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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No: 2003N-0338
Food and Drug Administration Obesity Working Group; Public Meeting

Hoffmann-La Roche Inc. (hereinafter "Roche"), based in Nutley, New Jersey, is a prescription pharmaceutical company that is part of the Roche Group, a research-based health care company that ranks among the world's leading manufacturers of pharmaceuticals and diagnostic products. In recent years, Roche has focused its pharmaceutical research and development in a number of therapeutic areas, including HIV/AIDS, Hepatitis C, cancer and obesity. We are pleased to have this opportunity to provide comments to the FDA Obesity Working Group.

In 1999, after more than 2 decades of research, Roche received FDA approval for Xenical (orlistat), an important therapeutic advance in the treatment of obesity. Non-systemically acting Xenical is a gastrointestinal (GI) lipase inhibitor that is indicated for obesity management, including weight loss and weight maintenance, when used in conjunction with a reduced-calorie diet in individuals with body mass index (BMI) of ≥30 kg/m2 and BMI ≥27kg/m2 with risk factors (e.g. hypertension, diabetes, dyslipidemia etc.). Notably, Xenical is also indicated for reducing the risk of weight regain after prior weight loss.

As the first FDA-approved prescription treatment for obesity that does not act as an appetite suppressant, but rather by interfering with the action of gastrointestinal lipase in the GI tract, Xenical gave medical professionals a new tool in the battle against obesity. Orlistat, unlike any other drug on the market, exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit has a positive effect on weight control. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%. Orlistat therefore reduces total energy intake to produce a significant weight loss.

Orlistat's unique molecular structure allows it to bind to the active site of GI lipase and block that enzyme's activity. The enzyme is thus unable to break triglycerides down into their component parts. A significant proportion of dietary fat therefore remains undigested and unabsorbed, passing through the GI tract unchanged. However, 70% of ingested fat is digested in the normal fashion, ensuring sufficient absorption of essential free fatty acids. This is because on average, dietary fat accounts for 34% of daily energy intake, although healthy eating guidelines recommend that it should make up no more than 30% of calorie intake. When taking Xenical, patients are advised to take a multivitamin supplement containing fat-soluble vitamins to ensure adequate nutrition.

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Given our commitment to the area of obesity treatment, we applaud FDA's Obesity Working Group for its efforts, and in particular for its decision to include pharmacological approaches in its agenda. The potential utility of pharmaceuticals in addressing the obesity crisis in this country has been neglected, and we urge the agency to make therapeutic approaches to obesity a major emphasis of its recommendations, strategic plans, and outreach to other governmental bodies addressing obesity. To that end, in the interest of providing further perspective on the issue, our comments will address the agency's specific questions relating to medical interventions for obesity.

Medical interventions, including drug therapies, are critically important in addressing the obesity crisis.[1] To combat the growing obesity epidemic, FDA and various other agencies under the auspices of the U.S. Department of Health and Human Services (HHS) must make every effort to promote and foster drug therapies for obesity.[2] The following comments outline: (a) the problem of obesity and its co-morbidities; (b) the complementary nature of pharmacological and diet/exercise interventions; (c) the important role of therapeutics in addressing obesity and co-morbidities; (d) current evidence to support the safety and efficacy of pharmacological approaches to obesity and co-morbidities; and (e) the potential posed by further obesity drug research.

I. What is the available evidence that FDA can look to in order to guide rational, effective public efforts to prevent and treat obesity by behavioral or medical interventions, or combinations of both?

Recently, HHS Secretary Tommy Thompson said "in America, approximately two-thirds of adults are either overweight or obese. The nation's children and adolescents are heavier than they have ever been. People who are overweight or obese have a greater chance of developing high blood pressure, high blood cholesterol or other lipid disorders, type 2 diabetes, heart disease, stroke and certain cancers. Overweight and obesity may soon cause as much preventable disease and death as cigarette smoking."[3] According to Dr. Julie Gerberding, Director, Centers for Disease Control and Prevention, Obesity is the "No. 1 health threat" in America today.[4] Dr. Gerberding said that 65 percent of U.S. adults are either overweight or obese.[5] She noted that in 2000, 38.8 million adults were classified as obese in America and in Louisiana, Mississippi, and West Virginia, 25 percent of adults are obese-not merely overweight.[6] Gerberding termed such rates of obesity "a catastrophe for our country."[7] Despite the availability of treatment options, the proper utilization of these options continues to elude health professionals. As a result, obesity continues to grow as one of the major healthcare problems of the 21st century.

