

# Weight Loss and Maintenance:

**Putting Weight into Weight Loss Claims** 

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Janaki Iyer, PhD, Research Scientist Najla Guthrie, President/CEO Mal Evans, PhD, Scientific Director The global epidemic of overweight and obesity- 'globesity' has taken over many parts of the world and has become a health concern<sup>1</sup>. The World Health Organization (WHO) reports nearly 39% men and women (about 2 billion adults worldwide) over the age of 18 to be overweight in 2016, a 20% rise from 1975<sup>2</sup>. Obesity has risen 10-fold in children in the past 4 decades with 213 million children classified as overweight <sup>3</sup>. In 2016, 67.9% of Americans were overweight. In Canada, the prevalence of overweight men and women is 40% and 27.5% respectively<sup>4</sup>. The United Kingdom has reported an obesity boom in the past decade<sup>5</sup>. In North America, the rise in obesity is linked with the staples of the modern western diet and lifestyle- hyper palatable processed junk foods, super-sized burgers with extra-large fries in combination with sugary sodas and a lack of physical activity. The spread of the overweight pandemic to developing nations has been attributed



to the globalization of western food habits and chains such as McDonalds and KFC resulting in some of the most underdeveloped countries reporting a worrying rise in obesity<sup>6</sup>. The highest such increases have occurred in the world's two largest populations- India and China<sup>7</sup>. Approximately 32.2% of the Chinese population is overweight with urban areas showing the highest prevalence<sup>8</sup>. The phenomenon is spurred by a

growing middle class, busier and more sedentary lifestyles and the adoption of Western fast food culture. Quick fixes to shed excess pounds and get high school skinny again are in great demand- Think Atkins, Pritikin, Paleo, protein bars, Master Cleanse, low carb, 0 fat, vegan, meal replacements, and many other "programs" presented as a halo of health that one could possibly imagine. However, such overly generalized recommendations, extreme diet and exercise regimens, have doomed weight loss to be virtually impossible to attain and maintain. This white paper takes a critical look at popular weight loss claims, proposes new concepts for study design and a Global Index for measurement of weight loss for claims substantiation.

#### Weight Management Markets

The global weight loss market is predicted to grow by approximately 5.5% over the next decade reaching \$85.61 billion by 2025<sup>9</sup>. Market drivers include greater awareness of health and wellbeing, an expanding consumer base due to prevalence of overweight and obesity, and higher disposable income in developing nations<sup>10</sup>.



North America and Europe have been the largest players in the global market, with the U.S. market accounting for onethird of sales<sup>11</sup>. Of commercial weight loss chains, Weight Watchers (45%). Nutrisystem (14%)and Jennv Craig (13%) dominate the

\$2.3 billion domestic market<sup>12</sup>. However, revenue for weight loss services is forecasted to decrease at an annual rate of 0.2% over the next five years.

In the U.S., the \$66.3 billion domestic weight-loss industry provides services to over 97 million Americans seeking to lose weight<sup>13</sup>. A 2011 Gallup poll reported 63% of Americans have seriously attempted to lose weight at some point, and 29% were currently trying to lose weight. The American weight-loss market is evenly divided between the weight loss product sector (e.g. supplements, meal replacements) and the weight loss services sector (e.g. weight loss centres, counselling), occupying 49.3% and 50.7% respectively. The total market grew by 2.2% in 2016 and is projected to grow by an additional 2.8% in 2017 <sup>13</sup>.

The market for weight loss in Canada, is worth \$11 billion in retail sales according to Euromonitor <sup>4,14</sup>. Meal replacement products have dominated the sector, being responsible for 81% of revenue in 2013 on the back of 5% of growth over the previous year. The market for weight loss supplements remains relatively stagnant at \$35 million in Canada<sup>15</sup>.



Anti-obesity initiatives implemented by UK government, such as the Change4Life campaign (2009) and the Healthy Lives, Healthy People program (2011) have emphasized weight reduction and provided an

impetus for growth in the weight management market <sup>16</sup>. Indeed, the industry has demonstrated strong growth in 2017, framed by rising consumer health awareness and high obesity prevalence. Diet plans and exercise remain the most popular weight loss strategy <sup>17</sup>, however sales of diet friendly food and supplements continue to grow. Market for diet food increased by 7% between 2008 to 2013 <sup>17</sup>.



