Strategic Issues

The Business of Obesity: Trends in Developing and Commercializing Therapeutics for the Worldwide Marketplace

By

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- Obesity is the most prevalent, fatal chronic disease of the twenty-first century and is increasing at rates only seen with infectious diseases. Obesity causes 300,000 premature deaths each year and accounts for $93 billion in medical expenses annually.
- The issue of obesity transcends health emerging as a global problem that will remain with us for years to come.
- The Food and Drug Administration (FDA) must balance the new status of a health crisis and "obesity as disease" with the troubled well-publicized fiascos such as Phen-fen and OTC products like ephedra.
- Despite advances in scientific understanding, diagnosis, and drug development, substantial unmet needs must be translated into opportunities.
- Sales for the two approved drugs- Meridia and Xenical- have been disappointing. Forming partnerships between innovators and big pharma offers risk sharing and will achieve greater revenue faster and

ultimately provide more value for an emerging pharma or biotech company.

- Regulating, developing, and financing drugs for the obesity market were among topics discussed at the "World Obesity Congress and Expo," a conference sponsored by Global Business Research, Ltd.& Business Access LC (Nevada City, CA). It was held July 12-13 at the Washington Hilton, Washington, DC. The article provides selected highlights.
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The anatomy of an epidemic

Obesity is a side effect of the success of genes for survival in an atmosphere of plenty. Over the last decade alone, obesity has increased 70%, occurring in all population subsets- young, old, rich, poor, black, and white. Two-thirds of all Americans are overweight or obese. And it is not just in the US. In the past 20 years, obesity has increased at alarming rates. About 900 million adults worldwide are overweight, including about 5% of the world's children.

Obesity is defined as "an abnormal increase in fat in the subcutaneous connective tissue" and quantified by Body Mass Index (BMI), calculated by weight in kilograms divided by height in meters squared. **See Table 1: Obesity and Body Mass Index.** An obese person has a BMI of 30 to 40, while those in category of 40 or above are morbidly obese. Obesity results from insufficient caloric expenditure caused by lack of movement or exercise and/or excessive caloric intake. Calorie intake rose from 1774

kilocalories per day in the two-year period of 1989 –1991 to 2002 kcal/day in 1994 to 1996. Technology has enabled food costs to decline as the costs of being inactive have also declined. One in four persons do not exercise at all.

Obesity is responsible for about 400,000 deaths per year and is related to a host of adverse health consequences:

- Type 2 diabetes (majority of cases are obesity related)
- Heart disease
- Stroke
- Hyperlipidemia
- Hypertension
- Several types of cancer
- Gallbladder disease
- Sleep apnea
- Mood disorders
- Eating disorders
- Gout
- Osteoarthritis
- Perhaps other conditions such as Alzheimers disease, back pain.

Eric Finkelstein, RTI International (Research Triangle, NC), presented the adverse financial consequences of obesity in the US. Medical costs are over $90 billion per year. About 9% of aggregate medical spending goes to treating obesity-related disease; these costs now rival those created by smoking. Each taxpayer pays about $180 per year on obesity-related medical costs for public sector health plans, which accounts for about half of obesity-attributable dollars paid by Medicare and Medicaid. Employers and

employees also subsidize the costs of obesity for those with private insurance. In addition, absenteeism due to illness rises with BMI Finkelstein has developed an "Obesity Cost Calculator" that employers can use to quantify the costs of obesity to their firm. Finkelstein sees the best argument for interventions may rest in these financial arguments relating to government and business.

Obesity is both a personal and societal issue. Thus, genetics may load the gun, but environment pulls the trigger. According to Gerard Musante, Ph.D., founder of Structure House (Durham, NC), for success interventions must be multifaceted. The interplay of advertising, parental influences, environmental influences, psychological factors, social factors, and physiological factors affect obesity. A direct link exists between urban sprawl and health: where people walk less, weigh more, and suffer from elevated blood pressure. Physical education is no longer a mainstay in schools; Illinois the only state to require daily physical fitness education. Given the current trends, only a concerted effort on many fronts will curb the obesity epidemic.