A variety of effective options exist for the management of overweight and obese patients, including dietary therapy approaches such as low-calorie diets and lower-fat diets; altering physical activity patterns; behavior therapy techniques; and pharmacotherapy. Recently, a National Heart Lung and Blood Institute (NHLBI) panel reviewed weight loss strategies that could also be used to foster

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[1] National Heart Lung and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (NIH Pub. No. 98-4083).

[2] Id.

[3] Message from Tommy Thompson, Secretary of Health and Human Services, *available at* www.phila.gov/fitandfun/Message_from_Tommy_Thompson.html (last visited Nov. 20, 2003).

[4] Julie L. Gerberding, Testimony at Meeting of the National Health Council (Oct. 28, 2003).

[5] Id.

[6] Id.

[7] Id.

long-term weight control and prevention of weight gain. The panel's recommendations emphasize the potential effectiveness of weight control using multiple interventions and strategies, including: dietary therapy, physical activity and pharmacotherapy.[8] Specifically, the NHLBI panel reviewed 86 articles to determine how effective dieting was for obese individuals. The articles indicate strong and consistent evidence that an average weight loss of 8 percent of initial body weight can be obtained by dieting. Additionally, twenty-three articles were reviewed by the NHLB panel to determine the effect of physical activity on weight loss. The articles revealed strong evidence that physical activity alone resulted in modest weight loss for obese adults.

An NHLBI review of 44 pharmacotherapy articles provided strong evidence that pharmacological therapy (which has generally been studied along with lifestyle modification, including diet and physical activity) using dexfenfluramine, sibutramine, orlistat, or phentermine/fenfluramine results in clinically significant weight loss in obese adults when used for 6 months to 1 year. Strong evidence also indicated that appropriate weight loss drugs can augment diet, physical activity, and behavior therapy in weight loss. Specifically, the articles and the NHLBI panel concluded that weight loss drugs approved by the FDA for long-term use may be useful as an adjunct to diet and physical activity for patients with a BMI of >= 30 with or without concomitant obesity-related risk factors or diseases, as well as for patients with a BMI of >= 27 with concomitant risk factors or diseases

A. Overview of Obesity and Co-morbidities as a Medical problem; the Range of Available Medical Interventions.

Obesity is linked to numerous medical problems including cardiovascular disease, Type 2 diabetes, certain types of cancer, arthritis, respiratory, and sleep problems.[9] Annual medical costs for an obese person are 37.7% higher (approximately $732 higher) than those of normal weight persons.[10] Nationwide, the cost of diseases associated with obesity has been estimated to be $117 billion per year for direct and indirect costs.[11] Additionally, obesity related problems result in a decreased life expectancy of seven years.[12] A greater decrease in life expectancy is seen in obese smokers. The average decreased life expectancy for obese smokers is 13 to 14 years.[13] Additional studies have demonstrated: (1) Obesity has roughly the same association with chronic health conditions as does twenty years' aging; this greatly exceeds the associations of smoking or problem drinking; and (2) a 36% increase in inpatient and outpatient spending associated with obesity versus 21% for current smokers.[14]

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[8] National Heart Lung and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (NIH Pub. No. 98-4083).

[9] Expert Panel on the Identification and Treatment of Overweight Adults. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Arch Intern Med 1998; 158: 1855-67.

[10] Finkelstein et al., 2003. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults.

[11] Julie L. Gerberding, M.D., M.P.H., Director, Centers for Disease Control and Prevention. Testimony before the Committee on Appropriations, Subcommittee on Labor, HHS, Education and Related Agencies of the United States Senate. CDC's Role in Promoting Healthy Lifestyles (Feb. 17, 2003). Over the past 20 years, the occurrence of obesity has doubled in adults and children, with current rates of 60% of adults and 15% of children as overweight or obese.

[12] Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L. *Obesity in adulthood and its consequences for life expectancy: a life-table analysis.* Ann Intern Med 2003; 138:24-32.