The market size for weight management products in France reached around US \$282 million in 2011. Meal replacement products accounted for 50% of

the market value, led by the French-based company, Nutrition & Sante SAS at around 26% value share. Over 20 remaining players in the meal replacement sector contributed to less than 10% of market shares each. Weight loss supplements recorded their second largest sales in 2011, gaining approximately US \$100 million in revenue. However, the market for supplements has declined since 2007 given safety issues and more stringent French legislation concerning dietary products <sup>18</sup>.



China's weight management sector is dominated by domestic companies that secure almost 39% of market sales. Slimming tea is the most popular product among Chinese consumers and represents over 57% of total

industry sales. Meal replacement products, a relatively new category, has also recorded substantial growth at 17% in 2011. Weight-loss supplements have seen continued decline from 2008–2011 due to ingredient safety concerns. Between 2015 and 2016, the Chinese weight-loss industry witnessed a 7.9% growth resulting in a total of US \$1.37 billion in sales <sup>8</sup>.

#### Popular Diet Types and Trends in the Weight Loss Industry



#### Pills May be Easy to Swallow but the Claims are Not

"The science just isn't there." Jessica Rich, Director of the FTC's Bureau of **Consumer Protection** 

> FTC targets unsubstantiated weight loss claims

> > High-Tech Pharma

LeanSpa

CortiSlim

Xenadrine EFX

- CortiStress Sensa
- Trim spa
  - Green Coffee Bean
- L'Occitane HCG Diet Direct
- 1-a-day Weight Smart USP Labs LLC
- Acai

Weight loss industry in the U.S. reaches out to a large target audience. The Federal Trade Commission (FTC) scrutinizes advertising practices which includes regulating weight loss marketing and claims. The FTC has been waving the proverbial red flag to create consumer awareness against outrageous, deceptive, and illegal claims to protect the reasonable consumer.

FTC released a report stating that a huge proportion of marketers used deceptive beforeand-after pictures, false testimonials, unsubstantiated claims that promise weight loss beyond what is possible<sup>19,20</sup>. Similarly, the Regulation for Health and Nutrition Claims aims to regulate the untruthful and unsubstantiated claims about food products in the European Union (EU).

"False and misleading advertisements are about as credible as a note from the Tooth Fairy" Deborah Platt Majoras, Federal Trade Commission Chairman



In January 2014, the FTC announced charges against the marketers of Sensa for using deceptive and misleading claims. Sensa's claims of "sprinkle, eat, and lose weight" ended up costing them \$26.5 million to settle charges of their unsubstantiated claims.

"Resolutions to lose weight are easy to make but hard to keep, and the chances of being successful just by sprinkling something on your food, rubbing cream on your thighs, or using a supplement are slim to none. The science just isn't there." Jessica Rich, Director of the FTC's Bureau of **Consumer Protection** 

One of the more outrageous claims was put forth by marketers of Green Coffee Bean Weight-Loss Supplement. They claimed that consumers could expect to lose 17 pounds and 16% body fat in just 12 weeks without any diet or exercise. The clinical trials that touted the product's effectiveness were found to be severely limited and the FTC imposed a \$9 million fine for using deceptive claims to redress the judgement of this case.





Another FTC settlement centered on the companies which marketed the products Final Trim and AF Plus and earned over \$16 million in just three years. The defendants had no scientific basis for their claims. The settlement requires the defendants to surrender assets valued at more than \$1.5 million.

#### Weightless Weight Loss Claims

Popular claims such as 'fast and easy', 'Ancient remedy', 'Scientific breakthrough', 'Weight loss without diet or exercise! Eat all your favourite foods!' and 'Never diet again! Lose 30 pounds in 30 days!' are prevalent. Unfortunately, these claims are not supported by competent and reliable scientific evidence. To combat the extent of false advertising in the weight loss industry, the FTC has compiled a list of seven statements that warrant a closer "gut check" by consumers.



Source: Federal Trade Commission. *Gut Check: A Reference Guide for Media on Spotting False Weight Loss Claims*. (2014).

## **Competent Reliable Scientific Evidence Supporting Weight Loss**

# **Regulatory Guidelines for Struture Function Claims**

FDA targets...

- Mean absolute or % change in body weight between groups given investigational product (IP) vs. placebo
- Proportion of subjects in IP who lose >5% of their baseline weight vs. placebo
- Blood pressure, Lipid panel, glucose, HbA1c, waist circumference

EFSA and Health Canada targets...