FDA Approval and Oversight Trends

Lester M. Crawford, D.V.M., Ph.D., Deputy Commissioner of FDA and chair of the FDA Obesity Working Group (OWG), reported that in March 2004 recommendations were made to the Agency to combat epidemic. They are:

- Improve food labeling
- Urge restaurants to voluntarily provide calorie and nutrition information

- Follow through with plans for the development of obesity therapeutics. According to Crawford, the report notes that ideally individuals will avoid becoming overweight or obese through diet and exercise, but it also recognizes that extremely obese individuals are likely to need medical intervention to reduce weight and mitigate other adverse health consequences.

The OWG also urged the FDA to convene an advisory committee to address challenges, as well as gaps in knowledge of existing therapies, to continue discussion with pharmaceutical and medical device sponsors about new obesity medical products, and to revise and reissue for comment the 1996 draft guidance for the Clinical Evaluation of Weight-Control Drugs.

Mark Mansour, Morgan, Lewis, & Bockius LLP explained how the 1996 draft that sets forth the Agency's recommendation for the design and conduct of Phase I through III clinical studies to demonstrate the effectiveness and safety of weight loss medications. Effective criteria include:

- A mean weight loss in the drug treated group that is 5% greater than the mean weight loss in the placebo group following one year of treatment
- The proportion of patients that lose at least 5% of their baseline weight must be greater in the drug vs. the placebo group. Under the 1996 criteria sibutramine (Meridia®) was approved in 1997 and orlistat (Xenical®) was approved in 1997. Dexfenfluramine was approved in 1996 and withdrawn in 1997 for safety reasons. In April 2004 the FDA ruled that ephedra-containing supplement may no longer be sold in the US. Reasons: The totality of the data showed little benefit from products with ephedra other than modest short-term

weight loss while raising blood pressure and otherwise stressing the circulatory system. **See Table 2: Current Approved Drugs.** In April 2004 FDA sent warning letter to 16 dietary supplement distributors making false and misleading claims over the Internet. In December 2003, the Federal Trade Commission (FTC) announced a "Red Flag" education campaign to assist media outlets in screening out false weight loss ads.

Who should pay for treatment?

According to Dwight "Pete" Fullerton, Ph.D., R.Ph., Strategic Pharmacy Innovations (Seattle, WA), FDA approval may only be the first step to broad acceptance for reimbursement. In order to maximize information, more persuasive information about drugs designed specifically for obesity is needed. FDA and some manufactures are "gun shy" from past controversies like Phen-fen. The role of obesity in costly chronic diseases is far from precise and quantifiable, and the culpability of genetics vs. behavior will further cloud the issue of who should be financially responsible. Fullerton recommended the following approaches to making a compelling case for a therapeutic:

- Build a convincing case that health outcomes will cause other medical costs to go down; just showing a link is not enough.
- Use Academy of Managed Care Pharmacy (AMCP) dossiers to help show the value of your product.
- Utilize health-outcomes modeling when long term studies have not been completed.

- Go beyond safety and efficacy and show short term cost savings, impact on emergency room visits, and need for specialists.
- Use a model that includes indirect costs such as productivity, absenteeism, workers compensation, etc.

To convince managed care of reimbursement needs, drug developers must build their cases based on economic modeling predicated on solid data, as well as aggressive patient support with disease management programs. In other words, managed care demands, "Show us the value."

Better marketing for the science-based obesity market involves putting the customer first, according to Greg Kitzmiller, Indiana University School of Business. Focusing on the customer is more than the job of the people in public relations; it is the job of everyone in a company to understand the customer. This is not just a set of buzzwords like TQM but a true cultural change. To build the customer-focused concept, management must focus on identifying and satisfying consumer needs to ensure the organization's long-term profitability objectives. The whole firm from the telephone operator to salesperson to shipping dockworker must think "customer." He emphasized that companies working in this area must understand seven common myths about obesity. **See Table 3: Common Myths About Obesity**

Obesity as Disease

Morgan Downey, J.D., Executive Director, American Obesity Association, (AOA) spoke on the future of obesity and public policy. The AOA mission is to have obesity, the most prevalent, fatal chronic disease of the twenty-first century, recognized and regarded as a major disease

epidemic in the United States and abroad. The association advocates research, health insurance reimbursement, prevention programs, education, consumer protection, and an end to discrimination.

Downey emphasized the present Washington public health paradigm is that obesity is a behavior and that diet and exercise will solve all problems. However, the new paradigm that obesity is a disease is confirmed by the definition of obesity and the definition of disease. A disease is defined as "an interruption, cessation or disorder of bodily functions, systems, or organs." Likewise like a disease, obesity has identifiable signs and symptoms: excess accumulation of adipose tissue, endocrine organ effects, increased glucose, elevated cholesterol and triglycerides, decreased HDL, pain, breathlessness, and effect on fertility.