[13] Fountaine KR, Redden DT, Wang C, Westfall AO, Allison DB. *Years of life lost due to obesity.* Jama. 2003;289:187-93.

[14] Strum *Health Affairs* 2002; 21:245-253.

i. Type 2 Diabetes and Endocrine System Complications

An increased risk of Type 2 diabetes is strongly associated with obesity. Type 2 diabetes, itself among the fastest growing diseases in America today, can lead to serious, life-threatening complications such as blindness, kidney disease, nerve damage, and heart disease.[15] According to Dr. Reza Yavari, an endocrinologist at Yale University School of Medicine, abdominal fat is particularly dangerous "because it secretes hormones and other factors that counter the action of insulin."[16] In addition to type 2 diabetes, other complications with the endocrine and metabolic system associated with obesity include metabolic syndrome, insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, and polycystic ovary syndrome.[17]

ii. Cancer

According to a *New England Journal of Medicine* report, obese individuals are more likely to die from cancer than the average American.[18] Specifically, the study, which tracked over 800,000 people during a 16-year period, found that in the United States, obesity contributes to 14% of all cancer deaths in men and 20% of all cancer deaths in women.[19] Further, the study concluded that 90,000 cancer-related deaths could be prevented yearly if Americans maintained a healthy weight.[20] According to the study, esophagus, colon, gallbladder, prostate, breast, uterus, cervix, and kidney cancer are all associated with obesity.[21]

iii. Other Medical Complications Associated With Obesity

It is generally agreed that a wide range of additional medical complications arise in obese people.[22] Moreover, it is clear that certain diseases are directly related to an individual's BMI.[23] For example, studies have shown that individuals with higher BMI have a greater likelihood of being afflicted with:

- Gastrointestinal complications such as gallstones, pancreatitis, abdominal hernia, NAFLD (steatosis, steatohepatitis, and cirrhosis), and possibly GERD;[24]
- Cardiovascular complications such as hypertension, coronary heart disease, congestive heart failure, dysrhythmias, pulmonary hypertension, ischemic stroke, venous stasis, deep vein thrombosis, and pulmonary emolus.[25]
- Respiratory complications such as abnormal pulmonary function, obstructive sleep apnea, and obesity hypoventilation syndrome.[26]

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[15] Mokad A, Bowman B, Ford E, et al. *Prevalence of obesity, diabetes, and obesity related health risk factors.* 2001. JAMA 2003;289:76-79.
[16] Brody, Jane. *Personal Health: Diabetes Candidates Can Reduce the Risk*, N. Y. Times, Jan. 15, 2002.
[17] American Gastroenterological Society, AGA Technical Review on Obesity. Gastroenterology 2002; 12:882-932.
[18] Calle E, Rodriguez C, Walker-Thurmond K, Thun, M. *Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults.* New Eng. J. Med., April 24, 2003.
[19] Id.
[20] Wang, L. *Excess Body Weight Associated With Higher Risk of Cancer Mortality.* U.S. Department of Health and Human Services, J. of the Nat'l Cancer Inst., 95:707. May 21, 2003.
[21] American Gastroenterological Society, *AGA Technical Review on Obesity.* Gastroenterology 2002; 12:882-932.
[22] National Heart Lung and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (NIH Pub. No. 98-4083).
[23] Id.
[24] American Gastroenterological Society, *AGA Technical Review on Obesity.* Gastroenterology 2002; 12:882-932.
[25] Hubert HB, Feinleib M, McNamara PM, Castelli WP. *Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study.* Circulation 1983; 67:968-77.

- Musculoskeletal complications such as osteoarthritis, gout, and low pain back. Gynecologic complications include abnormal menses and infertility.[27]
- Genitourinary complications such as urinary stress incontinence. Ophthalmologic complications include cataracts.[28]
- Neurological complications such as idiopathic intracranial hypertension and Alzheimer's disease.[29]
- Postoperative complications such as atelectasis, pneumonia, deep vein thrombosis and pulmonary embolus.[30]

As is evident by the wide range of diseases that are associated with obesity and a high BMI, this is a multi-faceted problem that is linked with a cascade of related medical problems. Moreover, it is evident that unless action is taken, obesity will have an enormous physical and economic impact on our society. It is essential, therefore, that HHS, FDA and a number of other governmental and private institutions work together to limit the effect this disease has on our society.