- Reduction of body fat (5%) (DEXA, MRI, CT) but not by BIA (bio-impedance analysis) vs. placebo
- Reduction in BW should be attributed to fat reduction and not lean body mass
- BP, Lipid panel, glucose, HbA1c, waist circumference
- Can use studies on diet and physical activity for bench marking

#### Duration of studies: at least 12 weeks

The recent past has seen a surge in the number of clinical trials undertaken for evaluating the efficacy of weight loss products. A placebo controlled randomized controlled trial (RCT) evaluated the efficacy of a product containing plant extracts from Sphaeanthus indcus and Gacinia mangostana on weight loss in healthy overweight adults and found significant reductions in body weight and waist and hip sizes <sup>21</sup>. Other trials have evaluated the efficacy of several dietary supplements to promote or facilitate weight loss <sup>22,23</sup>. Among the dietary supplements that have been identified, the molecular mechanisms of action of some of these has been well documented. The mechanisms of action for polyphenols from Irvingia sp. were elucidated via in vitro studies, where an inhibition in the expression of peroxisome proliferator-activated receptor gamma (PPARy, a receptor that regulates fatty acid storage and glucose metabolism) and leptin were observed. RCTs evaluating the weight loss effects following the consumption of I. gabonensis extract showed both statistically and clinically significant weight loss <sup>24</sup>. Similarly, forskolin- the active ingredient from Coleus foskohlii is a potent stimulator of cyclic AMP which activates the hormone-sensitive lipase and promotes the release of fatty acids from adipose tissue <sup>25</sup>.

Some clinical trials evaluating the effectiveness of forskolin to promote weight loss have shown that it is effective in reducing body fat and lean body mass in women but not in men <sup>26,27</sup>. Other products such as fucoxanthin and chitosan have been shown to be effective in weight loss. However, caution must be exercised while interpreting studies

from clinical trials as all aspects of the study design, inclusion/exclusion criteria must be considered to understand the clinical relevance of any significant findings. Case in point, despite knowledge of the mechanisms of action of products such as green coffee extracts, extracts of the plants *Garcinia cambogia* and *Hoodia gordonii*, there is insufficient clinical evidence supporting the effectiveness of such products <sup>28</sup>.

# The Complexity of Weight Loss

Weight loss is a difficult problem to characterize and address, in contrast to the popular perspective that a simple calorie deficit would result in weight loss. In truth weight loss is a multifactorial issue which involves a complex interplay between genetics, gut microbiota, hormones, and several signaling pathways.



#### Genetics



Approximately 25-70% of body weight variability could be attributed to genetics<sup>29</sup>, with recent studies using linkage analyses, single nucleotide polymorphism (SNP) analyses, candidate gene identification and genome-wide association studies showing that >600 chromosomal regions could be involved in the biological response responsible for body

weight control<sup>30</sup>. The idea of gene-nutrient interactions has given rise to the field of nutrigenomics where the relationship between genetic polymorphisms and variations in physiologic responses to identical foods in different individuals is studied. The SNP dependent variability in the endogenous responses to different food products may be due to specific gene allele-regulated mechanisms of absorption, biotransformation, metabolism and excretion of nutrients<sup>31</sup>.

#### **Gut Microbiota**

The collection of microbes that humans carry in their guts is called the gut microbiota, and is unique to everyone.

Gut bacteria harvest energy, and determine how individuals metabolize different foods<sup>32</sup>. The microbiota impacts brain, liver, muscle, large intestine, etc., and hence distinct differences between the aut microbiotas of obese and healthy individuals have been observed <sup>33</sup>. The American diet has been associated with a higher Firmicutes to Bacteroidetes ratio. A higher Firmicutes to Bacteroidetes ratio has been observed in obese



This figure, "Gut Microbiota", has been modified from "Figure 1. Gut microbiota and its influence on obesity and the metabolic syndrome.", from <u>"The role and influence of gut microbiota in pathogenesis and management of obesity and metabolic syndrome"</u> by Parekh, P. J., Arusi, E., Vinik, A. I. & Johnson, D. A., used under <u>CC BY 4.0</u>. "Gut Microbiota" is licensed under <u>CC BY 4.0</u> by KGK Science.

individuals compared to their leaner counterparts <sup>34</sup>. A recent study has classified the



Bacteroidetes to Firmicutes ratio as per BMI and reported that obese individuals have a higher proportion of Firmicutes compared to non-obese individuals in a Ukranian population<sup>35</sup>. Studies on a Japanese population reported similar ratios of higher

Firmicutes to Bacteroidetes ratio in obese versus non-obese individuals <sup>36</sup>. However, further detailed research is being carried out to ascertain the association of exact ratios of Bacteroidetes to Firmicutes with obesity, and in general, the changes in these ratios are considered an association, but are not assigned causality to obesity.

