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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

AND ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

Monday, January 23, 2006

8:00 a.m.

Holiday Inn Select
Versailles Ballrooms
8120 Wisconsin Avenue
Bethesda, Maryland

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. WOOD: Good morning. I an Alastair Wood. I think we are ready to get started and why don't we begin by going around the table and having the committee and others at the table introduce themselves? George, why don't we start with you?

DR. GOLDSTEIN: I am George Goldstein. I am a Board certified pediatrician, with 17 years of practice experience who realized he would never reach perfection and went into the industry thereafter. I have been in industry for 30 years and recently retired. I chaired the American Academy of Pediatrics Clinical Pharmacology Section, where I had the pleasure of meeting Dr. Wayne Snodgrass, among others. I have been in prescription drug development regulatory affairs and chaired the Orphan Drug Commission for industry. It is a pleasure and a privilege to be here. Thank you.

DR. RYDER: Steve Ryder. I am an internist and a diabetologist. I have been in

industry for about 25 years, and had the pleasure of learning from Dr. Goldstein and many on this committee. I am a full-time employee of Pfizer and a non-voting industry representative to the Endocrine and Metabolic Drugs Advisory Committee.

DR. CAPRIO: I am Sonia Caprio, from Yale. I am a pediatric endocrinologist and my area of research and interest is child obesity and type 2 diabetes in children.

DR. BENOWITZ: Neal Benowitz. I am from UC San Francisco. I am an internist and a clinical pharmacologist and medical toxicologist, and I am a member of the EMDAC committee.

DR. CARPENTER: I am Tom Carpenter. I am in the Pediatric Endocrine Section at Yale. I have served on this committee and have a primary interest in bone and marrow disorders but clinically practice pediatric endocrinology as well.

DR. BLASCHKE: I am Terry Blaschke, clinical pharmacologist and internist from Stanford University and member of the EMDAC.

DR. FOLLMANN: I am Dean Follmann, head of statistics at the National Institutes of Allergy and Infectious Diseases.

DR. PARKER: Ruth Parker, general medicine at Emory University. I am on the EMDAC committee.

DR. SCHAMBELAN: Morris Schambelan, at the University at San Francisco. I am an endocrinologist and run the division at San Francisco General Hospital, and I am a member of the Endocrine and Metabolic Drugs Advisory Committee.

DR. WOOD: I am Alastair Wood and chair of this committee, and I am an internist and clinical pharmacologist from Vanderbilt.

LT LYONS: I am Darrell Lyons. I am the executive secretary for the Nonprescription Drugs Advisory Committee.

DR. GRIFFIN: Marie Griffin. I am an internist and pharmacoepidemiologist from Vanderbilt University.

DR. WOOLF: I am Paul Woolf, from Crozer Chester Medical Center. I am on EMDAC and this is

my "swan song."

DR. CLYBURN: I am Ben Clyburn. I am an internist from the Medical University of South Carolina and an EMDAC member.

DR. TINETTI: I am Mary Tinetti, internal medicine and geriatrics at Yale, and I am on EMDAC.

DR. SNODGRASS: I am Wayne Snodgrass, a pediatrician and clinical pharmacologist at the University of Texas.

DR. PATTEN: I am Sonia Patten. I am an anthropologist on the faculty of Macalester College, in St. Paul, Minnesota. I am the consumer representative associated with EMDAC.

DR. COLMAN: I am Eric Colman. I am a medical officer from the Division of Metabolic and Endocrine Products at FDA.

DR. PARKS: I am Mary Parks, Acting Director in the Division of Metabolic and Endocrine Products, FDA.

DR. LEONARD-SEGAL: I am Andrea Leonard-Segal, Acting Director, Division of Nonprescription Clinical Evaluation at FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Deputy Director, Office of Drug Evaluation II.

DR. WOOD: Thanks very much. The next item on the agenda is for Darrell to read the conflict of interest statement.

Conflict of Interest Statement

LT LYONS: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee's participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions:

In accordance with 18 USC Section 208(b)(3), the following participants have been granted waivers, Dr. Terrence Blaschke for consulting on an unrelated matter for a competitor, for which he receives less than $10,001 per year.

Dr. Thomas Carpenter for serving on a speakers bureau for a competitor. He receives less than $10,001 per year, and lectures on matters unrelated to orlistat and its competing products.

Dr. Marie Griffin for consulting on an unrelated matter for a competitor. She receives between $10,001 and $50,000 per year.

Dr. Alastair Wood for consulting on an unrelated matter for a competitor. He receives less than $10,001 per year.

Dr. Neal Benowitz for consulting on an unrelated matter for the sponsor and for serving on the advisory boards for two competitors on unrelated matters. He receives less than $10,001 per year per firm. In addition, Dr. Benowitz has been granted a waiver under 21 USC 505(n) for his spouse's ownership of stock in two competitors. These stocks are valued from $5,001 to $25,000 each.

Dr. Ruth Parker for serving as co-editor on an unrelated journal supplement supported by an unrestricted educational grant from a competitor.

She receives less than $5,001 per year.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Steven Ryder and Dr. George Goldstein have been invited to participate as industry representatives, acting on behalf of regulated industry. Dr. Ryder's and Dr. Goldstein's role on this committee is to represent industry interests in general and not one particular company. Dr. Ryder is employed by Pfizer. Dr. Goldstein is a retired employee of Sterling Drugs.

In the event that discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current

or previous financial involvement with any firms whose products they may with to comment upon. Thank you.

DR. WOOD: Thanks very much. Let's move on to the first presentation. Andrea?

Welcome and Introductory Comments

DR. LEONARD-SEGAL: Dr. Wood and members of the joint committee, good morning. It is a pleasure for me to welcome you this morning on behalf of the Division of Nonprescription Clinical Evaluation and the Division of Metabolic and Endocrine Drug Products.

I am just going to say a couple of words that I hope will offer you a backdrop for today's meeting. I will touch on the historical approach to approving weight-loss drugs by prescription and over-the-counter, and I will say a few words about obesity and the condition of being overweight. I will touch on the regulatory history of orlistat; regulatory requirements for non-prescription marketing; and I will wrap up by just outlining today's agenda.

FDA's approach to approving prescription weight-loss drugs has mirrored the treatment recommendations in the National Institutes of Health guidelines over about the last decade or so, and you will hear more about this from Eric Colman in a little while. As such, the target populations for drug therapy have been the obese population with a body mass index of at least 30 kg/m

2 and the

overweight population with a BMI of at least 27 kg/m2 who also have other risk factors for cardiovascular disease and mortality, including things like hypertension and diabetes mellitus and dyslipidemia.

By contrast, the approach to over-the-counter weight-loss drug availability has been guided by the over-the-counter monograph. I know that some of you may not be familiar with the over-the-counter monograph, but Arlene Solbeck will, hopefully, remedy that for you also a little later this morning. Suffice it to say that in 1982 an advance notice of proposed rulemaking was published in the Federal Register which recognizes

weight control as an over-the-counter indication, however, the treatment indication is not based upon BMI.

In addition to cardiovascular risk factors, the NIH's 2000 guidelines, which are in your packet, list non-cardiovascular conditions for which obese patients are at risk. The guidelines mention osteoarthritis, gynecological abnormalities, gallstones and stress incontinence.

However, it is also important to note that the medical literature is replete with articles demonstrating non-cardiovascular risks of being overweight in addition to being obese. Examples would be this month's Annals of Internal Medicine, article by Hsu et al., that shows that the condition of being overweight is an independent risk factor for end stage renal disease in addition to the condition of being obese.

As a rheumatologist, I can tell you that for years we have known that the condition of being overweight and the condition of being obese is a risk for osteoarthritis development and also both

of these conditions worsen the state of osteoarthritis if it already exists. We know that osteoarthritis begets physical inactivity, and the 2000 NIH guidelines state that physical inactivity is an increased risk for cardiovascular disease and diabetes. For osteoarthritis weight loss of around ten pounds can make a huge difference in terms of function and pain.

Now let me turn to the regulatory history of orlistat. Xenical or orlistat 120 mg was approved in 1999 as a prescription product. It is a pancreatic lipase inhibitor for obesity management, and the sponsor is Roche Laboratories. The product is as doses of 120 mg three times a day to be taken with a fat-containing meal.

There are two indications. The first is obesity management including weight loss and maintenance when used with reduced calorie diet. The second is to reduce the risk for weight gain after prior weight loss.

The target population mirrors the 2000 NIH guidelines in that we are talking about a BMI of at

least 30 or a BMI of at least 27 with other risk factors, and the duration of therapy is not limited by labeling.

In December, 2003 the labeling for Xenical was updated to include efficacy and safety data for obese adolescents ages 12-16. However, there is no pediatric indication per se in labeling.

Now, the reason we are here today is to talk about Alli. I hope I am pronouncing that correctly. This is orlistat 60 mg. The product is brought to us by GlaxoSmithKline and it is to be taken as one or two capsules, that is, 60 or 120 mg with each fat-containing meal, not to exceed six capsules daily. The indication is to promote weight loss in overweight adults when used along with a reduced calorie and low-fat diet. The target population is overweight adults at least 18 years of age, and there is a proposed duration of treatment of six months.

Now let's shift gears and talk about the regulatory requirements for nonprescription marketing. Everything we do at FDA is, as you

know, within a regulatory milieu and the regulation that you need to know about for today's meeting is the 1951 Durham Humphrey Amendment to the Food, Drug and Cosmetic Act. This amendment formally differentiates prescription from nonprescription drugs.

Two criteria carve a niche for prescription drugs. The first is that the drug can be used safely only under supervision because of the drug's toxicity, other potentiality for harmful effect, other method of its use and collateral measures necessary to its use. The second is if the drug is approved as the result of a new drug application for use under professional supervision, maybe because it is the first in its class or for some other reason. Otherwise, the drug should be available without a prescription. In essence, the Durham Humphrey Amendment says that if a product doesn't fit into this prescription niche it defaults to being over-the-counter.

So, what kinds of things do we need to know when we are thinking about moving a drug from

the prescription to the nonprescription realm? We want to ask does the product have an acceptable safety profile? Does it have low potential for misuse and abuse? Does it have a reasonable therapeutic index of safety? Can the condition to be treated be self-recognized? When used under the nonprescription conditions, is the product safe and effective? Do the benefits outweigh the risks in the over-the-counter setting? So, the issue that we are going to ponder today is does orlistat meet the regulatory requirements for nonprescription marketing?

So, what is going to go on here? After I am done speaking, we will hear a little bit more about the history of weight-loss drug approval both in the Rx and OTC settings. Then we will hear from GlaxoSmithKline. Then we will have a break and the committee can perhaps avail themselves of some of the high-fat, high-calorie food that I see on the table over there. Then FDA will speak about safety and efficacy of orlistat and we will talk about the label comprehension study and the actual use study

that were available for us to review. Then we will have lunch, committee discussion, the open public hearing and then committee deliberations.

So, I thank you for the work that you are about to do for us this morning and we look forward to a very interesting day.

DR. WOOD: Thanks very much. Unless there are specific questions, let's go straight on to the next speaker. Eric, do you want to take that?

History of Weight-Loss Drugs

DR. COLMAN: Good morning. My goal for the next 30 minutes is to provide you with an overview of the regulatory history of prescription weight-loss drugs, which dates back about five decades. I have decided to break this into three parts, beginning with the original approval of the amphetamines and the amphetamine congeners, and then move on to a period where all weight-loss drugs were approved for short-term use only, and then conclude with the current era where we have prescription drugs for obesity that are used long term.