B. Complementary Nature of Pharmacological and Diet/Exercise Interventions.

The National Institutes of Health (NIH) has noted that no one technique will guarantee an individual achieves a healthy BMI, but rather, various techniques and strategies must be employed to achieve effective weight control.[31] These strategies include dietary therapy, increased physical activity, pharmacotherapy and surgery. More often than not, a combination of these strategies is necessary for an obese individual to lose weight and continue to maintain a healthy BMI.[32]

i. Drug Therapies and Medications

Pharmacological treatment of obesity can be tremendously beneficial to patients when it is used in conjunction with lifestyle changes, including behavior modification and regular physical activity. It is beyond cavil that drug therapies provide a non-surgical alternative for obese people who have difficulty losing weight through diet and exercise.[33] Most effective drug therapies function by producing a caloric deficit sufficient enough to result in weight loss.[34]

Physicians who treat obesity have increasingly recognized that pharmacotherapy is an essential component of any successful treatment regiment. While physicians have long recognized that drug treatment should be used to achieve short term weight loss, they have just begun to recognize the need for pharmacotherapy as a part of long-term weight management programs.[35] As obesity management expert George Bray notes: "the observation that patients regain weight after stopping drug treatment for obesity argues for the proposition that drugs work only when taken and not that

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[26] Id.
[27] Id.
[28] Id.
[29] Id.
[30] American Gastroenterological Society, *AGA Technical Review on Obesity*. Gastroenterology 2002; 12:882-932.
[31] National Heart Lung and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (NIH Pub. No. 98-4083).
[32] Id.
[33] Bren, L. *Losing Weight: More Than Just Counting Calories*. FDA Consumer Magazine.
[34] National Heart Lung and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (NIH Pub. No. 98-4083).
[35] Id.

the drugs are ineffective."[36] Thus, he concludes, weight loss drugs are best used for both short-term weight loss and long-term weight management. Unfortunately, many physicians have not adopted this approach due to the many obstacles they face to ensure that their patients have access to obesity drugs.

ii. Unapproved Interventions

The proliferation of unapproved medical interventions presents risks of unsafe weight-loss strategies. The FDA should provide clear guidance to consumers on differentiating approved from unapproved approaches. For example, dietary supplements and exercise devices intended for weight loss purposes are not approved treatments for obesity and often lack any clinical data on safety and effectiveness. Given the increasing interest in obesity, there is a growing need for FDA to promote the appropriate education of consumers regarding the differences between approved and unapproved products for weight loss.

C. General Overview of Important Role of Therapeutics in Addressing Obesity and Co-morbidities.

As discussed above, there is substantial evidence that existing obesity drugs produce levels of weight loss that would be extremely meaningful in addressing the current obesity crisis facing the United States. For example, according to the National Institute of Diabetes and Digestive Kidney Diseases, appetite suppressants correlate with an average weight loss of five to 22 pounds above that expected with non-drug obesity treatments.[37] Similar efficacy findings have been demonstrated for orlistat in seven clinical trials including 4,173 patients throughout Europe and the United States. A one-year study focused on Type 2 diabetes, and four 2-year studies focused on weight loss and weight loss maintenance. The conclusion of the studies was that the addition of orlistat to a "conventional weight-loss regimen" has three benefits: (1) oral glucose tolerance was significantly improved; (2) progression to impaired glucose tolerance was slowed; and (3) control in type 2 diabetes was improved.[38] Additionally, a recent study concluded orlistat produced significantly greater improvements in body weight reduction than appetite suppressants.[39]

Moreover, NIH has said that studies show the success of weight-loss medications in fighting the co-morbidities associated with obesity.[40] Specifically, studies show that weight-loss medication treatments "lower blood pressure, blood cholesterol, and triglycerides (fats) and decrease insulin resistance (the body's inability to use blood sugar)."[41] Although no one medication for obesity is ideal for all purposes, it has become clear that medications such as Xenical are an important non-surgical option for treatment of obesity comorbidities.

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[36] Bray G. *Evaluation of drugs for treating obesity.* Obesity Research 3: 425S-434S (1995).