## Hormones

Hormones play an important role in the metabolic function, hunger, body fat composition, lean body mass distribution and overall well being and play a pivotal role in maintaining a healthy body weight.

Hormones that help MANAGE weight <sup>37</sup>		
Hormone	Produced by	Function
Leptin	Adipocytes	Inhibits hunger;
		decreases before eating and increases after eating
Ghrelin	Stomach	Increases appetite; increased before eating and decreased after eating
Insulin	Pancreas	Regulates how the body utilizes and stores glucose and fat
Glucagon	Pancreas	Released in response to low blood sugar levels; uses stored fat for to produce energy
Glucagon-like peptide-1 (GLP-1)	Gut	Promotes the feeling of being full
Peptide YY (PYY)	Gut	Supresses appetite after meal
Hormonal balances that LEAD to weight gain <sup>38</sup>		
Hormone	Produced by	Function
Cortisol	Adrenal Gland	Regulates energy; mobilizes energy by transporting fats from fat reserves
Thyroxine (T4)	Thyroid Gland	Help in the metabolism of energy; low levels of T4
Thyroid stimulating hormone (TSH)		stimulate the pituitary glad to produce TSH to increase T4
Estrogen	Ovarian cells	Sex hormone; when overproduced it can lead to insulin resistance and increases blood sugar

Hormonal imbalances lead to severe metabolic disruptions which may result in uncontrollable weight gain in men and women and therefore considering hormonal levels have merit in developing weight loss interventions that help shed pounds without shedding tears.

#### **Molecular Biology**

Although, significant advances in understanding the physiology of weight loss have been made, the molecular biology of weight loss is not completely determined. At the molecular

level, body weight is regulated by several complex signal transduction pathways and endocrine control systems. Leptin and insulin signaling important pathways that are two influence- glucose transport, glycogen lipogenesis, synthesis, lipolysis<sup>39,40</sup>. gluconeogenesis and The past few years have seen an increased interest among researchers in demonstrating the involvement of other signal transduction pathways, endocrine factors and gut microbiota in regulation of body weight <sup>41,42</sup>.



Given this information, attempts to

characterize the molecular biomarkers involved in weight loss have also been made. One important example of which is AMP-activated protein kinase (AMPK), which is a key molecule in the carbohydrate, lipid and protein metabolism; as well as involved in regulating transcription factors and mitochondrial biogenesis. Consequently, the effect of



change in these factors resulting from changes in metabolic status is also being evaluated simultaneously, which will further enable the use of such markers for weight loss.

The potential for detecting AMPK activity as a biomarker for weight loss may aid in understanding the regulation of this enzyme. Activation of

#### Did you know...

Humans produce two types of fat tissue:

- <u>White fat</u> is relatively inert and stores energy as triglycerides
- **Brown fat** is metabolically active and burns energy to produce heat. Brown fat is rich in mitochondria cellular powerhouses that responsible for energy expenditure. Brown fat plays a role in temperature regulation and protection against obesity<sup>44</sup>

Researchers have proposed various means of increasing the volume and activity of brown fat in the body. White fat can also be transformed to <u>"beige"</u> fat, a tissue that behaves like brown adipose tissue.

• Activation of uncoupling protein 1 (**UCP1**) triggers the production of beige fat while increasing activity of brown fat<sup>45</sup>

• Sirtuin 1 (SIRT1) and brain derived neurotrophic factor (BDNF) are endogenous browning stimulators<sup>46,47</sup>

AMPK in select target tissues has been reported to improve conditions such as obesity, type-2 diabetes and dyslipidemia <sup>43</sup>.