Obesity is recognized as a disease by the National Academy of Sciences, World Health Organization, National Institutes of Health, International Classification of Diseases #278, Food and Drug Administration, Federal Trade Commission, Social Security Administration, and several associations and textbooks. It is not recognized as a disease by the public, Medicare*, Medicaid, and private insurance. Those who argue that obesity is not a disease contend that the condition is a personal choice. Therefore, they reason that because obesity is self-inflicted, it is not a disease and deserves no sympathy. But Downey countered with the question of personal responsibility compared to what? Many other conditions, such as sexually transmitted diseases, lung cancer, or sports injuries, are the result of personal choices. He rebuts that the claims are not justified and asks just how effective must a treatment be for consideration. This attitude holds obesity to a miracle cure standard where with other chronic diseases, such as

Alzheimers and Parkinsons disease, drugs do not cure but may make the patient better for a short period of time.

According to Jeremy Nobel, MD, MPH, Harvard School of Public Health, obesity should no longer be viewed as a lack of will power but as a chronic disease model, where the patient and practitioner must understand that it requires a lifelong effort. The focus needs to be on making the patient healthier not merely leaner. Supporting data show that as little as a 10% makes a difference in health symptoms. Lessons learned from other chronic disease management initiatives need to be applied to obesity management, according to Nobel.

A Market of Unmet Needs

Obesity is garnering much attention in the press and other areas because it is a major risk factor for serious medical conditions. For example, over 55 percent of those with hypertension are obese. Carole Gleeson, Decision Resources, Inc., showed startling epidemiology figures. The total prevalence of obesity in the three major regions- Japan, Europe, and the United States- will continue to grow 2 % over the next ten years. In the US alone the number will expand from 68 million people to 88 million in 2013.

Today, few pharmacological options are available to patients if diet and exercise fail. While many physicians favor drug treatment of obesity, some are hesitant because of the insufficient efficacy of currently marketed drugs. To address unmet needs, Gleeson listed the following essentials:

- Safe and effective drug therapies that would result in a 10 percent weight loss; however, patients want and expect 20 %.
- Reimbursement for antiobesity therapies.
- Wider array of drug options

- Physician education and skill building
- Patient awareness/motivation

Certain drivers and constraints will shape the future of the obesity market. The leading driver is that the prevalence of obesity will continue at a steady pace, especially as the medical community recognizes obesity as a disease. There will be a continued demand for new agents that offer long-term maintenance of weight loss. The down side of the picture is led by the lack of reimbursement of third-party payors. Doctors, likewise, will be reticent to treat obesity with a drug until clinically long-term effective drugs enter the market. A final constraint is that research has only begun to unravel the etiology and pathophysiology of obesity.

Gleeson emphasizes the high unmet need and increasing prevalence of obesity point to both challenges and the following opportunities in this market:

- The newest drugs- sibutramine and orlistat- are far from optimal; great commercial opportunity exists for a drug that improves on current therapies in efficacy, safety, and cost.
- Physicians assail the cost of therapy as a major reason for noncompliance and stopping treatment; a low-cost alternative would be a blockbuster.
- While acceptance of obesity as a medical condition is increasing, the behavioral support system of dieticians, behavior therapists, and exercise physiologists are currently lacking in most facilities. Establishing comprehensive services and full funding for them will be a major hurdle.

- Because of the complex nature of obesity, research challenges abound. Scientists have identified potential useful targets for treating obesity but identifying the subpopulations that can benefit from these therapies is a major scientific challenge.

Despite the high prevalent population of obese people in the seven major markets, the total market for antiobesity agents only reached $520 million in 2002. Gleeson foresees that in 2012, the market will grow 18 % annually to $1.7 billion, driven by the increase in the obesity population and the availability of new agents as follows: orlistat, 5%; ATL-962, 15%; other peripheral acting agents, 3%; sibutramine, 7%; CNTF, 10%; rimonabant, 40%; other centrally-acting agents, 20%.

