hoped to look better by losing weight.

There is no question that, in recognition of the risks associated with being overweight, many Americans are using dietary supplements to reduce weight. In March 2007, researchers

⁴⁹ Financial support for this study was provided by GSK.

⁵⁰ See e.g., First of its kind national survey finds misinformed consumers rely on unproven weight loss products. October 22, 2006. (Accessed January 3, 2008, at http://www.csra.uconn.edu/pdf/National_Dietary_Survey.pdf). See also abstracts of Pillitteri JL, Shiffman S, Rohay JM, Harkins AM, Wadden TA, Pettinico G, Burton SL. Interaction with physicians among overweight adults in the United States. Poster session presented at: NAASO, The Obesity Society 2006 Annual Meeting; October 2006; Boston, MA; Pillitteri JL, Shiffman S, Rohay JM, Wadden TA, Harkins AM, Burton SL, Pettinico G. Dietary supplement use for weight loss among US adults. Poster session presented at: NAASO, The Obesity Society 2006 Annual Meeting; October 2006; Boston, MA; Pillitteri J, Burton S, Shiffman S, Rohay J, Harkins A, Pettinico G. Consumers' use and beliefs about dietary supplements for weight loss. Poster session presented at: 10th International Congress on Obesity; September 2006; Sidney, Australia. (Exh. 27).

⁵¹ Pillitteri JP, Shiffman S, Rohay JM, Harkins AM, Burton SL, Wadden TA. Use of dietary supplements for weight loss in the United States: results of a national survey. *Obesity*. Forthcoming 2008.

from the CDC reported that the use of supplements for weight loss is common among many segments of the U.S. adult population and that many adults are long-term users of weight loss supplements.⁵² Moreover, it is also evident that a substantial percentage of adolescents (ages 14-19) also use supplements. One recent study found that almost half of the adolescents in the study had used supplements in their lifetime and that almost a third had used supplements in the past month.⁵³ Similarly, the Landmark Survey found that, of those adults who have made a serious weight loss attempt, at least one-third (34%) used dietary supplements to lose weight. It appears that many overweight individuals are so desperate to lose weight that they frequently try one supplement product after the other in their quest to improve their health.

Significantly, while many Americans use dietary supplements to lose weight, they are also confused and misinformed in their reliance on such products. The Landmark Survey revealed that:

54% of respondents believe that weight loss supplements have been tested and proven to be safe before they can be sold to the public;

46% of respondents believe that weight loss supplements must be tested and proven to be effective before they can be sold to the public;

64% of respondents believe that FDA requires the labels of weight loss supplements to include warnings about potential side effects;

50% of respondents believe that weight loss supplements are either very effective or somewhat effective in helping people lose weight; and

37% of respondents believe that herbal supplements are safer than over-the-counter and prescription medicines.

These figures are especially troubling because it is not at all clear that this confusion could be corrected when patients see their healthcare professionals. The CDC has found that most patients do not discuss the use of supplements with their physicians.⁵⁴ That finding was confirmed by the Landmark Survey, which reported that less than a third of those surveyed indicated that they would consult a physician about weight control. And, of those who would consult a physician, only 24% used FDA-approved treatments to aid in weight loss while almost twice as many (46%) had used weight loss supplements. The latter results are, perhaps, not that surprising in light of another recent survey that evaluated physicians' level of understanding of the regulation of dietary supplements. That study, which was conducted by researchers at Johns Hopkins University School of Medicine, found that almost one-third of physicians who had

⁵² Blanck HM, Serdula MK, Gillespie C, et al. Use of nonprescription dietary supplements for weight loss is common among Americans. *J Am Diet Assoc* 2007;107:441-7. (Exh. 28).

⁵³ Wilson KM, Klein JD, Sesselberg TS, et al. Use of complementary medicine and dietary supplements among U.S. adolescents. *J Adolesc Health* 2006;38:385-94. (Exh. 29).

⁵⁴ Blanck HM, Serdula MK, Gillespie C, et al. Use of nonprescription dietary supplements for weight loss is common among Americans. *J Am Diet Assoc* 2007;107:441-7. (Exh. 28).

completed internal medicine residency programs were unaware that dietary supplements did not require FDA approval or submission of safety and efficacy data before being marketed.⁵⁵

2. Overweight Americans Are Being Bombarded and Misled by Fantastic and Unsubstantiated Claims That Use of Dietary Supplements Will Result in Effective Weight Loss

As demonstrated by the studies cited above, including the Landmark Survey, many Americans are increasingly looking to dietary supplements as a way to lose weight, improve their health, and reduce their risk of disease. At the same time, however, it is clear that many patients (and apparently even physicians) lack a basic understanding of dietary supplements and FDA's authority to ensure the safety and efficacy of such products. Those who market weight loss supplements appear to be acutely aware of this confusion and, to drive sales,⁵⁶ are repeatedly making "magic bullet" claims about their products that promise rapid and effective weight loss. Of course, manufacturers also aggressively advertise their supplements over the airwaves, with some companies running extensive "infomercials" about their products. In both venues, supplement manufacturers capitalize on the fact that such products are available without a prescription and they present a "natural" solution that is less demanding than special diets and increased physical activity.

As can be seen from the handful of examples below, the manufacturers of weight loss supplements have not hesitated to extol the purported benefits of their products:

". . . a new category of bifurcated weight loss compounds providing both quick weight loss and incredible energy combined into a single, powerful Super Pill."

". . . a breakthrough in the fight to lose weight" and "works to help your body burn fat and calories, while also helping you fight cravings and boosting your energy."

". . . a weight loss supplement formulated to address key factors involved in effective weight control including metabolism, appetite, satiety, and nutrition."

". . . helps the body's insulin metabolize fat, convert protein into muscle, and turn sugar into energy, supporting weight loss and the development of lean body mass."

". . . flips your hunger switch on demand so you just don't want to eat. Result - caloric intake is reduced. . . fat disappears automatically. Fires up your fat-burning engine (without ephedra) causing significant, undeniable weight loss!"

⁵⁵ Ashar BH, Rice TN, Sisson SD. Physicians' understanding of the regulation of dietary supplements. *Arch Intern Med* 2007;167:966-9. (Exh. 30).

⁵⁶ In 2000, total sales of weight loss supplements in the United States were reported to be \$4.7 billion. *See* Consumer Healthcare Products Association. (Accessed January 3, 2008, at www.CHPA-info.org). This figure underestimates actual sales since many sales of supplements over the internet and through direct response television are not easily tracked or captured. In 2005, the Institute of Medicine estimated that Americans spent \$18 billion per year on dietary supplements. Institute of Medicine. *Dietary supplements: a framework for evaluating safety*. Washington, DC: National Academy of Sciences, 2005. (Accessed January 3, 2008, at http://books.nap.edu/openbook.php?record_id=10882&page=1).

". . . the first reliable diet pill with lipotropic ingredients and powerful appetite suppressants to greatly increase energy, burn fat and crush cravings – all at the same time."