The first drug approved by FDA for treatment of obesity was an amphetamine, desoxyephedrine, and this was back in 1947. The indication read "as an adjunct to therapy of obesity." By 1960 FDA had approved five amphetamine congeners, which I have shown you here. I want to share with you the labeling indication for diethylpropion. In this case, the drug was indicated for the treatment of obesity in any patient, including the adolescent, geriatric and gravid, as well as special risk situations of the cardiac, hypertensive and diabetic. So, just about everybody could take that drug.

Shortly after that, in 1962, Congress passed the Kefauver-Harris Drug Amendments. For the first time this legislation required that drug companies submit to FDA evidence that their drugs were effective. Because the legislation did not have any bearing on drugs approved before 1962, the Commissioner asked the National Academy of Sciences if they would review all of the available efficacy data for the drugs approved between 1938 and 1962.

That was roughly 3,000 drugs. It was a major task.

Back then it was the psychiatrists who were evaluating the wight-loss drugs. So, this panel was charged with looking at the available evidence and rendering an opinion on whether or not these weight-loss drugs were effective. They spent about three years doing that and ultimately they concluded that, in fact, these drugs were less than effective for the treatment of obesity. Some of the reasons they cited for that were, one, the trials were of short duration; the weight-loss effect tended to plateau early; and there was no available evidence that the drugs altered the natural history of the disease.

It was clear, however, that additional longer-term data were needed. FDA received the panel's recommendations and they did agree that there was insufficient evidence to support a conclusion that these drugs were effective as weight-loss agents. So, they turned back to the companies and said, look, you have to go out and conduct adequate and well-controlled trials and

prove to us that these drugs are, in fact, effective for obesity.

One of the fallouts of that is that it required that FDA come up with some definition of efficacy of weight-loss drugs. At first they turned to an external panel of consultants and asked this group to help them answer that question. This group ultimately came back and said we think you should define efficacy as statistical superiority of drug to placebo. In other words, as long as the numerical weight loss on drug is greater than the numerical weight loss on placebo and those differences are statistically significant that should qualify as an effective weight-loss drug.

This group explicitly declined to require some biological superiority, for example, some minimum loss in terms of percentage of excess weight, and there were some in the agency back at this time that were in favor of this kind of endpoint. But shortly after this, the advisory committee endorsed the use of statistical

superiority criteria and that was what the FDA adopted as their official policy.

They were able to put this new efficacy definition to use when they conducted their amphetamine anorectic drug project. This was a meta-analysis of the data from the trials that FDA required manufacturers to go out and get following the DESI review process. It involved all amphetamines and amphetamine congeners, and at this point fenfluramine had been thrown in the mix; it hadn't been approved yet. There were over 200 trials or more than 10,000 patients. The average duration of the studies was 3-24 weeks, however most were 12 weeks or less.

At the end of the day when they finalized their analysis, it did turn out that patients treated with active drug lost a fraction of a pound more a week than those treated with placebo. More importantly, the differences were statistically significant.

With this information in hand, FDA was ready to make an official proclamation on the

weight-loss drugs, and they did this in 1973. As I just mentioned, the data did support efficacy as they defined it. However, there were a lot in the agency who had a lot of concerns about these drugs, mainly related to the limited usefulness, and they listed some of these limitations as, again, only a fraction of a pound more a week lost for drug versus placebo. The weight loss plateau'd early after the drugs were started. Weight was regained after the drug was stopped. That is something that today you would not think anything of; that is what would be expected. Back then, they saw that as some kind of weakness in the drug. Finally, there were no data on the effects of the drugs on the morbidity or mortality associated with obesity. Again, people back in the '70s were talking about these things. They were talking about mortality and morbidity associated with weight loss so it is not a real recent phenomenon.

But the biggest concern at this point was a growing abuse of the amphetamines and, to a lesser extent the amphetamine congeners. Illicit

use in the country was rampant. Taken together, the FDA came up with what they considered a compromise position where these drugs would stay on the market. They would maintain their obesity indication but they would be limited to short-term use. So, around 1974 all the weight-loss drugs--every one of them--had this indication. It said, indicated in the management of exogenous obesity as a short-term adjunct (a few weeks)--and "a few weeks" was actually in the label like that--in a regimen of weight reduction based on caloric restriction. The idea was that if you only took the drugs for a few weeks you couldn't become physically addicted and since the drugs did most of the work in the early weeks, it seemed logical back them to do this.

One of the consequences of that short-term indication I have shown you here, on this graph. This shows the rates of prescriptions from the '60s up to 2000 but I just want to focus your attention around in here. This is about the time when the short-term use indication went into effect and you

can see a gradual, continual decline in the rates of obesity drug prescriptions until you get to the early '90s where you see this rather dramatic increase.

That dramatic increase was due to the phen-fen studies. These studies actually began back in the early '80s. Dr. Michael Weintraub and colleagues at the University of Rochester hypothesized that if you treat patients with fenfluramine and phentermine you would get much more weight loss than if you used either one alone. So, they set out to do some long-term studies and these studies in a large way really helped transition drug treatment from short to long term.

Another important event in the '80s was a 1985 NIH consensus conference called Health Implications of Obesity. I want to spend a couple of slides on this conference. One of the questions asked up front was, well, what is obesity? There were some definitions proposed: Excess of body fat frequently resulting in significant impairment of health--simple enough. It turned out that obesity

was considered a 20 percent or more increase above desirable body weight. Desirable body weight was determined by looking at life insurance actuarial data and finding what BMI was associated with a lower risk of death.

It turned out, using some life insurance tables, that this 20 percent increase above desirable weight was roughly correlated with a body mass index of 27. Again, body mass index is a patient's weight in kilograms divided by height in meters squared. You will be seeing a lot of BMI values in the remainder of my presentation.

This conference also addressed the issue of who should be treated for weight loss. It didn't address what form of weight loss--diet, exercise or drug; it just make a recommendation that these people should try to lose weight. Obviously the people who were obese, and that would be 20 percent or more above desirable body weight, a BMI of 27, they should lose weight. For people with lesser degrees of adiposity if they had co-morbidities--diabetes, cholesterol problems,

osteoarthritis--it might be beneficial if they too would lose weight.

There were two major outcomes of this consensus conference in my mind. One was the official proclamation by the medical community that obesity was a disease, and that had a lot of ramifications over the years. The other outcome was a recommendation that physicians begin to routinely measure their patients' BMIs to assess health risk. So, soon after this you start to see a BMI of 27 being equated with obesity and a risk. Unfortunately, a BMI of 27 was often referred to as overweight. Those terms were used interchangeably, which is unfortunate given what we use today.

I want to jump ahead to 1992. This is an important year for a number of reasons in the regulation of prescription drugs. NIH sponsored a conference on drug treatment of obesity. The final phen-fen results were published and my Division took over the regulatory oversight of the weight-loss drugs from the Division of Neuropharmacology. We began working on an obesity

drugs guidance document, which I will discuss at greater length in a few minutes.

I will take these one by one. There were a lot of interesting comments that came out of this workshop. One was an observation that although most other chronic diseases are treated with long-term drug therapy, drugs have played essentially no role in the treatment of obesity in America. And, this is 1992.

This was more amazing given the fact that there was evidence that modest weight losses reduce complications and risk factors of obesity. What was accounting for this? Well, you are looking at them--state and federal regulatory controls hindered or precluded drug use for longer than a few weeks. There was a special plea to the FDA to go back and reevaluate the process by which weight-control drugs are evaluated and approved. So, we had folks down at NIH telling the FDA you really need to do something.

The phen-fen results were published, the final results. This study reported that some obese

patients, you could treat them with fenfluramine plus phentermine for out to 3.5 years and some would lose significant amount of weight and they would maintain that weight over a full 3.5 years. This was a new concept. This was a new paradigm that had been demonstrated. There was a lot of comment from the press on this.

I want to share with you some of those comments. One newspaper remarked in response to this study that it showed that obesity could be treated the way chronic disease, say high blood pressure or arthritis, are. In those diseases, drugs can be taken indefinitely to keep symptoms in check.

In terms of the medical community, Dr. Albert Stunkard, a well-known obesity researcher at the University of Pennsylvania, remarked that the phen-fen study points to the way things are going to go, i.e., we are going to treat obesity long term with drugs.

Finally, Dr. Michael Weintraub, the lead author of the phen-fen studies, noted that these

drugs were not for the moderately overweight and if you just wanted to lose ten pounds and look better at your high school reunion, you shouldn't take these two drugs. By the way, Dr. Weintraub at one point was the head of the OTC Division here, at FDA.

I mentioned two slides back that at the NIH workshop they said, FDA, please, reevaluate your approval process. In two days, in January of 1995, that is exactly what FDA did when they convened an advisory committee along with some of the most prominent obesity experts in this country. The tone of that meeting was started early when an FDA official made the announcement that the biggest change FDA was hoping to bring about was the approval of obesity drugs for long-term use.

There were a lot of things discussed at that meeting. I just want to spend some time on three aspects of the obesity guidance, the duration and size of the phase 3 trials, criteria to define efficacy and the appropriate patient population. I will go through each one of those separately.

So, in '96 FDA did publish their guidance for clinical evaluation of weight-control drugs. Recommendations for duration and size of the phase 3 studies recommended that at least 1,500 patients be studied for one year under placebo-controlled conditions to assess efficacy. For safety, it was recommended that 200 to 500 of these patients continue on in an open-label manner a second year, again, to get some additional safety information.

In terms of efficacy, by 1995 we started to see a lot of literature, a lot of people saying that in obese individuals as little as five to ten percent reduction in body weight could bring about tangible improvements in physical health. Often these were surrogates but, nonetheless, you could see improvements in glucose; you could see improvements in blood pressure; you could see improvements in HDL and triglycerides. So, there was a lot of debate about whether five percent or ten percent should be the efficacy criterion. Ultimately, FDA decided on five percent and it was expressed in two ways, a mean weight change of five

percent greater in drug versus placebo, or if the proportion of patients losing five percent of baseline weight is greater in drug versus placebo treated patients that drug would be considered effective. I will point out that our European counterparts settled on a ten percent criterion, which is certainly more rigid.

As for the patient population, the guidance recommended that individuals with a BMI of 30 or more, or 27 to 29.9 with a co-morbidity, these were the people who were appropriate for drug therapy. Now, how they arrived at these numbers is a little bit of a mystery. It is admittedly arbitrary to some extent but for years at this point a BMI of 27 or more was considered obesity and by tagging it with at least one co-morbidity it was certainly increasing that patient's baseline risk for an adverse health outcome.

If you were to look at some graphs that depicted body mass index and risk of death, when you got to 30 you would see the line notably increase the slope. So, using these two criteria

really was an attempt to optimize the therapeutic risk/benefit profile by targeting patients whose baseline risk of adverse health and expected benefits of drug treatment would outweigh the known and the unknown risks of drug therapy.

So, with the guidance in place, we were now in a position to enter into the long-term drug treatment phase. That officially took place in 1995 when dexenfluramine was approved for the long-term treatment of obesity. This was the first obesity drug approved in over 20 years by FDA. As you know, it has a short half-life. It was taken off the market a year after it showed up because of concerns over valvulopathy. Two months after that sibutramine was approved for the long-term treatment of obesity and then, finally, orlistat, the drug that we will be discussing today, was approved in 1999.

I wanted to show you some of the language from the orlistat labeling, the indications section. You will be seeing this in later presentations as well: "Indicated for obesity

management including weight loss and weight maintenance in conjunction with a reduced calorie diet; also indicated to reduce the risk for weight regain after prior weight loss." Once again, the population that is appropriate for this drug is people with a BMI of 30 or more or 27 to 29.9 in the presence of at least one other risk factor.