According to Alexander Young, Ph.D., president of Mirabila (San Diego, CA), a company that contracts business development for venture capital firms, investment banks, biotechnology companies and pharmaceutical companies, the huge obesity market is out there as predicted by the success of current and past weight-loss businesses such as herbiceuticals, OTC medications, bariatric surgery, liposuction, Phen/fen clinics, and fitness and weight loss centers. He also emphasized how poorly understood and complicated mechanisms can lead to unanticipated side effects. For example, Fenfluramine/Phentermine was launched in 1995 for an off-label combination therapy and withdrawn in a flurry of doubt in 1997. Dexfenfluramine was approved in 1996 and withdrawn in 1997.Topamax was approved in 1997 for epilepsy and had a Phase III trial for obesity pulled in 2002. Meridia was launched in 1998 and withdrawn by the Italian government in 2002.

Therapeutic Development for Obesity

According to Jose Caro, MD, Lilly Research Laboratories, (Indianapolis, IN), the FDA's fast-track drug approval mechanism is being expanded to obesity and diabetes drugs. Under fast-track, drug makers can hold meetings with FDA staff to get feedback on their development plans, submit their new drug applications in sections rather than all at once, and request their study be judged using surrogate rather than primary endpoints under an accelerated approval process.

Today only about 4% of obese people (US) are getting prescription medicine to treat their condition. If obesity were treated as often as hypertension, 66% of obese people would receive prescription medication. Obesity is just as bad as hypertension in causing co-morbidities and social economic burdens. Lilly Internal Market Research (2003) revealed that 28% of obese patients are using non-traditional means, such as other prescriptions, over-the-counter products, surgeries, extreme diet/exercise to treat their obesity. Fen-Phen peak sales was $650MM worldwide in 1996-1997 before withdrawal.

Caro said that a multi-platforms approach must be take to the treatment of obesity. Effective treatment may need to modify more than one of the following systems:

- Brain and the translation system- what kind of food and is it the right amount?
- Effector system or energy balance; how can the body make the correction?
- Messenger system in the peripheral tissues.

The industry obesity pipeline shows several compounds in development**.** **See Table 4: Selected Compounds in Development.** Two products are near

approval and may be on the market soon. Carole Gleeson sees rimonabant (Acomplia® Sanofi-Aventis) as the most promising agent emerging from the obesity pipeline in 2006. In a double-blind, placebo-controlled study, 1036 obese patients, who also had dyslipidemia were randomized to receive daily treatments of 5 mg or 20 mg rimonabant or placebo. Patients were also placed on a reduced calorie diet for a period of one year. After one year, patients treated with the highest dose of rimonabant lost an average of 8.6 kg body weight whereas those receiving placebo only lost 2.3 kg. Nearly 75 % of those receiving the higher dose lost at least 5% of their body weight compared to 42% of patients on the lower dose and 28% of those receiving placebo. The most common side effects were nausea and dizziness, which occurred more often in patients receiving the highest dose. Participants did not exhibit increased blood pressure or heart rate when compared to those on placebo. The weight loss in preliminary trials was similar to that of orlistat and sibutramine. The drug acts on multiple pathways within the CNS. Its less expensive oral formulation makes dosing easier and will make it a strong competitor. Sanofi-Synthelabo (New York, NY) plans to market the drug as a preventive medication for cardiovascular health.

A second product is Regeneron's (Tarrytown,NY) Axokine®, a modified form of a naturally-occurring protein called Ciliary Neurotrophic Factor (CNTF). In preclinical models of obesity, Axokine signals the satiety center of the brain to decrease food intake. In a Phase II trial, obese people lost weight during a twelve-week period. A Phase III pivotal trial began in 2001 with about 2000 patients enrolled. In March 2003 results of the double-blind, placebo- controlled showed many individuals lost weight, but the average weight loss was limited by the development of antibodies. Additional studies were initiated as part as part of the Phase III program

designed to assess the function after short-term dosing periods and to measure weight change after cessation of short-term treatment. To date, Axokine has demonstrated a favorable safety and tolerability profile in clinical trials.

Obesity Treatment Methods

Weight is a part of a cycle of nutrients that are taken into the body with interactions from the nervous system, endocrine system, and energy storage system and metabolism involving adipocytes, liver, and muscle. Co-morbidities result from the breakdown of homeostasis of multiple complicated systems. Three target areas include drugs that affect the central nervous system (CNS), metabolic modifiers, and those that are thermogenic.