In addition to making such fantastic claims about their products, supplement manufacturers also frequently state outright or imply that their products have been clinically tested or proven to be safe and effective for weight loss. For example:

". . . a patented, breakthrough Ephedra Free formula, combines an effective complex of clinically proven ingredients to increase metabolic rate, promote weight loss, and increase energy."

"Extensive research on our product has shown that there are literally no side effects This product is safe and can effectively burn fat to help with weight loss."

"But now, a revolutionary, all-natural weight-control compound offers new hope. . . . the first and only clinically proven, safe, and effective weight-control compound designed for children and adolescents. . . ."

"The results of a clinical research study conducted on . . . weight loss and weight management solutions are revealed – proving that [this product] helps people lose twice as much weight than with diet and exercise alone."

"Clinically proven to deliver weight loss results. . . . - You'll be looking and feeling great in no time!"

". . . a truly powerful, safe, clinically proven fat-loss tool, perfect for anyone"

Despite such claims, most supplement manufacturers have little, if any, credible evidence or studies that support such statements.⁵⁷ As a result, millions of U.S. consumers are being victimized by manufacturers of fraudulent weight supplements. Indeed, that was precisely the conclusion of the Federal Trade Commission ("FTC"), which reported in October 2007 that more Americans are being defrauded by weight loss products than any other fraudulent activity studied by the agency.⁵⁸ In this consumer survey, the FTC found that 2.1% of consumers – almost 5 million U.S. adults – purchased and used fraudulent weight loss products in 2004. The FTC further reported that there were an estimated 8.3 million total purchases of weight loss products

⁵⁷ See *infra* at notes 75-109.

⁵⁸ Federal Trade Commission. Consumer fraud in the United States: the second FTC survey. Washington, DC: Federal Trade Commission, October 2007. (Accessed January 3, 2008, at <http://www.ftc.gov/opa/2007/10/fraud.pdf>). That conclusion follows the FTC's report in 2002 finding that 55% of claims within advertisements for over-the-counter weight loss products were either false or misleading and there was a much higher frequency of questionable claims being made in 2001 than in 1992. See Federal Trade Commission. Weight loss advertising: an analysis of current trends. Washington, DC: Federal Trade Commission, September 2002. (Accessed January 3, 2008, at <http://www.ftc.gov/bcp/reports/weightloss.pdf>).

during that year.⁵⁹ For the purposes of this survey, the FTC only considered individuals to be victims of fraud if they lost only a little of the weight that they had expected to lose or they did not lose any weight at all. Thus, the FTC figure is a conservative assessment of the magnitude of these fraudulent activities.

To be sure, in recognition of this problem, FDA and the FTC have pursued enforcement actions and other measures against weight loss supplement manufacturers.⁶⁰ In October 2004, for example, FDA issued warning letters to numerous manufacturers and distributors of weight loss supplements advising them that their claims were in violation of the FDCA because they could not be substantiated. The FTC has also brought numerous actions against supplement manufacturers for making unsubstantiated claims in their advertising about weight loss products.⁶¹ Yet, while certain firms have stopped making unsubstantiated statements about weight loss supplements, others have not.⁶² Moreover, still other companies have sprung up to make similar, but not identical, claims that almost certainly also cannot be substantiated. As a result, despite the laudable efforts of FDA and the FTC to stem the tide of misleading claims made for weight loss supplements, many overweight Americans who are seeking to reduce their risk of disease by losing weight are, instead, being lured into using supplements for which little or no scientific evidence exists to demonstrate that they actually work.

C. THE FDA MUST FIND THAT WEIGHT LOSS CLAIMS FOR SUPPLEMENTS ARE DISEASE CLAIMS UNDER ITS EXISTING REGULATIONS AND ON THE BASIS OF SUBSTANTIAL LEGAL PRECEDENT GOVERNING STATEMENTS ABOUT OTHER RISK FACTORS

1. The FDA Has Consistently Taken the Position That a Supplement Bearing Claims That It Will Prevent or Treat a Risk Factor Is a Disease Claim

To address the problems described above and thereby protect the public health, FDA must treat weight loss claims for dietary supplements as "disease claims" under the FDCA. Specifically, under Section 403(r)(6) of the FDCA, a manufacturer of a dietary supplement may not claim that its product will "diagnose, mitigate, treat, cure or prevent a specific disease or class of diseases." 21 U.S.C. § 343(r)(6). That is, a supplement manufacturer may not make disease claims about its product. On the other hand, this provision does allow dietary supplement labeling to bear a statement that "describes the role of a nutrient or dietary ingredient

⁵⁹ For the purposes of this study, the FTC defined the term "weight-loss" product to include nonprescription drugs, dietary supplements, skin patches, creams, wraps, or earrings. Nonetheless, there can be no question that a substantial percentage of products in this category consists of dietary supplements.

⁶⁰ In November 2004, FDA issued a draft guidance entitled *Guidance for Industry: Substantiation for Dietary Supplement Claims Made under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act*, available at <http://www.cfsan.fda.gov/~dms/dsclmgui.html>. See also *FDA Announces Major Initiatives for Dietary Supplements*, November 4, 2004. (Accessed January 3, 2008, at <http://www.fda.gov/bbs/topics/news/2004/NEW01130.html>).

⁶¹ In January 2007, the FTC recovered \$25 million from four companies that had been engaged in deceptive advertising of weight loss products. See *Federal Trade Commission reaches "New Year's" resolutions with four major weight-control pill marketers*, January 4, 2007. (Accessed January 3, 2008, at <http://www.ftc.gov/opa/2007/01/weightloss.shtm>).

⁶² Food and Drug Administration, Center for Food Safety and Applied Nutrition. *List of distributors and manufacturers receiving warning or advisory letters for unsubstantiated weight loss claims*, November 4, 2004. (Accessed January 3, 2008, at <http://www.cfsan.fda.gov/~dms/wl-list2.html>).

intended to affect the structure or function in humans" or that "characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function." 21 U.S.C. § 343(r)(6)(A). A manufacturer making such "structure/function claims" must also be able to substantiate that such statements are truthful and not misleading. 21 U.S.C. § 343(r)(6)(B).

In January 2000, FDA promulgated regulations ("the structure/function rule") that established ten separate and independent criteria for determining whether a statement about a dietary supplement is an impermissible disease claim or a permissible structure/function claim. 65 Fed. Reg. 1000 (January 6, 2000).⁶³ In pertinent part, one of those criteria provides that a statement will be treated as a disease claim if it states, explicitly or implicitly, that the product "has an effect on the characteristic signs or symptoms of a specific disease or class of diseases, using scientific or lay terminology." 21 C.F.R. § 101.93(g)(2)(ii). The FDA has indicated that this criterion includes a statement "that a dietary supplement prevents or treats *abnormal or unhealthy conditions or clinical measurements that are not themselves diseases but are markers of, or risk factors for, diseases.*" 64 Fed. Reg. 36824, 36826 (July 8, 1999) (emphasis added).