Switching from FDA to NIH, in 1998 and then again in 2000 NIH published their clinical guidelines on the identification and treatment of overweight and obesity. One important factor in this guideline was the reclassification of weight by BMI, and this was really following on the footsteps of the WHO which had done this back in the mid '90s. But at this point, normal weight was now going to be considered a BMI of 18.5 to 24.9 and overweight was going to be expanded. It was now going to be a BMI of 25 to 29.9. In the old days, part of this would be obesity. Obesity now was a BMI of 30 or more. These criteria were based on some epidemiologic data that show an increase in mortality with a BMI above 25 and a much greater

increase in mortality when the BMI reaches 30.

The NIH guidelines addressed the issue of who should be treated with medication. They state that weight-loss medications should be used only by patients who were at increased medical risk because of their weight and should not be used for cosmetic weight loss. Again, they identified the same population that we do as appropriate for drug therapy.

The guidelines also state that weight loss-medications should never be used without concomitant lifestyle modifications. Dr. Golden will show you some data which reinforces the importance of concomitant lifestyle medication. Finally, this document said that since obesity is a chronic disorder the short-term use of drugs is not helpful.

A year and a half ago we convened our advisory committee. Some members here were present at the September, '04 advisory committee. The goal of that meeting was to revise and update the '96 obesity drug guidance. I would like to share with

you three considerations that were discussed that day. I will take them one by one. We asked the committee about the size and duration of the trials. To refresh your memory, the '96 guidance recommended that about 1,500 patients be treated for a year under placebo-control conditions and that a subset go on to a second year of open-label study.

When asked about this, most of the committee members felt that the size of these trials should be driven by safety, not efficacy, because it would take far fewer patients to establish efficacy than safety. So, people were saying if you want to rule out an adverse event or a particular incidence rate, then you should power your study around that. There was clearly continued support for the one-year placebo-controlled exposure to show efficacy. There was less support for continuing a second year open-label exposure for safety. People questioned the utility of that. In terms of efficacy, there was not much discussion. People continued to

support this five percent criterion as an appropriate endpoint.

Patient population was a little more interesting. One issue we did discuss that will have direct bearing on today's discussion was the appropriateness of treating patients with BMIs of 25 to less than 27 with a weight-loss drug. Before I give you some of the committee responses, I want to share with you comments made by Dr. Katherine Flegal, who is a well-known body weight epidemiologist, who was present at our advisory committee and did speak to some of these issues.

In response to this particular issue, she was quoted as saying there is little information available concerning the health benefits of weight loss in this BMI range. Most studies of weight loss include few, if any, participants with BMIs of 25 to less than 27 and may explicitly exclude them.

With that as a little background, we asked the committee point blank should the FDA change the inclusion criteria to include subjects with BMIs of 25 to less than 27 if they had a co-morbidity. To

make a long story short, the majority of the committee members did not support at this time lowering the BMI criteria to include individuals with BMIs of 25 to less than 27, often citing a lack of data in this group of people. There was no doubting, however, that if a patient with a BMI of 25-27 was to be treated with a drug, you would certainly have to have much greater assurance of that drug's safety than if you were treating individuals with higher baseline BMIs and higher risk.

Before I get to my three concluding slides, I wanted to share briefly with you some of the thoughts of other organizations that endorse targeting drug therapy to patients with BMIs of 30 or more or 27 with a co-morbidity. Those groups that endorse this are listed here. Last year the American College of Physicians put out a drug guidance document for obesity. It was limited to a BMI of 30, just to obese individuals. The American Society of Bariatric Physicians has a much more extensive list of potential criteria to use to

identify patients who may benefit from drug therapy.

On my last three slides I just want to try to summarize some of the major themes over the years in the prescription drug treatment of obesity and some of the changes in those themes, beginning first with the observation that when the amphetamines and the congeners were approved drug treatment of obesity was thought of as a short-term adjunct to enhance will power or appetite. It has evolved now to a point where drug treatment is considered long-term adjunctive therapy of a complex chronic disease.

The definition of obesity has changed quite a bit over the years. Years ago, when the original obesity drugs were approved, obesity was often referred to as a 10-20 percent increase above ideal body weight. Again, body weight was based on looking at life insurance data to see what the lowest risk of death was and what the BMI corresponded to.

In the mid '80s we started to see a BMI of

27 being referred to as obese, often interchangeably with overweight. In the mid '90s obesity became synonymous with a BMI of 30. As I mentioned, more recently, overweight is now defined as 25 to 29.9 and obesity is 30.

Defining efficacy of weight-loss drugs has always been a major challenge. Initially, people felt that if a drug didn't take someone from obese to achievement of ideal body weight the drug wasn't effective--quite an ambitious goal; unrealistic. Over the years that has given way to more realistic goals. In the early '70s FDA was using a statistically significant increase. It had no bearing on clinical significance. In the '96 guidance we decided to adopt a five percent weight loss because we felt that you could tie that to tangible benefits.

On my final slide I just wanted to make a few comments about medical versus cosmetic weight loss because I think this is an issue that will come up today. All prescription weight-loss drugs have been approved to treat medical weight loss.

For sake of discussion, I have defined medical weight loss as long-term reduction in body weight and fat mass with improvement in physical health in high risk patients. Again, there is a general consensus that a five to ten percent reduction in weight in obese patients will bring about improvements in physical health. Some may be surrogates but certainly you believe that would ultimately translate into favorable outcome with things like cholesterol and blood pressure.

In contrast, we have cosmetic weight loss and I have to say, obviously, that cosmetic weight loss and medical weight loss are not mutually exclusive. Some individuals may get both, particularly those who are heavier, but the lower you go in terms of baseline risk I think it is more of a cosmetic issue. Again for the sake of discussion here, I have defined cosmetic weight loss as a short-term reduction in body weight and fat mass with improvement in physical appearance in low or zero risk individuals.

The big problem is how do you define

weight loss in terms of a percentage of weight loss. How much weight does someone need to lose for that to be considered cosmetic weight loss? It would obviously vary depending on the individual and I certainly don't have any idea of what value that would be.

But I think the most important issue related to medical versus cosmetic weight loss is when someone tries to make a risk/benefit assessment. With medical weight loss people lose weight; they have tangible, measurable improvements in their physical health and you can take those measurements and you can use those to weigh against the known and unknown risks of the drug. With cosmetic weight loss it is very difficult to quantitate benefit in terms of physical appearance. We have quality of life but that is certainly a softer endpoint than looking at cholesterol and blood pressure, etc.

So, the challenge here is to somehow make a reasonable risk/benefit assessment of a drug that, at least by some people if it is available

over-the-counter, will be used for cosmetic weight loss. I will be anxious to hear the committee's thoughts on this idea, as well as other related ideas throughout the day. Thank you.

DR. WOOD: Unless there are questions, we will move straight on to the next speaker.

History of the OTC Monograph

MS. SOLBECK: Good morning. My name is Arlene Solbeck and I am a regulatory review biologist in the Office of Nonprescription Products, Division of Nonprescription Regulation Development.

This morning I will present the history and the current status of the monograph for over-the-counter weight-loss drug products. First I will give a brief discussion of what an OTC monograph is and how it is established. Then I will briefly discuss the current status of the over-the-counter weight-loss control products for over-the-counter use.

In 1972 FDA began a review, which has come to be known as the OTC drug review, to evaluate the

safety and effectiveness of all OTC drugs. OTC monographs are part of this OTC drug review. When the OTC drug review began there were well over 100,000 OTC drug products on the market that needed to be evaluated for safety and effectiveness. These OTC drug products contained over 700 different active ingredients so, rather than evaluate each separate drug product, FDA determined that it would be more feasible to review them by therapeutic category and there are now about 100 therapeutic categories. Some examples of therapeutic categories are antacids, analgesics, antiseptics, laxatives, poison treatment and, for today's discussion, weight control--just to name a few.

OTC monographs are generated in a multi-step process. First, the active ingredients are initially reviewed by the advisory review panel composed of scientific experts from outside the FDA. These panels are somewhat analogous to modern-day advisory committees. These panels make recommendations that the ingredients and labeling

of OTC drug products be classified in one of three categories. Category I is for ingredients and labeling that are considered generally recognized as safe and effective. Category II is for ingredients and labeling considered not generally recognized as safe and effective. Category III is where the panel found the data was insufficient to classify an ingredient in either category I or category II, and the panel deemed that more data was needed.

Then the panel recommendations are published in the Federal Register in monograph form. These are the recommended regulations and rationale behind them. This first monograph is referred to as an advance notice of proposed rulemaking, or ANPR as abbreviated here on this slide.

Then FDA reviews the panel recommendations; seeks public comment from industry, consumers and other interested parties; and generates a proposed rule or tentative final monograph, which is abbreviated here on the slide

as TFM. This is FDA's first stated position on the safety and effectiveness of the different active ingredients.

The last step in the monograph process is to again seek public comment and additional data regarding the safety and effectiveness of active ingredients to formulate a final rule or final monograph, which is abbreviated here as FM.

In summary, the OTC monograph is a regulatory pathway for marketing OTC ingredients in drug products that have been recognized as generally safe and effective. It is a public process. It is ingredient specific, and the manufacturer can use these ingredients as per the specifications of the monograph without prior FDA approval.

For over-the-counter weight-control products a panel's report was published in 1982. The panel of experts that reviewed the submitted data was the advisory review panel and OTC Miscellaneous Internal Drug Products.

In their report, the panel evaluated OTC

weight-loss drug products for safety and effectiveness, and defined an OTC weight-loss product as an agent which reduces appetite and, thus, reduces or controls weight. You should note here that this definition reflects the fact that most of the ingredients being reviewed then were for appetite suppression.

The panel also recommended specific new statements for category I ingredients that could be listed on the labeling, and these are shown here, such as "helps control appetite" or "helps curb appetite." These also illustrate that the ingredients being considered at the time were primarily considered to be appetite suppressants. But I want to point out a couple which have more of a bearing on today's discussion. For instance, this one reads, "an aid to diet control in conjunction with a physician's recommended diet." The last one reads, "for use as an aid to control diet." In recommending these last two statements, the panel may have recognized that weight-control products could be used to assist consumers in their

weight-loss efforts by helping them control their diet in ways other than appetite suppression.

The panel recommended that the appropriate target population for these products was adult obese persons free of known underlying organic diseases. The panel described obesity as the type caused by overeating and sedentary lifestyle. The panel's exact definition of obesity, as stated in the report, is shown here and reads: an increase in body weight beyond the limitation of skeletal and physical requirements as the result of an excessive accumulation of fat in the body, that physical state in which the body weight in relation to height and body build is more than ten percent above the ideal weight determined from the Metropolitan Life Insurance Company table of desirable weights.

So, what is this table? This Metropolitan Life Insurance Company table of desirable weights was established in 1977 and is derived from actuarial data. These insurance statistics attempt to describe which desirable or ideal weight is the

weight for the height of the persons with the longest life spans, and those weights compose the table.

In their report, the panel stressed that significant weight loss can be achieved only if accompanied by reduction in daily caloric intake below the energy output. So, they recommended temporary use of such ingredients, and they recommended three months and in conjunction with a diet. The panel stated that three months was enough time to establish new eating habits.

The panel also recommended that the labeling contain the following statement: This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding three months because that should be enough time to establish new eating habits. So, in recommending this labeling, the panel recognized that behavior modification is a necessary part of weight control.

Regarding efficacy, the panel proposed some guidelines for determining the effectiveness of weight-control ingredients. The panel proposed that a 12-week treatment period would be sufficient to show weight reduction and maintenance. As I said previously, the panel felt that three months was sufficient time for establishing new eating habits.