CNS methods include neurotransmitter targets, serotonic reuptake inhibitors, cholinergic reuptake inhibitors, hypothalamus targets, anti-depressants, and anti-epileptics. The neurotransmitters serotonin and norepinephrine are released when the axon terminal on a presynaptic neuron is excited. The substances travel across the synapse to act of the target cell to either inhibit or excite it. For instance, the approved drug sibutramine works to inhibit the reuptake of these chemicals by neurons serotonergic and adrenergic receptors.

Metabolic modifiers include lipase inhibitors, fatty acid targets, cortisol-insulin modulation, angiogenesis inhibitors, leptin, and ghrelin. In the bloodstream cholesterol and fat-soluble vitamins are present. Triglycerides are converted by gastrointestinal lipase into monoacylglycerol and fatty acids. The formation of micelle in the intestinal lumen allows 90% of dietary triglyceride to be absorbed as monoglyacylglycerol and fatty acids. Cholesterol and fat-soluble vitamins are absorbed with lipids. With

orlistat, approximately 1/3 of dietary triglyceride is excreted unchanged in stool. Absorption of cholesterol and fat-soluble vitamins is also decreased. Although the drug did have long-term desired effects of weight loss when compared to placebo, certain undesirable gastrointestinal side effects, such as fatty, oily stools, fecal incontinence, and fecal urgency were noted. These side effects are probably the reason it is not a $3 billion drug.

Following the Money: Wall Street and Venture Capital

Albert L. Rauch, Ph.D., CFA, Vice President, AG Edwards & Sons, Inc., spoke of "big pharma" strategies for developing obesity therapeutics that consider revenue projections and risk. Roche Pharmaceuticals sales of Xenical in 2003 were $108 million in US revenue in 2003; Abbott's sales of Meridia were $68 million. Generic phentermine generated $86 million in 2003. Short-term outlook also includes off label us products such as Welbutrin (Glaxo), an anti-depressant that decreases hunger and various levothyroxines that increase metabolism.

Rauch presented the following strategic approach:

- Establish a "beachhead." The best immediate possibility is developing a product focused on treating Type II diabetes via weight reduction. This product would be used off label. This sub-set of the obesity population would lead to faster penetration of a smaller market and expand into a larger obesity overweight market. At present there are 11 Phase II products, 5 Phase II, and 3 in Phase III in development for diabetes with potential in obesity. **See Table 5: Leading Developers of Drugs for Obesity/diabetes.**

- Command a frontal assault. Develop products focused solely on weight loss. This approach involves establishing medical benefit to gain regulatory approval. The efficacy hurdle may be difficult to obtain. Likewise, it may be difficult to establish economic benefit. The legacy of phen-fen, the diet drug that was pulled from the market because of harmful side effects, may be difficult to overcome. The large problem of reimbursement looms and may be difficult to obtain.

T. Scott Johnson, M.D., founding partner of JSB Partners, L.P., an investment bank specializing in mergers and acquisitions, private financings, and corporate alliances, focused on how partnering offers advantages for emerging companies. Partnering can offer advantages both to small companies and large pharma. Small companies can push to Phase II then usually find the expenses and risk beyond their reach. For example, in the development of the product Xenical, Phase III trials involved 4800 patients followed for two years. Launch and marketing will require a combination of extensive detailing to primary care physicians, endocrinologists, OB-Gyn, and DTC advertising, demanding a costly sales force. The risk is staggering; many products have failed to achieve positive results even in late stages of clinical trials. Major players are more capable of rapid launch and greater ultimate revenue. Large pharma also benefits from partnerships. They may access innovation in a market, made complex due to many targets and pathways. Partnership with a small company give the advantages of risk sharing, efficient cost expenditure, and specialists who have worked in the discovery phase of the complex issues.

The potential for this market is huge. However, sales of the two drugs approved for the treatment of obesity have been disappointing. This makes

the tendency to make deals reflect this current reality rather than the enormous potential market. Thus, the onus of risk is usually placed on the innovator. In this spirit, a strong big pharma partner offers risk sharing and will achieve greater revenue faster and ultimately provide more value for an emerging pharma or biotech company with an innovative obesity product. It is worthwhile for a small company to look to big pharma, according to Johnson.