When FDA considered adoption of the structure/function rule, it reviewed specifically what could and could not be said about elevated levels of cholesterol. Following publication of the proposed rule, the agency reopened the comment period to seek further input on whether supplement manufacturers should be permitted to make claims such as "lowers cholesterol." *Id.* Based on an extensive review of this question, FDA concluded that "labeling [that] as a whole implies that the product is intended to lower elevated cholesterol levels" would constitute a disease claim. 65 Fed. Reg. at 1019. In support of that conclusion, FDA found that "an elevated cholesterol level is a sign of hypercholesterolemia and an important risk factor for heart disease." *Id.* Accordingly, through its consideration of claims about cholesterol, FDA made clear that Section 403(r)(6) of the FDCA and the agency's implementing regulations do not allow supplement manufacturers to state that their products will reduce a risk factor for a disease.

While establishing that fundamental principle, FDA clarified that it would not prohibit all statements by supplement manufacturers about cholesterol. Rather, the agency indicated that claims that a substance helps maintain normal function would ordinarily not be considered a disease claim, unless other statements or pictures in the labeling imply prevention of a specific disease or class of diseases. Under this exception to the general rule, FDA indicated that supplement manufacturers could claim that their products "help to maintain cholesterol levels that are already within the normal range." *Id.* The agency reached this determination after concluding that "a cholesterol level within the normal range is not a sign or risk factor of disease." *Id.* Therefore, in its analysis of disease claims and risk factors under the structure/function rule, FDA also made clear that supplement manufacturers could claim that their products help to maintain the levels of a condition that are already within the normal range.

Since issuance of the structure/function rule, FDA has consistently applied these principles to statements claiming that a supplement lowers cholesterol levels or other risk factors

⁶³ For the purposes of this rule, the term "disease" is defined to include a "state of health leading to" dysfunctioning of an organ, part, structure, or system of the body. 21 C.F.R. § 101.93(g)(1).

or abnormal or unhealthy conditions.⁶⁴ For example, in July 2002, FDA objected to the claim, "nutritional support for borderline cholesterol," because it implied that "the product is intended to treat elevated blood cholesterol levels and reduce the risk of disease, namely coronary heart disease."⁶⁵ Moreover, FDA has applied the rule to other abnormal or unhealthy conditions or clinical measurements that are risk factors for diseases. Thus, during the past seven years, FDA has repeatedly found that statements about reducing high levels of blood glucose⁶⁶ or high blood pressure⁶⁷ are disease claims because they purport to treat a risk factor for diabetes and hypertension, respectively. As described next, in light of the close association between overweight and particular chronic diseases, FDA must reach the same conclusion about weight loss claims.

2. The FDA Must Treat Weight Loss Claims as Disease Claims Because They Also Purport to Prevent or Treat a Risk Factor for Disease

Just as FDA has taken the position that statements about treating high cholesterol and other risk factors for disease are impermissible disease claims, the agency must also determine that weight loss claims are not permitted under Section 403(r)(6) of the FDCA. Many dietary supplement manufacturers claim that use of their products will reduce weight in overweight individuals – for example, by reducing body fat or by increasing metabolic rate – back to "normal" levels. Put another way, weight loss supplements are marketed with claims that they will bring an individual with an abnormal or high BMI down to a normal one. Weight loss claims are, therefore, entirely analogous to claims that a product will reduce high cholesterol, blood glucose, or blood pressure. Each of these types of claims indicate prevention or treatment of abnormal or unhealthy conditions or clinical measurements that are not themselves diseases but are markers of, or risk factors for, diseases.

When FDA reached its determination about claims that could be made by supplement manufacturers about cholesterol, it was mindful of the conclusions that had been drawn in the scientific community and at NIH about the risks associated with high cholesterol levels. There is also substantial evidence in the scientific record documenting the risks of being overweight. As demonstrated above, the past decade has witnessed the development of a substantial body of scientific literature confirming that the state of being overweight is a major risk factor for several serious and chronic diseases, including type 2 diabetes, cardiovascular disease, and cancer. In light of that literature, both NIH and the CDC have indicated that being overweight is an

⁶⁴ These decisions have been made by the agency in the context of reviewing marketing notifications from supplement manufacturers under Section 403(r)(6) of the FDCA. The agency reviews such notifications of claims and responds with a "courtesy letter" identifying any objectionable claims. *See* 21 U.S.C. § 343(r)(6).

⁶⁵ *See e.g.*, Wellness International Network, Ltd. Courtesy Letter (Ltr. 945; June 12, 2007); New Chapter, Inc. Courtesy Letter (Ltr. 888; June 5, 2006); Nutrition 21 Courtesy Letter (Ltr. 882; May 3, 2006); Source Naturals, Inc. Courtesy Letter (Ltr. 619, June 21, 2002). (Exh. 31).

⁶⁶ *See e.g.*, Healing Power, Inc. Courtesy Letter (Ltr. 885; May 23, 2006); USANA Health Sciences, Inc. Courtesy Letter (Ltr. 879; May 3, 2006); Anabolic Laboratories, Inc. Courtesy Letter (Ltr. 782; September 29, 2004). (Exh. 32).

⁶⁷ *See e.g.*, New Chapter, Inc. Courtesy Letter (Ltr. 935; April 3, 2007); New Century Company Courtesy Letter (Ltr. 873, Mar. 29, 2006); KNature Corp. Courtesy Letter (Ltr. 807; February 4, 2005); NOW Foods Courtesy Letter (Ltr. 799; December 6, 2004); Michael's Naturopathic Programs Courtesy Letter (Ltr. 730; October 15, 2003). (Exh. 33).

independent and significant risk factor for many diseases and other medical conditions.⁶⁸ Thus, just as FDA relied on the scientific literature in deciding to regulate claims about high cholesterol levels, the scientific record about the condition of overweight compels the same regulatory determination about weight loss claims.

Moreover, as with elevated cholesterol levels, the health risks of being overweight are now well-known, and there is a strong association in the public mind linking weight loss with significant health benefits, including the prevention of certain diseases. That is important because FDA also has previously indicated that public awareness and perception of an elevated level of a risk factor for a disease is a relevant factor in deciding whether to treat that statement as a disease claim. In the structure/function rule, for example, FDA declared that "[l]owering cholesterol is inextricably linked in the public mind with treating elevated cholesterol and preventing heart disease." 65 Fed. Reg. at 1019. As documented by the Landmark Study, the same can now be said of the link between weight gain and risk. Virtually all (94%) of the individuals responding to that survey understood that being overweight increases the risk of certain diseases, including diabetes and cardiovascular disease.

In addition, when FDA reached its determination about cholesterol, the agency also recognized the "compelling importance" of preventing heart disease through the use of approved drugs that have been shown to be safe and effective in lowering cholesterol levels. The FDA declared that the "use of possibly ineffective therapies in persons with elevated cholesterol, which can delay or prevent effective treatment, poses significant public health risks." *Id.* at 1019. This was particularly true because, as FDA acknowledged, it does not have the resources to review substantiation of the myriad claims accompanying supplements. The same situation applies to weight loss supplements. There is also compelling public health need to help overweight Americans lose weight, and at least one over-the-counter drug product (Alli[®]) has been approved by FDA as a safe and effective drug for that purpose. Because specious claims by manufacturers of weight loss supplements are diverting Americans from effective ways to lose weight, FDA must act to address these activities which undermine the public health.