The panel also proposed that the number of subjects in an efficacy study should be based on the assumption that if the study includes a diet, the average weight loss from a placebo product over a 3-month period would be approximately one 1.0 lb. per week, whereas the average weight loss from a test product over the same period should be approximately 1.5 lbs. per week, which is 0.5 lb. loss over the placebo.

Finally, the panel reviewed 113 ingredients and recommended that only two be classified as category I for weight loss. Those are phenylpropanolamine, which we nicknamed PPA, and benzocaine. The kinds of ingredients reviewed

were topical anesthetics, stimulants, nasal decongestants, vitamins and bulking agents, just to name a few. This did leave 111 ingredients remaining in categories II and III. So, after considering the recommendations of the panel and also public comments after publication of the panel's report, FDA did issue a TFM in 1990 to propose that the 111 ingredients be classified as not generally recognized as safe and effective.

This was finalized in 1990 and became nonmonograph. This left only two ingredients remaining in the monograph as category I. As I mentioned, these two ingredients that the panel recognized as category I were phenylpropanolamine or PPA and benzocaine. PPA and benzocaine were not included in the 1990 TFM and the 1992 final monograph because FDA was in the process of reviewing more data concerning their safety and effectiveness.

FDA recently published a proposed rule to reclassify PPA from category I to category II based on safety concerns. For benzocaine, a final

monograph is in progress that will address the adequacy of available data for benzocaine for weight reduction. FDA has reevaluated the data reviewed by the panel, as well as more recent data, and is reconsidering whether benzocaine should remain category I for efficacy.

In summary, the panel stated that OTC weight-control products are reasonable for temporary use, which they defined as three months, for assistance in weight reduction in an obese population and in conjunction with a diet. The panel recognized that a diet and other behavioral changes were important components of weight control.

In terms of category I ingredients, it is uncertain whether there will continue to be any ingredients in the weight-control monograph recognized as safe and effective for that intended use. Thank you.

DR. WOOD: Thank you very much. Before we go on, are there any questions that we have specifically for FDA? I guess I have one. It

seems to me that--I think this is probably for Eric--that it might just slip by that these drugs should not be used for cosmetic weight loss. Specifically, as you answer that, what are the indications for laxatives and, you know, should there be an indication that says not fewer than X bowel motions per week? It is not in there. Similarly for an Rx product like Viagra, should that say not fewer than so many erections per week? I mean, we are sort of taking this position that it shouldn't be used for cosmetic weight loss, and I understand the risk reduction issue, but for these other examples there is no risk reduction there.

DR. COLMAN: Yes, I think if you want to follow the precedent set with these other products you could certainly say that there is no reason you couldn't approve a drug for cosmetic weight loss. I think a lot of this obviously stems from the bad experiences that we have had over the years with obesity drugs. So, I understand that on the one hand there are people now who say, well, we have drugs approved for lifestyle enhancement, and it is

pretty difficult to quantitate the benefit and weigh it against the risk, but maybe it is safe to say that if I was the reviewer for those drugs I would have recommended non-approval.

DR. WOOD: Okay. Any other comments? Questions? Yes, Wayne?

DR. SNODGRASS: I have a question about the endpoint here. That is, there seems to be a 3-month, 1.5 pound per week, or something like that, kind of an endpoint. And, the data I am aware of from a lot of other studies from many years is that if you want to sustain weight loss maybe a pound a week at most or half a pound a week over a year or two years time and they take that long to achieve a significant weight loss, particularly somebody with a BMI greater than 30 and, yet, if our criteria are that it is 3 months or 6 months of use and a few pounds and then sort of imply that a large percentage of those patients will regain that weight after stopping, I would question kind of the criteria or endpoint we are using or what should be the expectation of an

effective treatment.

DR. WOOD: Is that addressed to anyone in particular?

DR. SNODGRASS: Perhaps someone at the FDA.

DR. WOOD: Eric?

DR. COLMAN: Do you want to summarize your question again?

DR. SNODGRASS: What is an effective weight loss endpoint? Is it that at the end of a year you have lost 25 pounds or 50 pounds? Or, is it that at the end of 3-6 months you have lost a few pounds and you think that a high percentage will regain that weight?

DR. COLMAN: Yes, the current guidance recommends that at the end of one year of treatment, if the mean weight loss in the drug-treated group is at least five percent greater than the mean weight loss in the placebo group we would consider that effective. Alternatively, if the proportion of patients who lost five percent of baseline weight is greater in drug versus placebo,

we would consider that an appropriate efficacy endpoint and conclude that that drug was effective.

DR. WOOD: That is going to come up in terms of the percent change with some of the doses. Right?

DR. WOOLF: I have a question. Are there data about either the intensity or duration of behavioral modification that is sufficient to sustain weight loss once a pharmacologic aid is withdrawn?

DR. COLMAN: Yes. Actually, later Dr. Golden is going to show some recent data that have been published that show a quite clear interaction in the effects of behavior modification with and without drug therapy.

DR. WOOLF: I am aware, but is a month of behavior modification sufficient? Three months? When does a patient have enough behavioral modification that they can have incorporated whatever it is they need to incorporate to keep their weight down?

DR. COLMAN: I don't have an answer for

that.

DR. WOOD: Let's hold that question and deal with that later. Is that fair? Dean?

DR. FOLLMANN: This is directed toward Eric. You mentioned earlier that you have this five percent criterion. I thought that was for prescription drugs and I was wondering if there was a distinction made in terms of a criterion for efficacy for over-the-counter drugs. On one of your slides you had sort of question marks where above you had five percent. So, is that an ambiguous area? Do you have guidance on that?

DR. COLMAN: Yes, this is the first time that the Division of Metabolic and Endocrinologic Drugs has been involved in a deliberation to make a weight-loss drug over-the-counter and the guidance document was solely focused on prescription weight loss. So, you will see numbers of five percent today presented because that is what we had for our prescription drugs but whether or not, for example, five percent weight loss has the same meaning in someone with a BMI of 25 versus 30 is a question

that I think needs to be addressed today.

DR. WOOD: Yes?

DR. CARPENTER: For Eric, in the early part of your presentation you presented a meta-analysis in which a statistically significant but not necessarily clinically significant difference appeared, I guess, in the amphetamine analysis. When statistical significance is evaluated in this setting does it have to apply to individual studies that were analyzed, or did that statistical significance emerge only with the meta-analysis combining all the studies?

DR. COLMAN: Unfortunately, I have never seen the final report of that project. I have seen some things that have been presented at meetings. Again, this study took place in the early '70s so I would imagine that statistical techniques were rather crude compared to today.

DR. CARPENTER: So, the follow-up is a standard that this committee should hold to is should it be individual studies or meta-analysis for this kind of judgment?

DR. COLMAN: You are speaking about today's deliberation. I think that is a question that needs to be discussed. We don't have an answer for it.

DR. WOOD: Yes, Dean?

DR. FOLLMANN: I would just amplify on that a little. For me, the issue is really going to be how big the difference is and whether that is meaningful either clinically or using some other criteria. If you have a big enough study, it will achieve statistical significance. So, even if you have a treatment that, you know, reduces weight by a tenth of a pound, if you have a big enough study you would show significance. So for me the big issue is the magnitude of the effect.

DR. WOOD: Well, I am not sure that is right. I think Andrea sort of addressed that in terms of an OTC switch. Remember, this is a drug that is approved already for Rx treatment so the issues that relate to today's discussion are really the ones that she outlined on her slides, I guess. Is that fair, Andrea?

DR. LEONARD-SEGAL: I think it is fair. I was also just going to comment, just as an addendum to your earlier question, that the over-the-counter environment does not have the same standard that was set in the prescription. Arlene Solbeck commented that the committee had recommended over 3 months 1 pound per week not under a drug and 1.5 pounds per week on drug over a 3-month period of time as their efficacy standard. That was back prior to 1982.

DR. WOOD: Curt?

DR. ROSEBRAUGH: I would just mention--and Charlie can add on to this--typically, if you are switching a drug from prescription to OTC and it is the same indication, I think the OTC folks feel that the efficacy criteria or the demonstration of efficacy should be the same whether it is prescription or OTC. So, it is kind of crucial to decide if it is for the same indication or not, and if it is we would have the same kind of criteria.

DR. WOOD: And one of the issues we are going to have to discuss is, is there a balance of

indications that is left after that indication is removed for Rx. Any other discussion? If not, we will move to the next presentation which is from Dr. Dent.

GlaxoSmithKline Presentation

Orlistat for Over-the-Counter Use

DR. DENT: Good morning. Prof. Wood, members of the joint advisory committee, members of the FDA, my colleagues are here today seeking your recommendation for the approval of orlistat 60 mg over-the-counter as a weight-loss aid.

My name is John Dent and I am a senior vice president of research and development at GlaxoSmithKline. As you have heard this morning, weight loss has long been recognized as an OTC indication but there are currently no FDA-approved products available without a prescription for weight loss. The purpose of our presentation today is to show you that orlistat is a safe, effective and appropriate drug to fill this important void; a tool to help people lose weight.

Managing one's weight isn't easy. If it

were, one-third of us wouldn't be overweight, and we are. It is costing the country over $100 billion a year. Two-thirds of Americans are obese or overweight. We are facing an overweight and obesity crisis in this country and it is not getting any better.

There is no magic pill for weight loss and orlistat is definitely not a magic pill. Orlistat is a tool that will help people control their calorie intake and modify their diet. Orlistat is not for everyone. Our target consumer is someone who is committed to losing weight and understands that it is a gradual process and is willing to modify their diet.

Orlistat is different from any other weight-loss drug. It is minimally absorbed. It has no known systemic effects. It has a remarkably good safety profile and, unlike previous OTC weight-loss drugs and current prescription weight-loss drugs, orlistat does not affect the central nervous system or have a negative impact on the cardiovascular system. It does not affect

appetite. It works by reducing the absorption of dietary fat, thereby decreasing calorie intake. It is most effective when it is used in conjunction with a low-fat diet.

Very briefly the history of orlistat, it was first synthesized in 1983. It was launched first in New Zealand and Argentina in 1998. It subsequently got approval in the European Union in 1999 and was approved by the FDA as a prescription weight-loss agent in 1999. In 2000 Roche Laboratories started a program to switch orlistat from prescription to over-the-counter. In 2003 they conducted an actual use trial. In 2004 GlaxoSmithKline licensed the rights to orlistat.

Orlistat is the most comprehensively studied weight-loss drug ever. Its efficacy and unparalleled safety have been documented in clinical trials involving over 30,000 patients in more than 100 different trials. In one study orlistat was studied in 850 people followed for four years. It has been used by more than 22 million people and is available in more than 145

countries.

Here are the components of our OTC label. The target consumer is the overweight adult. The proposed dosage form is a 60 mg capsule, taken one to two capsules up to three times a day with meals containing fat. This dosage range is designed to give consumers the flexibility so that they can get started slowly and learn how to modify their diet. This will help to minimize GI side effects and, in turn, increase compliance and increase the chances of successfully losing weight. The proposed indication is weight loss, and we are recommending six months of therapy, a time by which most people will have lost most of the weight they are going to.

We are proposing that OTC orlistat be indicated for both overweight and obese adults. You have already heard this morning that there is a distinction between overweight an obesity. Now, initially when Roche started their OTC development program, they were targeting orlistat only to people who were overweight, not obese. However,

two things were learned during the development program. Firstly, many people cannot accurately calculate their BMI even when they are given a chart. Secondly, people who are clinically obese, not surprisingly, consider themselves to be overweight.