[37] Id.

[38] *Initial studies in humans with the novel gastrointestinal lipase inhibitor Ro. 18-0647 (tetrahydrolipstatin).* Am. Jur. Clin. Nutr. 1992; 55:309S-13S.

[39] Stein, J. *Eco: Orlistat (Xenical) Plus Reduced Calorie Diet Beneficial For Obese Non-Diabetics.* Doctor's Guide Global Edit., May 31, 2001. Study was conducted by Prof. Hermann Toplak, Karl-Franzens University in Graz, Austria.

[40] National Institute of Health, Prescription Medications for the Treatment of Obesity (NIH Pub. No. 97-4191) June 2003.

[41] Id.

D. Evidence to Support Efficacy of Current and Future Pharmacological Approaches to Obesity and Co-morbidities.

In recent years, remarkable progress has been made in the understanding of the pathophysiology of obesity.[42] Specifically, studying the pathways of neurotransmitters, researchers developed a "feedback model" allowing them to understand the effect of pharmacological agents on the body.[43] The model examines the role of the brain in controlling the body with afferent neural hormonal and nutrient signals, as well as hormonal and other efferent controls in determining the body's metabolic state. It has been determined that by influencing the levels of serotonin or catecholamine, drug therapeutics can suppress appetite leading to reduced food intake, resulting in weight loss. Appetite suppressant therapeutics include serotonic drugs, adreneric drugs, and noradrenerig drugs. To date, the research has produced a variety of therapeutics with different pharmacological properties.

Other types of "feedback therapeutics" have also been developed. For example, Roche's Xenical inhibits the digestive system from absorbing fat.

A wide variety of research programs are underway that could produce further important therapeutic advances. Novel methods of treating obesity under development include products as diverse as:

- the use of PYY3-36, a digestive hormone produced by the digestive system, promotes a sense of fullness,[44]
- compounds that could block grehlin, a recently discovered stomach hormone that is believed to stimulate hunger,[45]
- products that would block Neuropeptide Y, a substance produced in the brain that increases appetite.

Given the enormity of the obesity problem, it is critically important for the agency – and HHS in general, to both support existing products and ensure every possible incentive for turning these research approaches into approved therapeutics.

II. What are the most important things that FDA could do that would make a significant difference in efforts to address the problem of overweight and obesity?

There is a general lack of understanding about the implications of obesity. Unfortunately, this directly affects an individual's ability to seek appropriate treatment for their disease. Currently, individuals are unaware of the broad implications of being obese. Additionally, health care providers are unaware of the comorbidities that accompany the medical condition. Perhaps even more importantly, policy makers do not appear to acknowledge obesity as a disease and thus support coverage of pharmacotherapy under Medicare and Medicaid. These misunderstandings result in a fundamental disconnect between obese patients and the health care system in which they must seek care. The disconnect inevitably leads to poor quality of care as well as higher costs. Proper labeling of obesity drugs and explicit and informative direct to consumer advertising would be instrumental

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[42] Essig MG. *Obesity Pathogenesis: Exploration of obesity development may lead to novel treatments.* Obesity, Fitness and Wellness Week. Dec. 14, 2002.

[43] Bray G. Handbook of Obesity, New York, Marcel Dekker, 1998:953-75.

[44] R. L. Batterham, et al. *Inhibition of Food Intake in Obese Subjects by Peptide YY3-36.* New Eng. J. of Med., Sept. 4, 2003.

[45] Id.

in overcoming the ignorance that exists about obesity by proving necessary and useful information to patients and the physicians who treat them.