Bernice Welles, M.D., Venture Partner, MPM Capital, presented promising emerging technologies and companies and showed how US IPO markets are at historic lows. Most of those with venture capital are looking for later state products, with the ideal being phase IIB. Although she believes obesity represents an opportunity to make profitable investments, less than 7% of venture capital investment made in 1999-2003 was focused in the area of metabolic disease. However, the positive side is a recent upswing in original papers published, drugs in development, and patents.

Obesity-related partnerships do represent attractive opportunities, according to Welles. In 1996, Amgen paid Rockefeller University $20MM to acquire the rights to develop and market leptin-based products. Other recent alliances include:

- Zymogenetics and Amgen (preclinical)
- Solvay and BMY for a cannabinoid type I receptor agonist, phase I
- Peptimmune and Genzyme for a pancreatic lipase inhibitor/fat binder
- Esperion acquired by Pfizer, Inc. for $1.3 billion for a CETP inhibitor now in Phase II

Such early stage alliances must weigh value creation versus value loss. Welles presented three investment examples made by MPM:

- Enteromedics (St. Paul, MN). The company originated as a device incubator for a reversible vagus nerve modulator that shrinks the stomach, impairs fat absorption, and increased the sensation of satiety. A current prototype is underdevelopment for obesity with the intent to displace bariatric surgery. (first funded 2002)
- Biovitrium AB (Stockholm, Sweden). Founded in 2001 as a spin-off of Pharmacia to focus on drugs to treat metabolic diseases, the company announced in 2002 an agreement with GSK to develop and commercialize 5-HT_{2C} receptor agonists for obesity and other medical disorders. In 2003 Biovitrium AB announced an agreement with Amgen to give exclusive rights to develop and commercialize their 11BHSD1 enzyme inhibitors for treatment of metabolic diseases and other medical disorders.
- Peptimmune (Cambridge, MA). This company has developed programs in autoimmune disorders and is broadening the focus to relate this research to obesity.

A showcase of future strategies for the treatment of obesity

Development of islet and gut peptide hormones

Christian Weyer, M.D., Director of Clinical Research, Amylin Pharmaceuticals (San Diego,CA), presented the development of islet and gut peptide hormones as anti-obesity targets. To date most efforts have focused on small molecules directed toward CNS targets involved in food intake and food regulation. However, islet and gut peptide hormones are normally

released in response to meals and are thought to play an important physiological role in the regulation of food intake and postprandial metabolism following the meal. Food intake is a complex behavior involving sensory, cognitive, post-ingestive, and post-absorptive mechanisms.

Building on their experience in the diabetes field, Amylin is with the metabolic properties common to all three conditions. The hormones include:

- PYY3-36 (AC162352 Obesity program). Peptide YY(PYY) is a naturally occurring 36 amino acid gastrointestinal peptide hormone expressed/produced in the entero-endocrine cells in the small and large intestine and secreted in response to meals. It is cleaved in vivo by the DPP-IV enzyme to PYY[3-36]. In two clinical studies the drug reduced hunger and food intake in both lean and obese subjects. The IND for AC162352 (synthetic PYY3-36) was submitted in December 2003 and is currently in Phase I.
- Amylin/Pramlintide (AC137 Obesity Program). This program uses existing clinical experience with pramlintide, a synthetic analog of the beta-cell hormone amylin. Amylin, a 37-amino acid peptide, co-related and co-secreted with insulin from pancreatic β-cells is deficient in diabetes. The synthetic analog is specifically engineered to overcome the tendency of human amylin to aggregate and adhere to surfaces and to form insoluble particles. The potency is equal or greater than human amylin. Clinical trials have shown a reduction in ad-libitum food intake observed in insulin-treating subjects with type 2 diabetes and in obese, non-diabetic subjects, as well as

significant reduction in body weight. Phase II studies are currently ongoing in obese subjects.

Gene expression targets

The genetic relationship to obesity is the target of investigation. **See Table 6: Selected Genes and Their Effects.**

According to Wei-Wei Zhang, M.D., Ph.D., President and CEO, GenWay Biotech, Inc., (San Diego, CA) growing evidence indicates that abnormality of the adiponectin gene and decreased production of adiponectin that is expressed in adipose tissue might be link obesity with metabolic and other obesity disorders. Recent pharmacological studies indicate that fat tissue itself plays a key role as an endocrine organ and produces various kinds of adipokines with adiponectin as one of them. Adiponectin has multiple potential therapeutic potentials, as well as a novel diagnostic marker. GenWay has developed recombinant functional adiponectin and its monoclonal antibodies.