Based on these observations, it became clear that separating these two populations for the OTC indication was an artificial distinction and so we agreed with the FDA that the indication should be expanded to include both populations, and realistically this makes good medical sense and it will allow the people who need to lose weight most the opportunity to use the product.

Now, as with many OTC development programs, the process is iterative and we used the feedback from our studies to inform the development of our label, especially after the actual use trial. The main changes were improvements in warning statements. However, it is important to point out that the majority of the key communications issues in our label remained

unchanged.

Orlistat will come with a wide variety of in-pack educational material that will help consumers to get the maximum benefit from the product. In addition, there will be a fee web-based support program which will be interactive, individually tailored to the user, designed to help them not only lose weight but maintain their weight loss.

With GSK's switch of nicotine replacement therapy in 1996 we gained experience in marketing products that require behavioral support. We have a demonstrated capability in maximizing the benefits and in minimizing any potential concerns, and we have a proven track record of promptly following up on and completing our phase 4 commitments.

In our presentation today Dr. Caroline Apovian will discuss the public health need for an effective OTC medication. Dr. Vidhu Bansal will discuss the extensive clinical program that demonstrates the safety and efficacy of orlistat

for weight loss. Dr. Saul Shiffman, an expert in behavioral research on how consumers use OTC medications, will tell you how consumers use orlistat. Mr. Steve Burton, vice president for weight control at GlaxoSmithKline, will summarize the behavioral support program that will help consumers receive the full benefits of orlistat. I will return to summarize and discuss our proposals to address and responsibly manage issues, in conjunction with the FDA, to ensure that orlistat can be safely used in an OTC setting.

We also have several national and internationally recognized experts to assist us in answering any questions that you have. It is now my pleasure to introduce to you Dr. Caroline Apovian, Associate Professor of Medicine and Director of the Center for Nutrition and Weight Management at Boston University Medical Center. Dr. Apovian?

The Public Health Need for FDA-Approved Weight-Loss Tool

DR. APOVIAN: Thank you. Good morning,

and thank you for the opportunity to talk to this panel about the largely unmet and urgent need for safe and effective tools to help Americans lose weight.

In the last 15 years that I have been doing research and treating patients in the field of overweight and obesity we have made tremendous progress. We have amassed an enormous body of data on the health risks of overweight and obesity, the benefits of weight loss, and on how to lose weight. But, as I will explain in this presentation, we still need wider access to a variety of evidence-based tools and strategies to help people use all that knowledge in the real world because knowing we need to eat less and move more is just part of the equation, putting those words into action can be very difficult, and 65 percent of our population is overweight or obese. We are losing the war against this epidemic.

These data from a recent Boston University School of Medicine study provide a look into the future. They suggest that over the long haul a

majority of Americans will become overweight and many will become obese. More than 4,000 white men and women, aged 30-59, were followed for more than 30 years as part of the Framingham heart study. Half of the people who entered adulthood without a weight problem ultimately became overweight. As you can see in these graphs, one in three people became obese, 30 percent men and women.

The fact is that you become obese by first becoming overweight. If we can help people who are overweight lose weight, whether they have risk factors or not, we can delay their progression to obesity and that is very important. The health risks of obesity are very well known. Less commonly known is that any amount of overweight can negatively impact health. Even in the non-obese population we see that increasing BMI is associated with an increased incidence of type 2 diabetes, cholelithiasis, hypertension and coronary heart disease.

The data on the left, from the Nurses Health Study, show that women with a BMI of 26 have

about a two-fold higher risk of coronary heart disease compared to women with a BMI less than 21. The data on the right are from the Health Professional Study follow-up, showing that men with a BMI of 26 were at 1.5 times greater risk of coronary heart disease than those with a BMI of 21. Note that the relationship between rising BMI and new onset diabetes is much steeper than that.

Clearly, we see that small amounts of weight gain can negatively impact health. Fortunately, small weight losses can have a positive impact. This summary slide shows that weight losses of between five to ten percent can significantly improve risk factors such as blood pressure, total cholesterol, HDL cholesterol and triglycerides. Because of data like these, we no longer believe that overweight and obese people have to lose large amounts of weight or achieve what we used to think of as an ideal body weight to see a positive health impact. In clinical practice we are moving away from the idea of a threshold for weight toward the concept of continued benefits for

each incremental kilogram of weight loss, as seen on the next slide.

In this meta-analysis, for every 1 kg or 2.2 lbs of weight loss significant improvements were seen in total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol, systolic and diastolic blood pressure. Based on data like these, healthcare organizations worldwide have adopted guidelines on the benefits of small amounts of weight loss. As Dr. Bansal will explain in her presentation, prescription orlistat was FDA-approved based on five percent weight loss as a marker of efficacy. Modest weight loss has also been shown to improve quality of life, co-morbidities such as sleep apnea, osteoarthritis, reflux, back pain, infertility and urinary incontinence.

Still, the reality is that many people find it very tough to lose even small amounts of weight. Staying motivated can be an enormous challenge. If they are trying and trying and aren't seeing results many people give up. In my

experience, this frequently leads to further weight gain and eventually to obesity. As a physician who specializes in weight management, I see the end result of this struggle, the tip of the iceberg, every single day. People who have been trying to lose weight for years but, instead, have kept gaining often develop co-morbidities. Remember, the vast majority of people aren't seeing physicians like me. They are out there struggling on their own.

The reasons for this have not really been studied. It may be that people feel that they should be able to lose weight on their own, or it may be embarrassment. Studies show that obese women are less likely to go to the doctor even for their routine screenings. It may be a cost issue. Insurance often doesn't cover weight management or weight-loss medications. Also, traditionally physicians haven't generally counseled their patients on weight loss. That is slowly changing but we, as a society, cannot wait for this; we have an obesity crisis. We need to provide people with

more strategies and solutions they can implement themselves right now.

Because even though there are no FDA-approved over-the-counter weight-loss aids, U.S. consumers are already spending a billion dollars a year out of pocket for nonprescription weight-loss products. Most are buying herbal and dietary supplements that make outrageous promises of quick and easy weight loss. People think that if it is being sold in a pharmacy it must be safe and it must work. But, in fact, many of these products contain ingredients of unproven safety and others may simply fail to deliver the promised benefit. Yet, people believe these unfounded claims and continue to buy these products. This tells me that there is a large unmet need for a proven safe, FDA-approved OTC weight-loss product.

In summary, overweight and obesity is a serious and growing epidemic in this country, putting our population at greater health risk than ever before. Fortunately, even modest weight loss can provide great health benefits. People are

trying to lose weight but not by going to see doctors. Instead, they are spending billions of dollars on unproven and potentially unsafe weight-loss products and it is clearly not working.

So, what can we, physicians, do about this? I believe we can and should become advocates for wide access to tools and products with proven safety and efficacy like orlistat. We need more drug options to treat overweight and obesity. We need to help people who are overweight lose weight before they become obese. Today we have an opportunity to help fill an important and currently unmet public health need for the consumer. Thank you.

Now I would like to introduce Dr. Vidhu Bansal, director of medical affairs at GlaxoSmithKline, who will present the efficacy and safety data on orlistat.

Safety and Efficacy--Orlistat 60-120 mg

DR. BANSAL: Good morning. I will present the efficacy and safety data that support the approval of orlistat OTC. The data support our

proposed indication, weight loss in adult consumers, and our proposed dose and duration, 60-120 mg to be taken for up to six months with meals containing fat.

I will begin with a brief overview of the 60 mg and 120 mg doses of orlistat; discuss its unique mechanism of action and efficacy at both doses. I will briefly show orlistat's impact on risk factors. I will also discuss the low potential of abuse and misuse with orlistat and show data that demonstrate orlistat's very well-established and favorable safety and tolerability profile.

We are seeking approval for the 60 mg capsule. It is the lowest effective dose. Our data demonstrate that the 60 mg dose meets the same criterion as the 120 mg dose. That is, a significantly greater proportion of subjects on 60 mg treatment achieved a five percent weight loss after one year compared to placebo. And, more relevant to our current label, orlistat 60 mg also meets this criterion at six months.

Orlistat works locally in the GI tract to limit the absorption of dietary fat. Normally triglycerides are broken down into fatty acids by pancreatic and gastric lipases so they can be absorbed in the small intestine. Orlistat inhibits lipases and blocks the digestion of up to 30 percent of dietary fat. As a result, roughly one-quarter or one-third of the fat calories are not absorbed.

Orlistat's mechanism of action results in some important benefits for the consumer. Unlike other weight-loss drugs, orlistat is not addictive. It has no negative impact on internal organs, including the cardiovascular system. It is minimally absorbed, by about two percent, and what little may be absorbed has no measurable effects on systemic lipase. Finally, since lipases have no feedback or compensatory mechanism, there is no residual effect once the drug is stopped.

In the next couple of slides I will show data that support our choice of dose. Here, we are looking at orlistat's effect at doses ranging from

30-400 mg as measured by how much fat is being excreted. At more than three times the 120 mg dose, there is very little additional excretion. That tells us that if somebody were to take more than the recommended dose they would get no additional drug effect. In this dose-ranging study weight loss at 60 mg and 120 mg was similar, and both were significantly greater at six months compared to placebo.

Doses below 60 mg were not efficacious and doses above 120 mg did not provide significantly greater benefit. Hence, we have chosen a starting dose of 60 mg to be taken with meals containing fat, with consumers having the choice to take two capsules if they wish.

I will now present our clinical studies. While both the 120 mg and 60 mg doses were tested, I will emphasize the 60 mg dose since the 120 mg dose has already been FDA approved. First I will outline the three controlled clinical studies that evaluated the efficacy and safety of orlistat for weight loss at 60 mg.

Study BM14149 was conducted in Europe. I will refer to this as the European two-year study. Study NM14161 was of similar design and duration, with a similar population of obese people. I will call this the U.S. two-year study. Study NM17247 was conducted following a request from the FDA to measure effects of orlistat in people classified as being overweight. I will refer to this as the U.S. lower BMI study. A key point to note is that the placebo group was an active comparator since subjects taking placebo were on a hypocaloric diet.

These studies were designed to test and quantify the additional weight loss achieved by adding orlistat to a low calorie diet. It is important to look at levels of dietary intervention in these studies to see if consumers will know how to take the drug in the OTC environment where levels of intervention are low.

In the European two-year study subjects got individualized nutritional counseling. That consisted of a review of a food diary and specific changes to be made to their diet once a month by a

dietitian, and they were advised to exercise.

The U.S. two-year study was done in a primary care setting where staff had no specialized expertise in treating obesity. Subjects received no nutritional counseling. They did receive written materials and were offered videos on healthy diet and exercise to use at their discretion. The written materials were similar to those we provided in our actual use trial and will provide in the OTC setting.

The U.S. lower BMI study had the least amount of intervention. There was no nutritional counseling; no specialists or dietitians on site. Subjects were handed reading materials about healthy eating and lifestyle, materials that the lead investigator, Dr. Jim Anderson, described as a "do it yourself" binder.

Regardless of the degree of intervention or overweight, the weight loss seen across all studies was similar and significantly greater with orlistat plus diet compared to placebo and diet.

Both the European and U.S. two-year

studies were placebo-controlled, double-blind, randomized, multi-center studies. Each had a four-week lead-in period where subjects were placed on a hypocaloric diet for the duration of the study. After the lead-in period subjects were randomized to receive placebo, 60 mg or 120 mg plus a hypocaloric diet.