A. Rapid Development of Clear and Reasonable Guidance Regarding Obesity Drug Product Standards and Labeling.

It is essential that FDA develop clear and reasonable guidance on obesity drug product standards and labeling. We believe that FDA should take the following actions: (1) provide guidance for prescription drug labeling for obesity medications, including encouraging statements regarding the benefits of weight loss, and the health risks associated with being overweight or obese; (2) provide guidance on advertising allowing pharmaceutical companies to educate the public on the health risks associated with obesity and the effectiveness of certain drugs when used as part of a weight management regimen; and (3) promote the education of physicians by encouraging the presentation of information on obesity drugs in physician offices.

i. Prescription Drug Labeling

It is essential that FDA adopt clear and reasonable guidelines for obesity drug labels, including directions for use for consumers, cautionary statements, and statements of the benefits of weight loss. Prescription drug labels should be consumer-friendly and easy "to access, read and use."[46] Labels should include easy-to-understand language including the following information for patients:

- Drug Therapy is Complementary to Diet and Exercise. Patients should be made aware that obesity drug therapy, in combination with lifestyle changes, is effective in treating obesity.
- Benefit of Weight Loss in Reducing Co-Morbidities. Included on the label should be information on studies showing that a 5% to 10% loss of initial body weight improves co-morbidities such as Type 2 diabetes, hypertension, and hypercholesterolemia.[47] The labels should disclose that drug therapies are an effective means, when combined with diet and exercise, to attain such a reduction in co-morbidities.
- Efficacy of Weight-Loss Medication. This would include information on the efficacy of weight-loss medication treatments in not only reducing weight, but also in lowering blood pressure, blood cholesterol, triglycerides (fats) and decreasing insulin resistance.[48]
- Unapproved Obesity Treatments. Drug labels should clearly distinguish between FDA approved drugs and unapproved obesity supplements and devices.
- The FDA should develop public education programs to assist consumers in selecting between the many treatments available in order to ensure that the public does not engage in inappropriate self care or use of unregulated and dangerous alternatives. This would help foster weight loss through drug therapies that have been determined by FDA to be both safe and effective.

The September 24, 1996 Draft Guidance for the Clinical Evaluation of Weight Control Drugs should be revised to encourage pharmaceutical manufacturers to communicate to physicians on

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[46] Summary Status Report on FDA Reinvention Goals, FDA/Office of Planning, Aug. 2000.

[47] Goldstein DJ. *Beneficial health effects of modest weight loss.* Int. J. Obes 1992; 16:397-415. See also Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D. *Long-term effects of modest weight loss in Type 2 diabetic patients.* Archs Intern Med 1987; 147:1749-53. See also Wangness M. *Pharmacological Treatment of Obesity: Past, Present and Future.* Minnesota Medical Association, Vol. 83, Nov. 2000.

[48] Prescription Medications for the Treatment of Obesity (NIH Pub. No. 97-4191), June 2003.

studies conducted on the efficacy of obesity drugs, the proper dosages of the drugs, drug interactions, and guidance on proper administration of the drugs. Package inserts and other labeling could effectively disseminate the information. Additionally, on the drug label, manufacturers should be able to communicate to patients truthful and non-misleading information on how the drug best complements diet and physical activity.

ii. Guidance on Direct-to-Consumer Advertising Campaigns

We strongly believe that the FDA should develop a guidance that promotes appropriate direct-to-consumer advertising of obesity prescription drugs.[49] In particular, this guidance would help pharmaceutical manufacturers understand how product advertising can be used to help alleviate public ignorance about obesity. Additionally, the guidance should instruct manufacturers on how they may promote pharmacotherapy solutions, facilitate patient use of appropriate weight loss tactics, and encourage consumers to pursue weight loss through appropriate therapy. Proper guidance on direct-to-consumer advertising could assist in the dissemination of important information on healthy weight loss strategies to the public and would be an important adjunct to any other public information programs the Agency may undertake with respect to obesity. FDA should engage in constructive dialogue with stakeholders (i.e. patient advocacy groups, regulate industry, and consumers) to draft the guidance to ensure its impact in addressing this important public health problem.

We also note that unlike Rx anti-obesity agents, promotion of OTC weight loss products are regulated by the Federal Trade Commission and not FDA. The difference in promotional regulatory processes results in OTC products being able to make broader efficacy claims without corresponding safety data. Many times these promotional claims are not based on any clinical data particularly data from controlled clinical trials. This difference in promotional activities can be confusing to patients/consumers as they are not knowledgeable of the differences in regulatory requirements for the promotion of Rx and OTC products. The patient/consumers goal is to find an agent that will help them lose weight and hence they must decide, based on the promotion of the Rx versus OTC products, which agent will likely help them meet their weight loss goal safely.