HMGene is a company that directly targeting adipose tissue. The discovery strategy identifies genes central to adipocyte physiology using HMGene's AdiposenseTM platform. This platform has identified and prioritized 139 putative obesity genes. After validating selected targets, the company generates therapeutics for human obesity. HM-21, an endogenous secreted protein, is a key protein that signals a known adipogenic pathway and is highly expressed in fat tissues. HMGene believes that HM-21 shows preclinical therapeutic potential and hopes to accomplish IND filing within two years. HM-12 is also a validated target illustrated by knockout mice that have a profound reduction in fat. This drug is a target for small-molecule therapy and NCE generation is currently in progress.

According to Mark Tepper, Ph.D., President & Founder Araios-CyTRX,(Worchester, MA), RNAi based molecular medicines will treat obesity and Type II diabetes. The company is developing powerful new RNAi gene silencing technology to drive the discovery and development of both traditional small molecules and new RNAi-based therapies. Araios plans to develop lead candidates through early proof of concept to the clinic.

According to Jeff Leighton, Ph.D., Founder and Director of Drug Discovery, Adipogenix, (Boston, MA), obesity can be effectively treated effectively at the fat cell level rather than indirectly by modulating the CNS mechanisms. Leighton discussed the use of functional human cell-based assays to screen for small molecules that modulate fat uptake, storage, breakdown, and burning. AdipoGenix is a biopharmaceutical company founded by members of the Obesity Research Center at the Boston University School of Medicine.

Sensory blockade

Chris Adams, CEO, Compellis Pharmaceuticals, (Boston, MA), presented a unique therapeutic approach using olfactory perception. Nasal administration of the calcium channel blocker diltiazem, now marketed for hypertension, has been shown to decrease food intake and weight gain in rats. The intranasal route tested against intraperitoneal and oral delivery showed a significant reduction in weight gain in a dose-dependent manner. Diltiazem is a proven drug with known toxicity and tolerable side effects. The drug is now in Phase I study with 50 clinical trial subjects in 8 groups.

* On July 23, after this conference, Medicare deleted the edict that obesity is not a disease; officials said they would consider paying for treatment but only if that treatment can be shown to work.

Table 1: Obesity and Body Mass Index

BMI=weight (kg)/height(m^2)

Normal BMI	18.5 – 25
Overweight	25-30
Obese	30-40
Morbidly obese	40+

Source: D&MD

Table 2: Current Approved Drugs

Name	Brand/company	Mode of operation	Price per day	Advanta
Orlistat	Xenical® /Roche (Nutley, NJ)	Lipase inhibitor	$3.50	5-10% of b weight is over 6 mo to 1 year; u 30% of pat maintai weight los to 2 years therapy
Sibutramine	Meridia®/Abbott (Abbott Part, IL)	Norepinephrine/serotonin/dopamine reuptake inhibitors	$3.60	5-10% of b weight is over 6 mo to 1 year; u 30% of pat maintai weight los two 2 year therapy
Phenteramine	Adipex/ TEVA (North Wales, PA)	Norandrenergic	$1.60	0.5kg/we weight lo over a fe weeks c therapy
Phentermine-R	Ionamine/CellTech (London, UK)	Norandrenergic	$2.00	Annual sa 2002 $7 M
Diethylpropion	Tenuate/Aventis	Noradreneric	$1.50	
Benzphetamine	Didrex/Pharmacia/Upjohn	Noradrenergic	$2.50	
Phendimetrazine	Bontril/Mallinckrodt	Noradrenergic	$5.25	

Source: D&MD

Table 3: **Common Myths About Obesity: Based on interviews of 5000 consumers by the Hartman Group, Belleview, WA**

Myth	Reality
People are concerned about obesity in their daily lives	Most think their own weight is average and are ambivalent about managing their weight
People look to media images to set the standards for weight	People look at their friends and social networks as the cues to decide to lose weight; they keep an eye on their friends; they do not look to their physician for advice
People blame manufacturers or food retailers for the obesity problem	Most see obesity as a very personal issue with personal responsibility
People link obesity with potential health issues	Most do not perceive themselves at risk for health problems despite their weight status
People use objective measures like BMI or body fat to determine their weight	Most use events, like looking in the mirror or at an old photograph to assess weight
People try to lose weight by changing eating habits	Most cite increased physical activity as the preferred way to lose weight rather than changing eating habits
Most dieters follow short tem diets that allow them to lose weight quickly	Most are using the moderation principle as a guide for dieting: small changes over the long term