In looking at the results of the European two-year study, this graph presents the percent change in body weight from baseline for the three treatment groups over a one-year treatment period. The orlistat plus diet groups at both the 60 mg and 120 mg doses had significantly greater weight loss than the placebo plus diet group. Furthermore, most of the weight loss occurred by six months, our proposed duration, and the efficacy of 60 mg and 120 mg is generally comparable up to six months as well.

Importantly, the results were similar in the U.S. two-year study. Even though there was a lower level of dietary intervention in this study, orlistat plus diet at both the 60 mg and 120 mg

doses had significantly greater weight loss than placebo plus diet. Orlistat also showed a positive impact on risk factors such as blood pressure and lipids.

Looking at the categorical analysis for the European two-year study as reflected in the responder rate on this table, the 60 mg dose at six months meets the same criterion for weight-loss drugs typically applied by the FDA to one-year data. Specifically, a significantly greater proportion of subjects on 60 mg and 120 mg treatment groups achieved at least a five percent weight loss compared to placebo. Orlistat 60 mg also meets the standard at one year, which isn't shown.

We see a similar pattern in the U.S. two-year study, again, significantly more subjects achieving at least a five percent weight loss compared to placebo at six months. Thus, we have two studies in which the 60 mg dose at six months achieved this criterion.

At the request of the FDA, Roche designed

an additional study to confirm that the pattern of weight loss in overweight subjects would be similar to that seen in obese subjects. The lower BMI study was a U.S.-based study in a primary care setting which had minimal dietary intervention. Only self-instructional materials were provided. There was no run-in period. Subjects were directly randomized to receive placebo or 60 mg of orlistat plus a hypocaloric diet. This study was 16 weeks in duration.

This study was designed and powered to determine if there was a significant difference between subjects on 60 mg of orlistat plus diet and subjects on placebo plus diet in mean weight loss over time. Significant weight loss was seen with 60 mg compared to placebo in the overweight population at four months. The mean weight loss seen was five percent. This is similar to what was seen in the studies I just presented in the obese population. I must emphasize that this study was not powered or designed to demonstrate the categorical weight-loss criterion for prescription

drugs.

Importantly, a significant improvement in risk factors, such as total cholesterol, LDL cholesterol, systolic and diastolic blood pressures was seen in this overweight population at four months, as shown on this slide.

Responding to the FDA's concern about weight loss in people with a BMI below 30, we have done an additional analysis supporting the efficacy of orlistat in the overweight population. This information is not provided in your briefing book.

We separately analyzed the data of overweight and obese subjects from the six-month clinical trials I just presented. All of these studies included the 60 mg and 120 mg doses. Using the categorical analysis as reflected by the responder rate to demonstrate efficacy, we found significant drug effect with both doses in the overweight and obese populations--overweight; obese. In other words, a significantly greater proportion of subjects on orlistat 60 mg and 120 mg in the overweight and obese populations had at

least a five percent weight loss compared to placebo.

To summarize the efficacy data, orlistat provided significantly more weight loss than placebo across all studies regardless of baseline BMI. This was true for the six-month studies, illustrated on the left, and the four-month study, illustrated on the right.

Turning now to orlistat safety, extensive clinical trial data and market experience show that orlistat has a very well-established and favorable safety profile. Overall, it has good tolerability; low withdrawal rates; low potential for drug interactions; and minimal impact on fat-soluble vitamins. The incidence of non-GI AEs was comparable in all treatment groups, as shown in your briefing book.

Some people on orlistat experienced GI side effects. Since orlistat works by inhibiting 25-30 percent of dietary fat, in the 60 mg group we see a consistently lower incidence of GI changes compared to the 120 mg group. For some events the

difference was significant. These effects are manageable by eating a low fat diet. They stopped after they stopped taking the drug. They mostly occurred and resolved within the first few weeks of treatment when people are still adapting to a low fat diet.

DR. WOOD: Before you leave that slide, can you go back one? How would somebody be counted here with fecal urgency and oily spotting? Do they appear separately, and is there a cumulative counting for all of these?

DR. BANSAL: I believe they appear separately. Whatever GI adverse event is considered the worse in severity is the one that appears; is one that is counted.

DR. WOOD: So, tell me which is worse, oily spotting or fatty oily stool? How do I make that judgment?

DR. BANSAL: It is dependent on the subject and how the reading was deemed by the primary investigator.

DR. WOOD: So, oily spotting--this is a

key issue, so oily spotting should be added to fatty oily stool to give you 35 percent? Is that right?

DR. BANSAL: No, I don't think--

DR. WOOD: Well, if you are only counting--

DR. BANSAL: I don't think that is true.

DR. WOOD: So, these must be double counted. Go through it again because I am still not clear. So, if you had oily spotting, that is the only time you appear on this table? Is that right?

DR. BANSAL: No, that is not correct.

DR. WOOD: Alright, then walk us through it more carefully because that is key.

DR. DENT: Prof. Wood, could I ask Dr. Jonathan Hauptman, who is the medical director for Roche, to elaborate on this point for you?

DR. WOOD: Sure.

DR. DENT: Thank you.

DR. HAUPTMAN: We looked at each individual adverse event and if a person had it, we

would include it there. If you totalled all these GI adverse events in looking at an individual that had any of them, the total percent was around 50 percent. They could have one or more. This just breaks it up as how many had fecal urgency; how many had fatty/oily stool. Then, if you actually would pool how many patients had any of these, it came to about 50 percent which meant, of course, that 50 percent didn't have any of these.

DR. WOOD: Right. But the point I am getting at is that presumably you could have fecal urgency, oily spotting and flatus with discharge all at different times during this six-month period.

DR. HAUPTMAN: And they are counted as an individual event for that patient.

DR. WOOD: Okay. Then when you see the 54 percent, that is anyone who had any of the above at any time during the six months. Right?

DR. HAUPTMAN: That is correct, 50 percent.

DR. BANSAL: We chose 60 mg as our

recommended dose for OTC because it demonstrates similar efficacy to the 120 mg dose and is more tolerable. In the 60 mg treatment group there were fewer GI side effects overall. There was significantly lower likelihood of experiencing effects within the first four weeks. And, within the first week there were one-third fewer side effects.

These findings are important. They demonstrate that the 60 mg dose is significantly more tolerable than the 120 mg dose for some GI side effects, especially in the early weeks of treatment when consumers decide whether to continue with the drug is right for them.

Overall, withdrawal rates were low and usually adverse events were not the reason for withdrawals. When adverse events were the reason, they were usually GI-related but, importantly, the vast majority of subjects with GI adverse events continued on orlistat.

For subjects on the 120 mg dose the withdrawal rate to GI adverse events was 5.4

percent and with the 60 mg dose it was 3.2 percent. This speaks to the high tolerability of orlistat in general and further supports our choice of dose.

Consistent with other orlistat trials, the highest rate of withdrawal was seen in the placebo group. This is believed to be related to the relatively low rate of efficacy for subjects on placebo.

Looking now at other safety issues, since prior diet drugs have been associated with a history of misuse and abuse we have looked at this issue extensively with regard to orlistat. We have not found any significant safety concerns. The data show that consumers would not be at any significant safety risk if they exceeded the proposed recommended dose. Studies with doses up to 1200 mg a day did not lead to an increase in adverse events. There is no dose-dependent or subjective effect with orlistat, and exceeding the proposed label dose does not result in additional efficacy.

As orlistat is not centrally acting, this

provides further safety reassurance. Furthermore, in use by more than 22 million people worldwide, there were seven spontaneous reports of overdose. No safety concerns were found. In a review of the worldwide literature, there have been four case reports of misuse. These four cases were in adult bulimics and there were no safety concerns related to the excessive use of orlistat in these cases. There have been no published reports of misuse by anorexics or teens.

Turning to the area of vitamins, based on its mechanism of action, orlistat slightly interferes with the absorption of fat-soluble vitamins but the effect of orlistat 60 mg and vitamin absorption at six months, our proposed duration of use, was very minimal. The mean values for these fat-soluble vitamins from multiple controlled clinical studies, with no vitamin supplementation, were consistently within the normal reference range. The incidence of two consecutive below normal vitamin levels was relatively low in the orlistat group at both doses

after six months of treatment.

As a prudent measure, the OTC label will instruct consumers to take a multivitamin daily two hours before or after taking the orlistat. Even if consumers take a multivitamin with orlistat much of the fat-soluble vitamins will be available for absorption.

Based on the mechanism of action and minimal systemic absorption, orlistat has a low potential for drug interactions. The only documented drug interactions on the prescription label are with cyclosporine and warfarin. A pharmacokinetic study has documented a mean 30 percent decrease in cyclosporine levels with concomitant use of orlistat. In a review of the literature and Roche worldwide safety database, there have been reports of low cyclosporine levels in association with orlistat use. Importantly, most of these cases had no clinical consequence for the patient.

The orlistat prescription label instructs to take the two drugs at least two hours apart to

prevent the reduction of cyclosporine levels in the blood. The OTC orlistat label will instruct consumers taking cyclosporine not to take orlistat.

In a review of the literature and Roche worldwide safety database there have been reports of elevated PT or INR levels in people taking orlistat and warfarin together. Therefore, the proposed orlistat OTC label instructs warfarin users to ask a doctor or pharmacist before using orlistat. Orlistat does not interfere with diabetes medications but people who take them may need to have dose adjustment as a result of changing their diet. This is the reason for the "ask a doctor or pharmacist" warning regarding diabetes medications on our label.

No clinically relevant drug interactions were seen when orlistat was taken in conjunction with other weight-loss products. However, no other published studies were found evaluating concomitant use of orlistat with other weight-loss products. We didn't see any drug interactions with phentermine or sibutramine. This is the reason for

"ask a doctor or pharmacist" warning on the label of our OTC label. Overall, there is very little potential for drug interactions with orlistat.

In summary, orlistat has been used successfully by millions of people in 145 countries, and studied in more than 100 clinical trials. In all clinical trials where weight loss was assessed orlistat plus diet was always significantly better than placebo and diet alone. Orlistat 60 mg has a safety and tolerability profile suitable for OTC use.

Now Dr. Saul Shiffman will present the results of our research on consumer use of orlistat.

DR. WOOD: Just before you get to that, you want everybody to take this drug with multivitamins? Right?

DR. BANSAL: That is correct.

DR. WOOD: Why haven't you packaged the multivitamin or don't you propose packaging a multivitamin with the product given that, you know, a fair number of people in the actual use study

don't end up taking the multivitamin? Wouldn't that be a better approach? Explain to me why you haven't taken that approach.

DR. DENT: May answer that question, Prof. Wood?

DR. WOOD: Yes.

DR. DENT: There are a number of components in answering that question. First of all, multivitamins and orlistat as an OTC drug have different labeling requirements. One is a dietary supplement; the other is a drug. Secondly, about 50 percent of the American people already use a multivitamin. If we co-package a multivitamin with orlistat, that may not be the multivitamin that people who buy orlistat want to use. Thirdly, there are logistical problems in the sense that you have to make sure that the expiry date of both products lines up at every point in time. So, what we do plan to do is include coupons in orlistat as it is sold over-the-counter which will be another way to encourage people to take a multivitamin with orlistat.

DR. WOOD: That doesn't sound very convincing to me. I mean, why the expiry dates are different--I mean that is not an issue. You can cope with that surely.

DR. DENT: Well, it is quite difficult to handle because of just the logistics. GlaxoSmithKline as a company doesn't have a multivitamin line that is appropriate.

DR. WOOD: So, the reason you can't get the expiry date right and you couldn't license a multivitamin--

DR. DENT: No, that is one of the reasons. There is also a problem with co-packaging because the labeling is different and you have to be able to see the label on the outside of the package. The third reason is that 50 percent of people already take a multivitamin. Let's say we co-package orlistat with whatever multivitamin and that is not the multivitamin that people are using, from their perspective that is an additional cost and a waste. So, we will include coupons that give people a discount on multivitamins within the

package.