Roche believes this is another issue which FDA should address in their constructive dialogue with stakeholders.

iii. Guidance on Studies Presented in Doctors' Offices

In an effort to rapidly disseminate information on obesity treatment, FDA should facilitate and encourage the presentation of evidence of recently completed obesity-related studies to physicians. The FDA should provide explicit guidance about the content and type of data industry may present to physicians on FDA-approved obesity treatments. Presentations in physicians' offices are a means to educate physicians on new developments in drug therapies, treatment options that suit individual patient needs, and the best available data on drug efficacy and proper usage. The presentations should emphasize the need for proper diet and exercise to complement any weight loss treatment.

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[49] 21 C.F.R. § 202.1 (2003).

B. FDA Should Broaden the Efforts of the FDA Working Group to Work With Other Agencies to Reduce Public and Private Barriers to Patient Access to Obesity Drugs.

Despite the extensive effort FDA is undertaking in creating a comprehensive strategic plan to confront obesity, the national obesity epidemic will continue unless FDA works with other governmental entities to expand both public and private avenues to therapeutic treatment. Difficulties of patients in seeking reimbursement for therapeutic treatment of obesity was cited as a key problem by a number of speakers at FDA's October 23 Public Meeting on Obesity. Additionally, it should be noted that eighty-one percent of physicians have said they would increase prescribing anti-obesity products if they were covered by insurance.[50]

Approximately 85% of Americans use some sort of private or government insurance to assist with health care costs.[51] However, few of these health care programs cover prescription drugs to combat obesity. This is true, despite mounting evidence demonstrating that the use of obesity pharmacotherapy can reduce the need for concomitant medications, thereby offsetting the cost of the obesity drug. Specifically, pharmacoeconomic modeling suggests that weight loss from obesity drugs could result in: (1) medical cost savings of $330 per patient in the first year and (2) twenty-four percent reduction in the need for future costly diabetes-related procedures.[52] Thus, to promote increased access to vital pharmacotherapy treatment, FDA should endeavor to include other government agencies and private payor insurers in the FDA Obesity Working Group specifically to promote increased patient access to these vital medications.

i. Current Barriers to Access in Medicaid

The Medicaid program is the primary means of obtaining prescription drugs for the low-income population in the United States, yet the program provides virtually no resources for the treatment for obesity. Specifically, Federal guidelines and state funding discretion has kept many Americans from receiving obesity-related treatment through Medicaid. Even though all states currently offer a prescription drug program for at least some Medicaid beneficiaries, few state Medicaid programs allow for the reimbursement of obesity drugs.

Under the Federal Medicaid statute, states do not have to reimburse beneficiaries for drugs used for anorexia, weight loss, or weight gain.[53] Under this exception, which was originally framed to treat weight issues – including obesity – as a cosmetic problem, some states have chosen to withhold Medicaid coverage of medication for the treatment of obesity. Only nine states currently cover anti-obesity pharmaceutical drugs. In twenty-nine, anti-obesity products are specifically excluded in state Medicaid programs. [54] This systematic denial of access to obesity treatment bars a significant portion of the population from prescription medication that could significantly improve their health and prevent an array of other medical ailments.

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[50] Data on File (Ref. 038-066) Hoffman-La Roche Inc, Nutley, NJ 07110.
[51] Health Insurance Coverage in the United States: 2002, U.S. Census Bureau (2003).
[52] Data on File (Ref. 038-066) Hoffman-La Roche Inc, Nutley, NJ 07110.
[53] Social Security Act §1927(d)(2), 42 U.S.C.A. §1396r-8(d)(2) (2003).
[54] American Obesity Association Fact Sheet on Medicare, Medicaid and Obesity, *at* http://www.obesity.org/subs/fastfacts/Obesity_Medicare.shtml.

FDA should use the efforts of the Working Group to support availability of obesity drugs by making its findings known to, and working with, government entities, both on the federal and state level, that assist in making these Medicaid drug-coverage determinations.

ii. Current Barriers to Access in Medicare

Medicare provides medical coverage for over 40 million Americans, yet Medicare currently provides no access to prescription drugs to treat obesity. As the potential for an outpatient Medicare prescription drug benefit draws nearer, it is imperative that any benefit include coverage for obesity drugs. Unfortunately, current versions of the proposed benefit would carry over the current Medicaid exclusion into the Medicare program.