A healthy weight loss promotes a wide spectrum of positive health effects bevond reduction of anthropometric values- decreases in adipose tissue or increases in muscle content -changes in the status of the lipid profile, glycemic markers, endocrine factors, oxidative angiogenic factors. stress. inflammatory markers, etc. An intervention targeting weight loss will cause changes in all the abovementioned factors associated with weight loss. Hence the approach of relying primarily on anthropometric

markers (such as weight, BMI, waist circumference) as the outcomes to evaluate weight loss needs to be reconsidered.

#### **Global Index for Weight Loss in Healthy Subjects**

Most claims in weight loss are made in the structure function arena where only healthy subjects must be considered for claim substantiation. Striking differences in the outcomes and endpoints before and after interventions are observable in disease populations in pharmaceutical clinical trials. However, the same ease of measurement is not encountered in healthy populations making claims substantiation challenging. Basing the efficacy of a product on a single primary end-point may be appropriate for the pharmaceutical industry in accordance with the one-disease-one-drug model. However, applying the same principles to



Icon made by Freepik from www.flaticon.com

dietary supplements is like trying to fit a square peg in a round hole! Weight loss supplements may have multiple ingredients that elicit improvements in several related parameters in a cascading manner which cannot be captured within the single endpoint model in the traditional RCT. This leads to unfruitful trials concluding that the interventions were ineffective, while in fact, the trial design was inadequate to substantiate the claim. The use of a global index that encompasses multiple health outcomes, and reflects improvements in these outcomes beneficial to the overall health status is of value. Under a global index for weight loss, measuring multiple endpoints which are interdependent on each other is potentially more appropriate to substantiate claims. The global index captures outcomes across different organ systems, which are otherwise difficult to capture in singleton endpoint trials which simply investigate a single organ/pathway in isolation. The use and suggestions about the value of a global index to objectively evaluate an intervention is not without precedence. Global measures or different combinations of questionnaires have allowed physicians to rapidly assess patient responses to therapies <sup>48</sup>. A recent publication recommends the use of a global index for cognition that encompasses multiple endpoints <sup>49</sup>.

The following figures outlines some of the biologically and clinically relevant outcomes associated with weight loss. Understanding changes that occur in different biomarkers under these categories when a person's physiology changes from healthy to pre-disease is critical in defining the components of a global index and the time points of their measurement.

Due to the multiplicity of factors affecting weight loss, otherwise healthy individuals might not respond in identical ways to dietary interventions that target weight loss, and hence some form of personalization must be incorporated into the trials that are designed to generate a global index.

#### N-of-1 studies and the RCT

The universal application of the RCT model to the supplement industry allows for bias, confounding observations, and muddled evidence. Unlike the pharmaceutical industry which aims at disease treatment; health is the underlying principle governing the supplement industry. Generalized claims of natural health products and dietary supplements challenging are to



substantiate. Robust randomized double-blinded placebo-controlled trials (RDBPCTs)

are considered as the gold standard by regulators. However, in RDBPCTs, the average benefits of an intervention across all individuals in a group are compared with the average benefits of a placebo across all individuals in another group. In the dietary supplement industry, it is challenging to unequivocally attribute the benefits of a single intervention to the product itself.

Several N-of-1 studies on numerous participants provide information for robust inclusion criteria in the traditional RCT model, and this design has been previously suggested. This design allows for more diverse populations to be studied within the RCT model for structure function claims substantiation. Given that healthy individuals may have unique responses to identical weight loss interventions owing to their genomes, gut microbiota, hormones and other factors, the N-of-1 model allows capture of endpoints and outcomes that are relevant to the product being studied.

The N-of-1 trial designs within the RCT model will address individual centric outcomes allowing the identification of an appropriate global index to capture the true potential of the weight loss product.

## **Fines Cost More than Trials**

Although the dietary supplement industry does not have profit margins equivalent to the

pharmaceutical industry, it is important to invest in robust clinical trials for claim substantiation of dietary interventions. A \$100,000 study would provide minimum scientific evidence to support the most basic claims that could be made on the investigational product,





= \$1 million = \$500 k

while larger, study designs implementing the augmented RCT and measuring a global index may cost around \$500,000. However, investing in a clinical trial that costs approximately \$500,000 pales in comparison to the several million-dollar fines that FTC levies on companies for making sales that are not based on substantiated evidences. This investment in a robust weight loss clinical trial may be considered an insurance premium against huge fines imposed by FTC.

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