DR. WOOD: But in your experience, about 25 percent didn't take multivitamins. Right?

DR. DENT: People coming into the actual use trial--50 percent of them were already using a multivitamin and an additional half of the remainder also started using multivitamins. So, there were 25 percent of the total who reported not taking a multivitamin with orlistat.

DR. WOOD: So, the system didn't work in 25 percent of the people.

DR. DENT: Twenty-five percent of the people did not take a multivitamin with orlistat as we encouraged them to.

DR. GOLDSTEIN: Alastair, one additional comment, there are matters related to manufacture and date of expiry that also, according to regulation, require a line-up, as Dr. Dent put it, and that would be an additional obstruction to this kind of approach of co-packaging.

DR. WOOD: Well, you can assign any expiry date you like. You can always bring the expiry

date down. So, I mean that is a ludicrous suggestion. Ruth, you had a comment?

DR. PARKER: Yes. You presented a very colorful slide about the plethora of products available for weight loss over-the-counter. I wondered if you could clarify are these drugs or products? You know, this would be the first one that is FDA approved and presumably everything else is not FDA approved but is available over-the-counter. So, this would be a drug and not a product and all this other plethora are--if you could just kind of clarify that. When I heard that I thought, gosh, there are a gazillion things out there over-the-counter for weight loss. We see them all the time, but sort of why FDA approved versus not, what is the status of that?

DR. APOVIAN: I was talking about the nutritional supplements. They come under the DSHEA Act, the nutritional supplements, and they are generally products of unproven safety and efficacy because they don't come under the same restrictions as FDA-approved over-the-counter products, as you

know.

The problem that I see with the consumer, as I said in my talk, is that many consumers don't understand the difference between an herbal supplement and, for example, an FDA-approved over-the-counter supplement. They think that if it is sold in the pharmacy it must work and it must be safe. I see many patients coming into my office who are on some of these herbal supplements. They very honestly tell me about them as if I thought that they were appropriate to use. So, I am very concerned about this.

DR. LEONARD-SEGAL: Dr. Parker, can I just make a clarification for you on this? Currently there are no FDA-approved over-the-counter weight-loss drugs. These products that they are referring to are dietary supplements that are out there. Our Division has nothing to do with them but people probably are availing themselves of their use.

DR. WOOD: Dean?

DR. FOLLMANN: Yes, I would like to ask a

question or two about slide CC-46 which was a combination of the three trials where you lumped the results by BMI. This is something that you hadn't prepared in the packet I believe.

One question is you have a cut point of BMI of 26.7. Was that just the lowest BMI observed in all the studies, or why that peculiar number?

DR. BANSAL: Yes, that 26.7 was the lowest BMI observed in those studies.

DR. FOLLMANN: Now, the two long-term studies had a run-in period and more extensive educational material, whereas the low BMI U.S. study had no run-in period and less educational materials. From my point of view, you know, it is not just the drug itself but the milieu of the environment, the instruction, etc., that we are evaluating here. So, there is an issue of lumping these.

Another question I had is for the 26.7 to 29.9 group, what percentage of those patients were from the low BMI U.S. study? If you don't have that now, if you could get that? Is the question

clear?

DR. BANSAL: The question is clear. I would like to first clarify. The three studies that we looked at that were pooled were the two long-term studies and the dose-ranging study. It was not the lower BMI study because that was a four-month study and I couldn't get results for six months. This was looking at studies that were at least six months in duration and had the 60 mg dose.

Secondly, to answer your question, looking at the percent of people who were at the lower end of the BMI range, about 20-25 percent of people were at a BMI 26.7, 27, the rest were 28 or higher.

DR. FOLLMANN: Thank you.

DR. SCHAMBELAN: I just wanted to clarify again the difference the consumer would experience in looking at a package for something which had gone through this process versus a supplement that hadn't. So, if you go to Costco, Walgreens or somewhere else you see a huge array of products. I obviously don't read the package when I buy my

ibuprofen.

DR. LEONARD-SEGAL: Over-the-counter drugs, drugs that we have approved, first of all the label contains a medical indication. A product that is not approved that would fall into the realm of a dietary supplement would have a different kind of an indication. It should be something along the realm of promoting health. I don't know what is on these products per se and maybe you can clarify some of the indications that you find on some of these dietary supplements, but that would be the difference. If a product makes a medical claim, then by definition it is a drug and it should have gone through this approval process.

DR. DENT: I would like to ask Mr. Shifkovic, regulatory director at GlaxoSmithKline, to give you a perspective on the sort of claims that are on DSHEA products.

MR. SHIFKOVIC: Just to reinforce what Dr. Segal had said, the dietary supplements that are out there do have a qualifier on them that says that they are not making a medical claim. But the

ingredients are sometimes kind of hidden and it does get to indications that are not appropriate for those products as dietary supplements. So, they sometimes kind of masquerade as drugs just in the kind of claims that they have but they clearly are not reviewed and approved the same way that drug products are.

DR. PARKS: Can I add something to that? Regarding the dietary supplements and over-the-counter drugs, on our side of the table here, we are not aware whether there is any data so that consumers can really make the distinction between a dietary supplement or an over-the-counter drug. I don't know if the applicant has any data to clarify that point.

DR. DENT: As we haven't got an OTC approved drug yet, we don't have any data for that. But it would be likely I think, given that it would be clearly advertised as the first FDA-approved over-the-counter weight-loss aid, that it should allow consumers, I think, to distinguish between something that is approved and something that is

merely under the DSHEA umbrella.

DR. WOOD: I guess one take-home message is that all these things that are advertised--if this was to be approved, the FDA needs to act more vigorously against some of these other compounds.

DR. LEONARD-SEGAL: I would just add that I think that this is a global problem for the over-the-counter drug group of products. We are always grappling with this. I believe it involved potentially some of both committee members who were involved with the lovastatin meeting. I think it came up at that meeting also that there are products that people take to reduce cholesterol, that that would be a drug claim. To promote healthy--who knows what--lipids in the body, or some such thing might be a dietary supplement claim. There are ingredients in some of these dietary supplements that do overlap but the problem is that the distinction is in the claim, not in the ingredient. It is something that we grapple with all the time.

DR. WOOD: Dr. Woolf?

DR. WOOLF: Nowhere in the materials that were given us, nor in Dr. Bansal's presentation, do we see data that the weight loss is either a fixed amount or proportional to baseline. Do people who are heavier lose more weight, or is it the same five percent across the board irrespective of starting weight?

DR. BANSAL: We saw a similar baseline body weight change whether overweight or obese and it was about five percent.

DR. WOOLF: So, heavier people didn't lose more?

DR. WOOD: Maybe lost more absolutely--

DR. BANSAL: Yes, absolute.

DR. WOOD: --but not more in proportion, is what she is saying. If I understand the answer, the answer is they lost a greater absolute amount of weight but the same proportion of weight.

DR. BANSAL: Yes.

DR. WOOD: Neal?

DR. BENOWITZ: In the European and U.S. two-year studies, you showed us data from one year.

Would you happen to have a slide of the body weight over two years of those two studies?

DR. WOOD: While you are looking for that, Ms. Coffin, did you want to say something?

MS. COFFIN: I just wanted to echo the confusion that is on the panel of doctors. The patients that are out there or the overweight individuals that are out are consistently confused with the labeling and with the packaging and they don't have an option otherwise. So, keep that in mind. As you guys are confused, you have a lot more knowledge and experience in dealing with overweight and obesity than the average U.S. citizen does.

DR. WOOD: Okay. You have an answer?

DR. DENT: Yes. Dr. Hauptman, please.

DR. HAUPTMAN: I don't have a slide to show that specific study but I do have a slide that shows long-term weight loss over four years, which I think might answer your question. Can I have the slide on, please?

This is a study that we did. It is a

3,300 patient parallel group, placebo-controlled study in Sweden looking at obese patients who are treated with diet and exercise and placebo or orlistat over four full years. What the data clearly show is that you see a decrease in weight over time. The maximum weight is about six months, maintained at 52, and over the rest of the time period you see that the drug effect, the orlistat minus placebo effect, is maintained, which you would expect from a drug that remains active but what has failed here is the diet and exercise portion so you see this increase over time, certainly not to baseline or below it but it is the diet and exercise portion and not the drug effect that seems to diminish. I hope that answers your question.

DR. BENOWITZ: Can you clarify, in the two-year studies was orlistat given for one year or for two years?

DR. BANSAL: In the two-year studies orlistat was given for two years. The first year it was given with a hypocaloric diet to look at

weight loss. For the second year it was given with a eucaloric diet. Patients were re-randomized after the end of the first year to either placebo, orlistat 60 or 120 with a eucaloric diet to look at weight regain.

DR. BENOWITZ: Why are there no data from that study available? I am curious to know if someone takes orlistat for a year and is followed up a year later is there a change in body weight that persists?

DR. WOOD: Why don't we hold that answer and let's move on to the next speaker, and then we will come back because we have a long time for discussion after that?

DR. GOLDSTEIN: Alastair, I think that one important thing that the panel must be aware of is the difference in the regulatory scheme. Products like herbal supplements and the advertising of that is regulated by the FTC, the Federal Trade Commission, sometimes in consultation with the FDA depending upon the product. But the FDA regulates all aspects of prescription drugs and the

scientific aspects, medical aspects, if you will, of over-the-counter products. But products such as the doctor mentioned, the herbal products, are Federal Trade Commission and the advertising of OTC products is also Federal Trade Commission, again with available consultation which is often the case with FDA.

DR. WOOD: Okay. Let's more on to the next speaker.

Consumer Understanding and Use in OTC Setting

DR. SHIFFMAN: Good morning. I will be presenting data on how consumers would use orlistat in a real-world setting. For clarity, I will organize the data in the context of six key questions that are critical for deciding for any drug whether it would be an appropriate over-the-counter product. Here you see those six questions, which may be familiar to you. They echo some of what Dr. Leonard-Segal showed you in her presentation.

First, can consumers recognize the OTC condition, in this case being overweight? Then, do

consumers understand the product labeling? Do they self-select appropriately? That is, do they follow the warnings on the label and correctly decide whether or not the product is right for them? Do they follow the instructions for using the product? And, when they use the product without the supervision of a physician, do they use it safely? Finally, are people satisfied with the product, its results and its tolerability?

Here is a preview of what you will see in the presentation. Data confirm that people do recognize their condition; they know when they are overweight. Studies show that people understood the orlistat label very well. Initial data showed poor self-selection. Some people incorrectly said that they could use the product. I will discuss this concern and how GSK is addressing it through label enhancements; through additional studies; and through programs targeted to the issues and populations of most concern. Finally, the data show that when people used the product on their own they used it correctly, safely and in accordance

with the label, and that they were satisfied with the results and with the product.

So, now let's look at the data, starting with an overview of the program. The orlistat OTC behavioral research program consisted of a series of studies, which are in your briefing book but I will focus on the most relevant studies which I will first show you in the order that they were conducted.

First, there was an actual use trial. This trial was conducted to see if consumers could correctly decide whether the drug was appropriate for them and to see how they would use it in a simulated OTC environment. I will also present data from label comprehension study #4 which tested consumers' ability to understand the product label which had evolved from the label used in the actual use trial. I will show you data from three additional self-selection studies which were conducted in specific populations and conditions of concern to test enhancements to the label. Finally, I will also show you data from a survey of

the U.S. population showing that people can recognize when they are overweight.