Source: Adapted by D&MD

Table 4: Selected Compounds in Development

Drug name/generic name	Company	Phase	Mechanism	Comments
LY 488756	Eli Lilly (Indianpolis, IN)	I	B-3 agonist	
SR14778	Sanofi (New York,NY)	I	CNTF inhibitors	
SLV319	Solvay	I	CNTF inhibitors	
MLN-4760	Abbott/Millenium (Abbott Park, IL)	I	Carboxypeptidase inhibitor	
SB418790	GSK (Research Triangle, NC)	I	B-3 agonist	
AC162352	Amylin Pharmaceuticals (San Diego,CA)	I	PYY3-36	A gut hormone in the news as the "eat less hormone"
ATL962/AZM-119	Alizyme (Cambridge, UK)	II	Lipase inhibitor	
NO1886	Otsuka Pharmaceuticals (Japan)	II	Lipoprotein lipase stimulant	
181171	GSK (London,UK)	II	Cholecystokinin CCK/agonist	
AD9677	Dainippon (Japan)	II	B-3agonist	
C27235	Merck (Whitehouse, NJ)	II	Unknown mechanism	
HMR-1426	Aventis (Strausbourg, France)	II	undefined	
AC137 obesity program Pramlitide	Amylin Pharmaceuticals (San Diego, CA)	II	Synthetic amylin analog of β-cell hormone amylin	Scientifically engineered to overcome problems of human amylin
Axokine®	Regeneron (Tarrytown, NY)	III	CNTF inhibitor	Results of first portion study released in March 2003; some concern about the build-

				up of antibodies
Rimonabant	Sanofi (New York)	III	CNTF inhibitor/ cannabinoid	
Topiramate	J&J Johnson	III/IV	Unidentified	

Source: D&MD

Table 5: Leading Drugs in development for Obesity/Diabetes

Compound	Company	Development phase	Mode of operation	Comments
181771	Glaxo (Research Triangle, NC)	Starting III	Glucagon-like peptide (GLP-1)	
815541	Glaxo	I	GLP-1	Top target in development- in licensed
823093	Glaxo	I	GLP-1	Top target in development
825964	Glaxo	I	GLP-1	Top target in development
427353	Glaxo	I	Beta-3 activator	
MK-041	Merck (Kenilworth, NJ)	II	GLP-1	
C-2735	Merck	I	Unknown	
C-5069	Merck		Unknown	
Muraglitzar	BMS/Merck	III	Dual/pan PPAR inhibitor	
Galida	AstraZeneca (London, UK)	III	Dual/pan PPAR inhibitor	
677954	Glaxo	II	Dual/pan PPAR inhibitor	
LY818	Lilly/Ligand	II	Dual/pan PPAR inhibitor	

AVE- 8134	Aventis	I/II	Dual/pan PPAR inhibitor	
AVE-0847	Aventis	I/Ia	Dual/pan PPAR inhibitor	
LY-929	Lilly/Ligand	I	Dual/pan PPAR inhibitor	
Exenatide	Lilly	Filing NDA 3Q04	GLP-1	Top target in development
LAF-237	Novartis (Basel, Switzerland)	III	GLP-1	Top target in development
AVE-0010	Aventis/New Zealand	PhaseI/Ia	GLP-1	Top target in development
DPP4-inhibitors	BMS	Clinical trials	GLP-1	

Source: D&MD

Table 6: Selected Genes and Their Effects

Gene	Presumed mechanism
Leptin (ob or Lep)	Appetite and energy expenditure
Leptin receptor (Ob-R or Lep-R)	Appetite and energy expenditure
B-2 andrenergic receptor	Energy expenditure
B-3 andrenergic receptor	Energy expenditure
Uncoupling protein-1 (UCP-1)	Energy expenditure
Pro-opiomelanocortin (POMC)	Appetite
Melanocortin-4 receptor (MC4R)	Appetite
PPAR-G (g1 and g2)	Adipocyte differentiation; insulin sensitivity
Low-density lipoprotein receptor (LDL-R)	Lipid traffic/metabolism

Source: D&MD