Both the Senate and the House passed Medicare prescription drug bills that include restrictions similar to those found in Medicaid.[55] Specifically, under these bills, Medicare will not reimburse for "drugs used for ... weight loss." Hence, obesity drugs will not be covered under the currently proposed new Medicare prescription drug program.

CMS has made numerous rulings that further confine obesity treatment options for Medicare recipients. Indeed, the current, but medically outdated, Medicare Coverage Issues Manual published by CMS establishes no treatment for obesity:

> "Obesity itself cannot be considered an illness. The immediate cause is a caloric intake which is persistently higher than caloric output. Program payment may not be made for the treatment of obesity alone since this treatment is not reasonable and necessary for the diagnosis or treatment of an illness or injury. However, although obesity is not itself an illness, it may be caused by illnesses such as hypothyroidism, Cushing's disease, and hypothalamic lesions. In addition, obesity can aggravate a number of cardiac and respiratory diseases as well as diabetes and hypertension. Therefore, services in connection with the treatment of obesity are covered services when such services are an integral and necessary part of a course of treatment for one of these illnesses."[56]

Nonetheless, the CMS manual allows for Medicare coverage of invasive gastric bypass surgery to treat extreme obesity.[57] Gastric bypass surgery is covered under the Medicare program "if (1) it is medically appropriate for the individual to have such surgery; and (2) the surgery is to correct an illness which caused the obesity or was aggravated by the obesity."[58] This results in perverse incentives that favor surgery over non-surgical treatment and actually encourage an obese individual to become more obese before obtaining medical treatment. Preventative medicinal treatment for obesity is not an option. Additionally, Medicare rarely allows for the treatment of obesity until the obese individual develops additional ailments (such as diabetes).

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[55] Medicare Prescription Drug and Modernization Act of 2003, H.R. 1, 108th Congress (2003). Both versions of H.R. 1 list the restrictions found in Social Security Act §1861(s)(2)(A) except both make an exception for §1861(s)(2)(e), allowing coverage for "Agents when used to promote smoking cessation."

[56] Medicare Coverage Issues Manual, HCFA Pub. 6, 35-26 (2003).

[57] Id.

[58] Id.

The FDA Obesity Working Group should engage HHS and CMS in a comprehensive approach to addressing the barriers to obesity treatment under the Medicare system, which prohibit meaningful access to pharmaceutical treatments for obesity. Additionally, the agency should work to promote coverage of obesity drugs under any new Medicare prescription drug program and as the program is implemented in the coming years.

iii. Current Barriers to Access from Private Health Insurers

Almost 70% of Americans use some sort of private health insurance to assist with the cost of medical care. However, most private health insurers do not include obesity treatment under benefit coverage. This policy mirrors the government's attitude toward obesity, choosing to treat it as condition rather than a disease.

Until the federal government begins to change its coverage policies in earnest and actively promotes the therapeutic treatment of obese persons, the private insurance sector is unlikely to do so. We strongly encourage the FDA, working with other federal agencies, to actively promote the coverage of medically necessary obesity drugs in order to improve the health of the nation and reduce the cost of treating obesity-related comorbidities.

III. Conclusion

We submit these comments in the hope that FDA will take the lead in promoting and facilitating the use of pharmacological approaches to obesity and its comorbidities. Through the issuance of clear and unambiguous guidance, FDA can facilitate the education of physicians and their patients about the therapeutic options available to them through both labeling and advertising. By issuing guidance in an expedited manner, FDA can acknowledge the epidemic-like nature of obesity in America and greatly improve the ability of physicians to treat obese patients. Importantly, an increase in physician and patient awareness and utilization of these treatments is likely to result in greater efforts to research new cures for this disease, thus bringing us even closer to a healthier national outcome. Finally, we would hope that FDA would actively engage with other agencies to promote access to these medically necessary drugs on par with access to other lifesaving treatments.

We applaud FDA's efforts to reach out to the public on this issue and hope that as the program is developed and guidance documents are drafted, FDA will continue to consult with stakeholders. Thank you for the opportunity to submit these comments. If Roche can be of assistance, please do not hesitate to contact us.

Respectfully submitted,

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