Finally, while much of the foregoing has centered on FDA's treatment of cholesterol as a precedent for FDA action on weight loss claims under 21 C.F.R. § 101.93(g)(2)(ii), it should be emphasized that the agency need not find complete consistency between the two claims to grant the action requested in this petition. That is because the structure/function rule authorizes FDA to find that a statement is a disease claim if it "otherwise suggests an effect on a disease or diseases." 21 C.F.R. § 101.93(g)(2)(x). In adopting this provision, FDA explained that this criterion is necessary to capture disease claims that may not fit into the nine criteria expressly enumerated in the regulation. 65 Fed. Reg. at 1030. Thus, FDA recognized that the nine criteria set forth in its regulations do not constitute an exhaustive list, and there may be other types of statements that imply disease treatment or prevention. To the extent that FDA believes that weight loss claims do not sufficiently parallel high cholesterol claims, the agency must nonetheless still restrict such claims under this separate provision in its regulations.

⁶⁸ National Institute of Diabetes and Digestive and Kidney Diseases. Do you know the health risks of being overweight? (Accessed January 3, 2008, at http://win.niddk.nih.gov/publications/health_risks.htm); Centers for Disease Control and Prevention. Overweight and obesity. (Accessed January 3, 2008, at <http://www.cdc.gov/nccdphp/dnpa/obesity/>).

D. TREATING WEIGHT LOSS CLAIMS AS DISEASE CLAIMS WOULD BE CONSISTENT WITH THE LEGISLATIVE HISTORY OF THE FDCA AND FDA'S EARLIER DETERMINATION ABOUT THE CONDITION OF OVERWEIGHT

1. The Actions Requested in the Petition Are Fully Consistent with Longstanding Congressional Intent to Protect the Public Health by Regulating Weight Loss Claims

When FDA issued the structure/function rule in January 2000, it allowed supplement manufacturers to make weight loss claims. That earlier determination, however, is entirely distinguishable from the actions requested in this petition. Specifically, in connection with issuance of its proposal for the structure/function rule in April 1998, FDA considered weight loss in the context of two of the ten criteria it had proposed for identifying whether particular statements constitute disease claims. These proposed criteria focused on statements claiming that a supplement is a substitute for another product that is a therapy for a disease and statements claiming that the supplement augments a particular therapy or drug. 63 Fed. Reg. 23624 at 23632 (discussing 21 C.F.R. §§ 101.93(g)(2)(vi) and (g)(2)(vii)). In the preamble describing these proposed criteria, FDA stated that a "claim that did not identify a specific drug, drug action or therapy (e.g., "use as part of your weight loss plan") would not constitute a disease claim under this criterion." *Id.*

In response to this proposal, several parties objected to FDA's position that supplement manufacturers could state that their products may be used as part of a weight loss plan. One party maintained that the reference to weight loss implies treatment of a disease – obesity. Another comment asserted that the legislative history underlying the FDCA shows that Congress intended weight loss claims to be treated as disease claims. 65 Fed. Reg. at 1027. In the preamble to the final rule, FDA agreed that supplement manufacturers could not claim that their products helped treat obesity since it is a disease. On the other hand, the agency indicated that being overweight is not a disease. Because "it is commonly understood that 'weight loss plans' relate to a broad range of overweight statuses," FDA reasoned that such plans "are not so narrowly associated with a disease treatment that a reference to use as part of a weight loss plan should be considered a disease claim." *Id.* Thus, in evaluating the application of two criteria in its regulations, FDA found that the statement "use as part of a weight loss plan" is an acceptable structure/function claim.

In connection with this determination and in response to one comment, FDA indicated that the legislative history underlying the FDCA does not require the agency to determine that weight loss claims must be treated as disease claims. On the other hand, FDA did not conclude that the legislative history precludes the agency from regulating weight loss claims under the Act.⁶⁹ To be sure, the 1938 amendments to the FDCA added the structure/function clause to the statutory definition of "drug" so that FDA had express authority to regulate deceptive weight loss

⁶⁹ The FDA also considered whether the case law "compels the conclusion" that weight loss products must be regulated as drugs. On the basis of its analysis of several cases, including *Nutrilab, Inc. v. Schweiker*, 713 F.2d 335 (7th Cir. 1983), *American Health Products Co. v. Hayes*, 744 F.2d 912 (2d Cir. 1984), and *United States v. Ten Cartons, More or Less, of an Article Ener-B Vitamin B-12*, 72 F.3d 285 (2d Cir. 1995), FDA stated that it "does not agree that . . . dietary supplements making weight loss claims must necessarily be regulated as drugs." 65 Fed. Reg. 1000, 1027 (January 6, 2000) (emphasis added).

products.⁷⁰ It does not follow, however, that with passage of the Dietary Supplement Health and Education Act ("DSHEA") (Pub. Law 103-417), Congress intended that weight loss claims only be treated as structure/function claims.⁷¹ Nothing in the legislative history surrounding the FDCA precludes FDA from treating such statements as disease claims, particularly where, as here, there is new information and a growing body of evidence indicating that the supplement is meant to treat a disease or a risk factor for a disease. That is precisely the conclusion that FDA reached when it determined that weight loss claims referring to obesity are disease claims; it should be no different for statements that a supplement will treat an abnormal or unhealthy condition that is a risk factor for disease.

The concepts of obesity and overweight have changed dramatically since the structure/function clause was added to the FDCA almost 70 years ago. If Congress were redrafting the statute with the benefit of today's science, it would not need the structure/function clause at all since weight loss claims would be viewed as disease claims. The fact that Congress, in enacting the structure/function clause, was limited by the science available in 1938 does not require FDA to limit itself in a similar manner. Rather, on the basis of current scientific information, FDA must seek to effectuate Congressional intent. Here, there is a longstanding intent of Congress to protect consumers from unsafe and/or ineffective products. The Senate report to the 1938 Amendments explained that FDA must regulate such products "if the consumer is to be protected against . . . preparations . . . which are worthless at best and some of which are distinctly dangerous to health."⁷² Given the close resemblance between the landscape of 1938 and the situation today, action by FDA to regulate weight loss claims would be fully consistent with Congressional intent to regulate claims that falsely promise weight loss.

2. The FDA's Previous Determination About Weight Loss Supplements Does Not Preclude the Agency from Treating Weight Loss Claims as Disease Claims Under Different Criteria in the Structure Function Rule

On the basis of the foregoing analysis, at least four key distinguishing points emerge and make clear that FDA's narrow decision about weight loss claims in 2000 does not serve as a precedent that prevents the agency from taking the actions requested in this petition.

⁷⁰ S. REP. NO. 74-361, at 3 (1935), *reprinted in* 3 A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND ITS AMENDMENTS 662. On the House side, one member captured the situation, declaring "these products have been known to cause death as well as serious illness—and yet they continue to be advertised and sold as 'safe.' Even though they may not be harmful, many of them are worthless." *See* Extension of Remarks of Hon. Caroline O'Day of New York in the House of Representatives, Feb. 24, 1937, 81 CONG. REC. A321 (1937), *reprinted in* 5 A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND ITS AMENDMENTS 490.

⁷¹ There is no indication that Congress, when enacting DSHEA, knew of the historical references to weight loss associated with the structure/function clause. After all, the FDCA was amended more than twenty times between 1938 and 1994, and Congress's thoughts on weight loss and the structure/function clause were not reflected in the statutory text, but rather hidden in the legislative history. These circumstances, combined with the fact that the FDCA is a voluminous statute, undermine the notion that the structure/function clause in DSHEA must be interpreted identically to the original structure/function clause in the FDCA.

⁷² S. REP. NO. 74-361, at 3 (1935), *reprinted in* 3 A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND ITS AMENDMENTS 662.

(1) In 2000, FDA authorized supplement manufacturers to make weight loss claims after determining that the condition of being overweight is not a disease. Here, petitioners are not asking FDA to reverse its finding that overweight is not a disease. Rather, petitioners are requesting the agency to take action on the basis of substantial scientific evidence establishing that the condition of being overweight is not itself a disease but rather a *risk factor for disease*.

(2) In 2000, scientific data linking the risk of disease with being overweight was not fully developed. Nor was there any information available about consumer perceptions and use of weight loss supplements to reduce risks. As a result, FDA did not then consider whether weight loss claims should be treated as disease claims under 21 C.F.R. § 101.93(g)(2)(ii) – the criterion that led FDA to regulate statements about risk factors such as high cholesterol and high blood pressure.

(3) In 2000, FDA reached its decision about weight loss supplements under two different criteria in the structure/function rule. That determination does not preclude FDA from now determining that such statements are disease claims under a *separate and distinct criterion* in the regulations. The regulations contemplate that each of the ten criteria was meant to be applied independently and prospectively in an evaluation of claims accompanying dietary supplements.

(4) In 2000, FDA found that neither the legislative history nor the case law "necessarily requires" the agency to determine that weight loss claims are disease claims. On the other hand, FDA did not (and could not) take the position that it lacks authority to treat such statements as disease claims. Indeed, that determination would be inconsistent with longstanding Congressional intent.

Accordingly, although FDA decided not to prohibit weight loss claims in 2000, that determination was based on then-existing scientific information and different regulatory criteria in the structure/function rule. Nothing precludes the agency from now finding, on the basis of new scientific information developed during the past decade, that weight loss claims are disease claims under criteria in FDA's regulations that were not previously considered by the agency. The FDA announced in its January 9, 2002 "Structure/Function Claims Small Entity Compliance Guide" that dietary supplement manufacturers "can look to medical texts and other objective sources of information about disease to determine if a label statement implies treatment or prevention of a disease."⁷³ This guidance and the rule itself therefore clearly contemplate the fact that as medical science evolves so, too, will the conditions that constitute the signs or symptoms of disease.

Finally, in this context, petitioners must emphasize that FDA is not required to engage in notice and comment rulemaking under the Administrative Procedures Act ("APA"), 5 U.S.C. § 553, before implementing the actions requested in this petition. That is because petitioners are not asking FDA to change its earlier interpretation of the way that two of the criteria in the

⁷³ Food and Drug Administration, Center for Food Safety and Applied Nutrition. Structure/function claims small entity compliance guide. January 9, 2002. (Accessed January 3, 2008, at <http://www.cfsan.fda.gov/~dms/scfmguid.html>).

structure/function rule apply to weight loss claims. Rather, petitioners are requesting FDA to apply a particular provision in its existing regulations to weight loss claims in light of the substantial body of scientific literature and consumer survey data developed during the past decade. An agency's application of its regulations to particular factual scenarios certainly does not require notice and comment rulemaking under the APA. Moreover, to the extent that FDA concludes that granting this petition would require the agency to modify its earlier statements about weight loss claims in the preamble to the structure/function rule, such statements constitute "advisory opinions" that can be modified at any time following notice in the Federal Register.⁷⁴

E. GRANTING THE PETITION WOULD SUBSTANTIALLY ADVANCE THE PUBLIC HEALTH BY REQUIRING MANUFACTURERS OF WEIGHT LOSS SUPPLEMENTS TO SUPPORT THEIR CLAIMS WITH SCIENTIFIC EVIDENCE BEFORE GOING TO MARKET

1. Manufacturers of Weight Loss Supplements Might Seek to Make Qualified Health Claims But Systematic Reviews Indicate That There Is Currently No Credible Scientific Evidence to Support Such Claims

If FDA were to treat weight loss claims as disease claims, then supplement manufacturers might seek to make weight loss claims for their products pursuant to the health claims process established under the Nutrition Labeling and Education Act ("NLEA"). Pub. L. No. 101-535, 104 Stat. 2353. The NLEA amended the FDCA to authorize the sale of dietary supplements pursuant to "health claims" that "characterize[] the relationship of any nutrient ... to a disease or health-related condition" 21 U.S.C. § 343(r)(1)(B). That provision has been construed by FDA only to authorize supplement manufacturers to make health claims directed at the reduction of the risk of contracting a disease.⁷⁵ And, that interpretation has been upheld by the courts. *See Whitaker v. Thompson*, 353 F. 3d 947 (D.C. Cir. 2004). Accordingly, to the extent that any manufacturer of a weight loss supplement seeks to avail itself of the health claims process, FDA may only approve claims that the risk of developing a disease could be reduced through the intake of a substance in the supplement. The FDA may not approve statements about a supplement where weight loss is the "pivot" of the health claim.

Moreover, to the extent that FDA is authorized to approve health claims under the NLEA, it may do so only "subject to a procedure and standard, respecting the validity of such claim, established by regulation of the Secretary," 21 U.S.C. § 343(r)(5)(D). To that end, FDA has promulgated regulations allowing for health claims where significant scientific agreement ("SSA") exists about the diet-disease relationship. 21 C.F.R. § 101.14. To satisfy the SSA standard, there must be relevant and high quality studies that provide qualified scientists with a

⁷⁴ Under FDA's regulations, statements in a preamble accompanying a proposed or final rule constitute "advisory opinions." 21 C.F.R. § 10.85(d)(1). The regulations provide that advisory opinions may be amended or revoked at any time, and notice of such action may simply be given in the Federal Register. 21 C.F.R. § 10.85(g); *Perry v. Novartis*, 456 F. Supp. 2d 678, 684 (E.D. Pa. 2006) (stating that an advisory opinion can be changed at any time and a change does not require notice and comment). Of course, FDA has the option of soliciting public comment on this citizen petition, as it has done with other petitions. The agency need not, however, engage in notice and comment rulemaking.

⁷⁵ *See* Letter from Joseph Levitt, Director, Center for Food Safety and Applied Nutrition, FDA to Jonathan Emord, Emord & Associates, Dietary Supplement Claim for Saw Palmetto Extract and Benign Prostatic Hyperplasia, May 26, 2000, at <http://www.cfsan.fda.gov/~dms/dspltr01.html>.

"high level of comfort" that the claimed relationship between the substance and the disease is scientifically valid. The FDA has also established interim provisions to govern pre-market review of "qualified health claims."⁷⁶ For these types of claims, FDA exercises its enforcement discretion based on the nature of the scientific evidence that exists to support such claims.

Specifically, under these latter procedures, FDA applies a sliding scale approach and determines, on a case-by-case basis, the degree of qualification needed so that consumers are not misled. Examples of FDA's sliding scale of qualifications are: Category B claims that may read "although there is scientific evidence supporting the claim, the evidence is not conclusive"; Category C claims that may read "some scientific evidence suggests . . . however, FDA has determined that this evidence is limited and not conclusive"; and Category D claims that may read "very limited and preliminary scientific research suggests . . . FDA concludes that there is little scientific evidence supporting this claim." The FDA has also denied outright a number of proposed qualified health claims because of the lack of "credible evidence" supporting the claims.

Petitioners have reviewed the standards set forth in FDA's interim guidance governing authorization of qualified health claims⁷⁷ and believe there is *no credible evidence* whatsoever to support any type of a qualified health claim for a weight loss supplement. In that guidance, FDA describes the nature and quality of scientific evidence that must exist to support particular types of qualified health claims.⁷⁸ In order to qualify for even the weakest of the qualified health claims (i.e., a Category D claim), a weight loss supplement manufacturer must demonstrate that studies of different design would generally result in similar findings even if some uncertainties exist. At the same time, a manufacturer must show that there is not a strong body of evidence against the claim – that is, a study or studies of high persuasiveness, quality, and relevance that do not detect an effect. If such studies exist, then FDA has "a sound basis for concluding that the claim is not valid."⁷⁹ In the case of weight loss supplements, there is no credible evidence to indicate that supplements themselves assist in weight loss or, even if they do so, that there is a commensurate risk reduction of disease from the use of any such supplements.

Indeed, during the past decade, several independent teams of researchers have undertaken extensive reviews of the scientific literature purportedly supporting the efficacy of weight loss supplements. Each of these studies has concluded that there is little, if any, evidence to support the efficacy of supplements marketed for weight loss. In 2005, scientists from the Office of Dietary Supplements at NIH declared that evidence supporting the efficacy of weight loss supplements is "inconclusive at present."⁸⁰ Similarly, researchers from Harvard Medical School

⁷⁶ Food and Drug Administration, Center for Food Safety and Applied Nutrition. Interim procedures for qualified health claims in the labeling of conventional human food and human dietary supplements. July 10, 2003. (Accessed January 3, 2008, at <http://www.cfsan.fda.gov/~dms/hclmgui3.html>).

⁷⁷ Food and Drug Administration, Center for Food Safety and Applied Nutrition. FDA's implementation of "qualified health claims": questions and answers. May 12, 2006. (Accessed January 3, 2008, at <http://www.cfsan.fda.gov/~dms/qhcqagui.html>).

⁷⁸ Food and Drug Administration, Center for Food Safety and Applied Nutrition. Interim evidence-based ranking system for scientific data. July 10, 2003. (Accessed January 3, 2008, at <http://www.cfsan.fda.gov/~dms/hclmgui4.html>).

⁷⁹ *Id.*

⁸⁰ Dwyer JT, Allison DB, Coates PM. Dietary supplements in weight reduction. *J Am Diet Assoc* 2005;105(5 Suppl 1):S80-6. (Exh. 34).

reported that many weight loss supplements have never been the subject of randomized human clinical studies and "no weight loss supplements meet criteria for recommended use."⁸¹ In still another study, investigators from the Universities of Exeter and Plymouth declared that there "is little convincing evidence that any dietary supplement is effective in reducing body weight."⁸² These conclusions were further confirmed by the School of Pharmacy at Creighton University.⁸³

These systematic reviews are particularly telling since they focused on the principal "active ingredients" that are included in weight loss supplements. While there are myriad weight loss products, most of these products actually fall into a few discrete categories based on their purported "active" ingredient or the mechanism of action through which these ingredients supposedly help individuals lose weight. Thus, weight loss supplements have been classified based on whether they purportedly: (1) increase energy expenditure; (2) modulate carbohydrate metabolism; (3) increase satiety or suppress appetite; (4) increase fat oxidation or reduce fat synthesis; or (5) block dietary fat absorption.⁸⁴ The foregoing systematic studies focused on the major ingredients in each of these categories of weight loss supplements. This is confirmed by a recent consumer research survey and an audit of retail outlets identifying the particular types of weight loss supplements typically purchased by consumers.⁸⁵

2. There Is Currently No Credible Scientific Evidence That Would Support a Qualified Health Claim for Any Ingredient in Any of the Five Categories of Weight Loss Supplements

It is beyond the scope of this petition to review all of the data that purportedly support the efficacy of weight loss supplements from these five categories. Nonetheless, the summary that follows makes clear that currently available data would not support even the weakest of the qualified health claims for any weight loss supplement for use in an overweight population.⁸⁶ There are conflicting results among the studies for each ingredient while, in most cases, there are studies of high quality that did not detect any effect on weight loss from these supplements. Moreover, many of the studies that purportedly support the efficacy of weight loss supplements may not be relied upon since the products actually contain a combination or amalgam of different ingredients. Furthermore, many of the studies involved short terms and small population sizes and, significantly, do not distinguish between overweight individuals and those whose BMI makes them obese. That is important because, to the extent that a qualified health

⁸¹ Saper RB, Eisenberg DM, Phillips RS. Common dietary supplements for weight loss. *Am Fam Physician* 2004;70:1731-8. (Exh. 35).

⁸² Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* 2004;79:529-36. (Exh. 36).

⁸³ Lenz TL, Hamilton WR. Supplemental products used for weight loss. *J Am Pharm Assoc* 2004;44:59-67. (Exh. 37).

⁸⁴ DeBusk RM. A critical review of the literature on weight loss supplements. *Integr Med Consult* 2001;3:30-1. (Exh. 38).

⁸⁵ Blanck HM, Serdula MK, Gillespie C, et al. Use of nonprescription dietary supplements for weight loss is common among Americans. *J Am Diet Assoc* 2007;107:441-7. (Exh. 28); Sharpe PA, Granner ML, Conway JM, et al. Availability of weight-loss supplements: results of an audit of retail outlets in a Southeastern city. *J Am Diet Assoc* 2006;106:2045-51. (Exh. 39).

⁸⁶ Many weight loss supplements are distributed as combinations containing various ingredients. There also does not appear to be any credible scientific data supporting the efficacy of such combination products.

claim could be made, it would need to be based solely on data involving overweight – not obese – individuals.⁸⁷ Finally, to the extent that any evidence exists at all, it would be even weaker if it were extrapolated to support a disease risk reduction claim – that is, the subject of a permissible health claim.

A brief description follows of the particular findings involving each of the principal ingredients in each category of weight loss supplement:

(1) *Supplements that Increase Energy Expenditure*

Bitter Orange: Also known as Zhi shi, bitter orange is derived from an Asian tree species (*Citrus aurantium*) and is widely regarded as a substitute for ephedra. The active ingredient in bitter orange is believed to be synephrine – a sympathomimetic amine that is structurally similar to epinephrine. There is "little evidence" that bitter orange is effective in weight loss.⁸⁸ In fact, a randomized, placebo controlled trial found no benefit for weight loss from bitter orange.⁸⁹ On the other hand, bitter orange and another supplement in the same category (Guarana) may have adverse effects similar to ephedra, including increased heart rate, blood pressure, and the risk of cardiac complications.⁹⁰

(2) *Supplements that Modulate Carbohydrate Metabolism*

Chromium: Chromium picolinate is a naturally occurring derivative of tryptophan that is claimed to promote weight loss by optimizing insulin signaling. "Insufficient evidence exists" to support the effectiveness of chromium, and many studies yielded "inconsistent results," were "poorly designed," and reported benefits that were refuted by other reports.⁹¹ The results of other studies, including three randomized clinical trials, did not show any differences in weight loss between treatment and control groups.⁹² Moreover, to the extent that any studies have shown slight weight loss from

⁸⁷ While qualified health claims may speak to a substance's ability to *reduce the risk* of disease, they may not characterize a substance as *treatment* for the disease itself. See Food and Drug Administration, Center for Food Safety and Applied Nutrition. FDA's implementation of "qualified health claims": questions and answers. May 12, 2006. (Accessed January 3, 2008, at <http://www.cfsan.fda.gov/~dms/qhcqagui.html>). To the extent that any scientific studies demonstrate the efficacy of particular ingredients for weight loss, then, they are relevant to the qualified health claims analysis only if such studies measured the effect of ingredients on overweight subjects (i.e., individuals at risk for obesity), rather than individuals who were already obese.

⁸⁸ Fugh-Berman A, Myers A. Citrus aurantium, an ingredient of dietary supplements marketed for weight loss: current status of clinical and basic research. *Expert Biol Med* 2004;229:698-704. (Exh. 40).

⁸⁹ Bent S, et al. Safety and efficacy of citrus aurantium for weight loss. *Am J Cardiol* 2004;94:1359-61. (Exh. 41).

⁹⁰ Hess AM, Sullivan DL. Potential for toxicity with use of bitter orange and guarana for weight loss. *Ann Pharmacother* 2005;39:574-5. (Exh. 42); Bouchard NC, et al. Ischemic stroke associated with use of an ephedra-free dietary supplement containing synephrine. *Mayo Clin Proc* 2005;80:541-5. (Exh. 43); Nykamp D, Fackih MN, Comptom AL. Possible association of acute lateral-wall myocardial infarction and bitter orange supplement. *Ann Pharmacother* 2004;38:812-6. (Exh. 44).

⁹¹ Lukaski HC. Chromium as a supplement. *Annu Rev Nutr* 1999;19:279-302; Lenz TL, Hamilton WR. Supplemental products used for weight loss. *J Am Pharm Assoc* 2004;44:59-67. (Exh. 37).

⁹² Bahadori B, Wallner S, Schneider H, Wascher TC, Toplak H. [Effect of chromium yeast and chromium picolinate on body composition of obese, non-diabetic patients during and after a formula diet]. *Acta Med Austriaca*

chromium supplements, the observed effect was found "not clinically meaningful."⁹³ Therefore, as one report recently concluded, there are "no independent effects of chromium picolinate supplementation on body weight or composition."⁹⁴

(3) *Supplements that Increase Satiety or Suppress Appetite*

Guar Gum: This dietary fiber is derived from the Indian cluster bean (*Cyamopsis tetragonolobus*). Soluble fiber is believed to absorb water within the gut, thereby causing increased satiety and lower caloric intake. The efficacy of this supplement was assessed in a meta-analysis of 20 double-blind, placebo-controlled randomized clinical trials. That meta-analysis indicated that guar gum is "not effective" in reducing body weight.⁹⁵ The consistency of the results among the individual trials confirmed the overall conclusion of this meta-analysis.⁹⁶ Other studies have reported adverse gastrointestinal events associated with guar gum.⁹⁷

Hoodia: Much attention has recently been focused on P57, a steroidal glycoside that is extracted from the South African plant species, *Hoodia gordonii*. P57 is believed to cause neurons within the satiety center of the hypothalamus to fire rapidly and thereby suppress appetite. While certain animal studies involving P57 have been published, there does not appear to be any publications in peer-reviewed journals involving human trials with *Hoodia* extract.⁹⁸ As a result, there is no credible scientific support for the efficacy of weight loss supplements containing *Hoodia* extracts.

(4) *Supplements that Increase Fat Oxidation or Reduce Fat Synthesis*

Garcinia: Hydroxycitric acid ("HCA") is contained within extracts of the fruit rind of *Garcinia cambogia*, a tree species native to India. HCA has been shown to inhibit citrate cleavage enzyme and suppress fatty acid synthesis. Nevertheless, clinical data to suggest that HCA may help in weight loss are "inconsistent" and most of the clinical

1997;24:185-7. German. (Exh. 45); Pasman WJ, Westerterp-Plantenga MS, Saris WHM. The effectiveness of long-term supplementation of carbohydrate, chromium, fibre and caffeine on weight maintenance. *Int J Obes* 1997;21:1143-51. (Exh. 46); Crawford V, Scheckenbach R, Preuss HG. Effects of niacin-bound chromium supplementation on body composition in overweight African-American women. *Diabetes Obes Metab* 1999;1:331-7. (Exh. 47).

⁹³ Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* 2004;79:529-36. (Exh. 36).

⁹⁴ Lukaski HC, et al. Chromium picolinate supplementation in women: effects on body weight, composition, and iron status. *Nutrition* 2007;23:187-95. (Exh. 48).

⁹⁵ Pittler MH, Ernst E. Guar gum for body weight reduction, meta-analysis of randomized trials. *Am J Med* 2001;110:724-30. (Exh. 49).

⁹⁶ Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* 2004;79:529-36. (Exh. 36).

⁹⁷ Dwyer JT, Allison DB, Coates PM. Dietary supplements in weight reduction. *J Am Diet Assoc* 2005;105(5 Suppl 1):S80-6. (Exh. 34).

⁹⁸ Lee RL, Balick MJ. Indigenous use of *Hoodia gordonii* and appetite suppression. *Explore* 2007;3:404-6. (Exh. 50).

studies are "confounded by methodological flaws."⁹⁹ Where there has been a randomized, double blind clinical trial involving HCA, it found no significantly greater weight loss in the treatment group than in the placebo group.¹⁰⁰

Conjugated Linoleic Acid ("CLA"): CLA is a group of linoleic acid derivatives produced by bacteria in the gut of ruminant animals. This compound is believed to inhibit lipoprotein lipase, an enzyme that breaks down fat for absorption. Data from human studies involving CLA are "equivocal and unconvincing."¹⁰¹ Several studies have found no changes in body weight or BMI.¹⁰² Moreover, based on an analysis of the results from 13 randomized, controlled trials, investigators reported that there is little evidence to suggest that CLA helps reduce body weight.¹⁰³ The authors of this study also reported that CLA may promote liver hypertrophy and insulin resistance, and therefore, may have adverse effects.

Pyruvate: This three carbon ketoacid is created in the body during glycolysis. Pyruvate is believed to manipulate fat metabolism by increasing fat oxidation and decreasing carbohydrate oxidation. Some studies have reportedly shown positive results with pyruvate but they had small sample sizes with short treatment periods, and patients greatly restricted their caloric intake during the study period. On the other hand, two double blind randomized clinical trials involving patients with a BMI greater than 25 found no significantly greater effects on weight reduction than were seen with placebo.¹⁰⁴ The results of these "rigorous clinical trials" have led investigators to conclude that the case for pyruvate as an aid to weight loss is "weak."¹⁰⁵

⁹⁹ Joyal SV. A perspective on the current strategies for the treatment of obesity. *Current Drug Targets – CNA & Neurological Disorders* 2004;3:341-56. (Exh. 51).

¹⁰⁰ Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent. *JAMA* 1998;280:1596-600. (Exh. 52); Rothacker DQ, Waitman BE. Effectiveness of a *Garcinia cambogia* and natural caffeine combination in weight loss: a double-blind, placebo-controlled pilot study. *Int J Obes* 1997;21(Suppl 2):53. (Exh. 53); Antonio J, Colker CM, Tornia GC, Shi Q, Brink W, Kalman D. Effects of a standardized guggulsterone phosphate supplement on body composition in overweight adults: a pilot study. *Curr Ther Res* 1999;60:220-7. (Exh. 54); Thom E. A randomized, double-blind, placebo-controlled trial of a new weight-reducing agent of natural origin. *J Int Med Res* 2000;28:229-33. (Exh. 55).

¹⁰¹ Dwyer JT, Allison DB, Coates PM. Dietary supplements in weight reduction. *J Am Diet Assoc* 2005;105(5 Suppl 1):S80-6. (Exh. 34).

¹⁰² Blankson H, Stakkestad JA, Fagertun H, et al. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. *J Nutr* 2000;130:2943-8. (Exh. 56); Risérus U, Berglund L, Vessby B. Conjugated linoleic acid (CLA) reduced abdominal adipose tissue in obese middle-aged men with signs of metabolic syndrome: a randomized controlled trial. *Int J Obes* 2001;25:1129-35. (Exh. 57); Smedman A, Vessby B. Conjugated linoleic acid supplementation in humans: metabolic effects. *Lipids* 2001;36:773-81. (Exh. 58); Risérus U, Smedman A, et al. Metabolic effects of conjugated linoleic acid in humans: the Swedish experience. *Am J Clin Nutr* 2004;79:1146S-8S. (Exh. 59).

¹⁰³ Larsen TM, Toubro S, Astrup A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* 2003;44:2234-41. (Exh. 60).

¹⁰⁴ Kalman D, Colker CM, Wilets I, Roufs JB, Antonio J. The effects of pyruvate supplementation on body composition in overweight individuals. *Nutrition* 1999;15:337-40. (Exh. 61); Kalman D, Colker CM, Stark R, Minsch A, Wilets I, Antonio J. Effects of pyruvate supplementation on body composition and mood. *Curr Ther Res* 1998;59:793-802. (Exh. 62).

¹⁰⁵ Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* 2004;79:529-36. (Exh. 36).

(5) *Supplements that Block Fat Absorption*

Chitosan: This cationic polysaccharide is derived from chitin harvested from the exoskeleton of crustaceans. Several studies involving well-designed, randomized controlled trials have failed to show any differences in weight loss.¹⁰⁶ Moreover, to the very limited extent that other studies may suggest efficacy for chitosan, investigators found "serious methodological limitations of the clinical evidence" and results that were "conflicting and short-term" and based on "poorly designed studies."¹⁰⁷ One report declared that "claims that chitosan is a fat-trapping weight-loss aid are not merely unsubstantiated, they are false."¹⁰⁸ Thus, there is also "considerable doubt" that chitosan is effective in reducing body weight in humans.¹⁰⁹

In sum, the foregoing analysis demonstrates that there is *no credible scientific evidence* to support any type of qualified health claim for a weight loss supplement for use by an overweight population. As a result, if FDA were to take the actions requested in this petition, manufacturers would not be able to market weight loss supplements without demonstrating, through additional scientific studies, that their products actually work. This requirement would obviously advance the public health since millions of Americans are currently relying on unproven and ineffective dietary supplements to lose weight and reduce the risk of disease. Moreover, the actions requested in this petition would also help address concerns about the safety of weight loss supplements. Adverse events have been reported in connection with a number of weight loss supplements.¹¹⁰ By requiring weight loss supplements to undergo pre-market review, FDA would shift the burden to manufacturers to show that their products are safe.¹¹¹ In light of the adverse events associated with ephedra, such action would obviously have significant public health benefits.

¹⁰⁶ Pittler MH, Abbott NC, et al. Randomized, double blind trial of chitosan for body weight reduction. *Eur J Clin Nutr* 1999;53:379-81. (Exh. 63); Mhurchu CN, Poppitt SD, et al. The effect of the dietary supplement, chitosan, on body weight: a randomised controlled trial in 250 overweight and obese adults. *Int J Obes* 2004;28:1149-56. (Exh. 64); Ho SC, Tai ES, et al. In the absence of dietary surveillance, chitosan does not reduce plasma lipids or obesity in hypercholesterolaemic obese Asian subjects. *Singapore Med J* 2001;42:6-10. (Exh. 65).

¹⁰⁷ Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* 2004;79:529-36. (Exh. 36); Lenz TL, Hamilton WR. Supplement products used for weight loss. *J Am Pharm Assoc* 2004;44:59-68. (Exh. 37).

¹⁰⁸ Gades MD, Stern JS. Chitosan supplementation and fat absorption in men and women. *J Am Diet Assoc* 2005;105:72-7. (Exh. 66).

¹⁰⁹ Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* 2004;79:529-36. (Exh. 36).

¹¹⁰ Pittler MH, Schmidt K, Ernst E. Adverse events of herbal food supplements for body weight reduction: systematic review. *Obesity Reviews* 2005;6:93-111. (Exh. 67).

¹¹¹ Under 21 C.F.R. § 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under applicable food safety provisions of the Act.

III. ENVIRONMENTAL AND ECONOMIC IMPACT

The actions requested in this petition are subject to a categorical exclusion from environmental assessment under 21 U.S.C. § 25.30(h) and 21 C.F.R. § 25.31. As provided under 21 C.F.R. §10.30(b), petitioners will provide data concerning the economic impact of the actions requested herein if such information is requested by FDA.

IV. CERTIFICATION

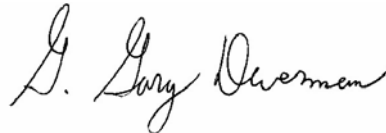
The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.¹¹²



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¹¹² Any correspondence from FDA relating to this petition should be sent to Bruce Manheim, Ropes & Gray LLP, 700 12th Street, N.W., Washington, D.C. 20005.