It is important to note that the self-selection studies and the survey were submitted to the FDA after the NDA was filed so the agency may not have had a chance to review them. So, with that as background, let's go to the questions for OTC consideration and we will review the data question by question.

So, the first question, are people able to identify whether they are overweight? Here we turn to data from a random-digit dial survey to collect a sample of U.S. adults. In the interview people were asked if they thought they were overweight. Their BMI was then calculated based on their self-reported height and weight and the data showed that those who self-identified as overweight generally were, 88 percent had BMI 25 and over; 11 percent had BMI 20-25; and one percent were below 20. Thus, the vast majority correctly self-defined as overweight according to official criteria. So, people can judge when they are overweight.

The next question for an OTC product is whether people understand the label. The methodology for label comprehension study #4 was standard for label comprehension studies. People were presented with the label and were given a series of scenarios in which they were asked if it was okay or not okay to use the product in each case, or what they should do in each case. There was a general population sample and a low literacy sample in the study, and you also see here the basic study demographics.

So, this study specifically tested whether by reading the label consumers understood the key label components--the indication; who should use the product; the directions for dosing; and the warnings or exclusions.

This table summarizes the comprehension that we saw in the general and low literacy populations for key communications objectives regarding use of the product. The data show across domains that comprehension was generally very good in both populations but with some slightly lower

values. I won't spend much time on these now but we can discuss them at greater length later.

Let me just briefly show you that people also understood the label warnings and exclusions very well, that is, who should not use the product, and that was true and consistent in both the general population and the low literacy population.

So, the next question is can people correctly determine if the product is appropriate for them? For that, we turn to the data from the actual use trial. In the actual use trial participants were recruited through community pharmacies by ads in the pharmacy and in the local paper. Subjects were given an orlistat OTC package and asked to decide if they could take the product or had to ask a doctor. Then a medical history was taken to see if they were right, that is, if they had any of the conditions or exclusions listed on the label.

Just a brief look at the study demographics, the sample that presented for the study was predominantly female, middle aged and

white and in these respects resembles the samples in most weight treatment studies. Overall, out of 681 subjects, 543 said that they thought that it was appropriate for them to use orlistat.

Before going into the self-selection results in detail, let me remind you that the actual use trial was done on a prior version of the label. While all of the warnings you see here were included in the label in the actual use trial, the ones on the left are no longer on the current proposed label. Recall that they were there in the first place, the ones on the left, to identify and exclude people who were obese or had obesity-related conditions. But as you heard from Dr. Dent, the FDA agreed that since orlistat is a weight-loss medication it should be available to obese as well as to overweight people. Accordingly, these conditions are no longer on the label, whereas these conditions, on the right, remain on the current label.

So, let's look at the self-selection results. First we will look, within the subset of

people who had a labeled exclusion, at the decisions that they made. So, the denominator are people with a condition or exclusion. Of the people who had any exclusion on the AUT label, only 23 percent made correct decisions to select out of orlistat. The detailed results by condition are in your briefing packet, but the self-selection rates didn't vary that much across conditions.

For the warnings on the proposed label the correct self-selection rate was 29 percent so this is the percent of people with conditions who made correct selection decisions. Let's go back though and look beyond the subset of people who had exclusions at the full sample of 681 people in the trial, focusing here on the conditions or exclusions that are on the current proposed label.

What you see is that the vast majority of people, 82 percent, didn't have a labeled exclusion that would limit their use of orlistat so orlistat was appropriate for them and they present no cause for concern. The remaining 18 percent had a condition or exclusion, and 29 percent of this

total, amounting to five percent of the entire group, made correct decisions, either saying they could not use orlistat or that they had to ask a doctor. So, altogether then 87 percent of the people presenting did not present any concern. They either reacted appropriately to their conditions or they didn't have a condition that raised any concern with orlistat. The remaining 13 percent of the total incorrectly thought that orlistat was okay despite having a labeled condition.

So, let's look at that 13 percent shown here condition by condition. This shows the number of people who made an incorrect selection decision as a percentage of the full sample of 681. Importantly, regardless of frequency, the exclusions that were of most concern were cyclosporine and warfarin users where the actual use trial only had a small number of cases.

So, to address concerns about cyclosporine and warfarin GSK modified the label to improve correct self-selection and retested it in samples

of persons with these conditions. Let me describe how the label was changed and what the self-selection results were based on the revised label.

For cyclosporine, GSK made the cyclosporine warning more prominent. First of all, it was broken out into its own bullet point and moved to the top as the first and presumably the most prominent warning. The label also explained what effect orlistat might have on cyclosporine to give consumers a clear reason to comply.

GSK then tested self-selection based on this new label in a sample of transplant patients on cyclosporine. Now, because there are relatively few transplant patients on cyclosporine, the research used the sample from around the country identified from a national online research panel and 46 cyclosporine users were enrolled and asked to evaluate a weight-loss product. Very importantly, they did not know that they had been selected because of their transplant and cyclosporine status to avoid sensitizing them or

biasing their responses. So, they looked at the orlistat label online and made a self-selection decision and 89 percent of cyclosporine users correctly indicated that the product was not appropriate for them. This represents good self-selection.

But because it still isn't perfect and this is such an important issue, GSK is proposing a program targeting transplant patients to ensure appropriate patient selection, and you will hear Dr. Dent describe that program shortly.

Similarly for warfarin, the label warning was highlighted by placing it on its own line with its own bullet point. It was also changed to "ask a doctor or pharmacist" because the issue with warfarin is that the people on warfarin need to be monitored and warfarin sometimes needs to be adjusted.

To test self-selection on this revision, 54 warfarin users were identified from clinical databases and they were again asked to review a weight-loss product, again without knowing why they

had been selected. After reviewing the label 72 percent appropriately said that they would have to ask their doctor or that they couldn't use the product at all. This was an improvement over the prior result of 50 percent. However, to boost compliance with this warning, GSK is planning a program that will include putting stickers on warfarin prescriptions warning about orlistat use. Dr. Dent will, again, be describing that program.

Finally, there were two additional groups that weren't formally on label warnings but for whom self-selection could potentially be an issue. One was teens and one was adults who might not be overweight or might even be underweight.

Starting with teens, even though orlistat has been proven to be safe and effective for teens, GSK felt that teen use should be under supervision of a physician so teens are excluded on the proposed label. To see whether teens would be interested in orlistat and whether they would select the product or buy it, GSK conducted a self-selection study among teens 14-17 years old.

Recruitment was via flyers for weight loss. You see the flyer here. And, placement of the flyers was specifically concentrated where teens hang out--stores like Abercrombies, Hollister, Claire's. You may not know these stores but as a father of teen girls, I can tell you they are teen magnets. Flyers were also placed in video arcades, high schools, and so on, again targeting teens.

Strikingly, despite the targeting the majority of people who responded to the flyers were adults--

[Laughter]

--all told, we recruited 147 teens who became the participants in the self-selection study. So, the 147 teens who had responded to the flyers were shown the label and 59 percent correctly indicated the product was not appropriate for them. Conversely, 41 percent thought it was. But when they were offered a chance to purchase the product, much as the participants in the actual use trial had been, only 13 percent expressed an interest in buying it. Among the 13 percent

interested in purchasing, two-thirds were at or above the 85th percentile of BMI for age, that is, they were classified as overweight or at risk for overweight. Conversely, one-third were considered normal weight. In other words, this amounts to 4 percent of the teens who responded to the ads and, importantly, none of those teens were underweight.

Another way to understand what is going on is to look at what the teens said why they thought orlistat might be for them, and you see here some of their verbatim responses. What is striking is that their responses indicate a reasonable approach to losing weight. Many of them talked about healthy dieting or liked the fact that it had a behavioral program.

So, keeping in mind that orlistat has been tested in teens and shown to be safe, that orlistat has no central nervous system effects, no subjective effects at all, and provides no immediate feedback it seems unlikely to be of sustained appeal to teens. Importantly, even if some teens do use orlistat, there really are no

significant safety issues.

Finally to determine whether orlistat would appeal to people who are not overweight or were even underweight, we can turn to the actual use trial. When we analyzed the BMI distribution of subjects who self-selected in the actual use trial we see, very importantly, that none of the self-selectors were underweight; 92 percent were overweight by official BMI standards or obese, and most of the remaining 8 percent were at the upper end of normal. This is reassuring because it suggests that orlistat largely appeals to the right segment of the population in terms of weight.

Now let's move on to talking about how people actually use the product. And, this is perhaps the most important question in testing an OTC product, do people use the product correctly once they take it home and use it on their own without supervision?

The usage phase of the actual usage trial addressed this question. The actual use trial was a three-month open-label study. People were

offered a chance to purchase orlistat and 237 bought and used it and were studied in the actual use phase. Now, when people purchased the product, in addition to the capsules themselves, they got a set of educational and behavioral material, some of which you see here--a food diary, a user guide, a dietary planner and other materials. What they didn't get was any instruction or counseling whatsoever. So, this was meant to model an OTC purchase where you pick up the product, take it home and use it on your own.

To collect data people were called by phone at 14, 30, 60 and 90 days or to the point where they had stopped using orlistat. The median duration of use was 77 days and a little over half of the sample used the product for the full 90 days.

Now let's look at how people actually took orlistat. This shows the number of occasions per day that people took orlistat as reported on day 14 and day 90. You can see that the vast majority of people reported using orlistat two to three times a

day, consistent with the labeling. In fact, 95 percent said that they used orlistat with meals as directed.

Consumers also followed directions for how many capsules to take on each occasion, shown here. Most people took one 60 mg capsule with each meal and some took two, as permitted by labeling. The use of two capsules per meal increased slightly here over time, consistent with the idea that people would learn how to manage the medication and the diet. But note that almost no one took more than two capsules on any occasion and, in fact, only one person ever took more than six capsules a day, which is the maximum stated on the label. So, people followed the directions when using orlistat.

Now, looking at whether subjects also followed other elements of the label that direct behavior change, we found that they generally did. They increased their vitamin intake. As you have heard, 75 percent or roughly three-quarters used a multivitamin. They modified their diet and increased exercise. Most people used the self-help

materials and found them helpful.

These findings are important because they show that people understood orlistat was not a magic weight-loss pill. They understood that the program required effort and behavior change on their part too. So, the actual use trial shows that people used the medication according to directions and made other behavioral changes as well.

Now, correct use of the product is, of course, related to product safety. To the question did consumers use the product safely when they used it without supervision of a physician, the data showed a benign safety profile, consistent with the controlled clinical trials and consistent with orlistat's non-systemic mode of action.

There were six serious adverse events and two were deemed possibly related to orlistat and these resolved without consequence. About 70 percent of participants had some adverse event during the study and, as we have already discussed, about half the participants experienced changes in

defecation patterns that can occur when eating a high fat meal while on orlistat.

Let's look at how people responded to these orlistat-specific adverse events. Remember, half of the subjects in the actual use trial didn't experience a defecation related event at all. One-third who did continued to use the product without interruption. Eight percent managed their events by temporarily stopping orlistat use and then resuming, and only nine percent of people discontinued because of an orlistat-related GI event.

So, the question is whether people found these events manageable and what is striking is that experiencing these GI adverse events was not correlated with dissatisfaction with the product, suggesting that people did find these manageable.

Patient satisfaction, conversely, was correlated with the amount of weight people lost. The vast majority of people said they were satisfied with orlistat and the number one reason they gave was that they had lost weight. Now, the

actual use trial was not designed or meant as an efficacy trial but people were asked how much weight they had lost each time they were interviewed. Over the trial, progressively more subjects reported losing weight and throughout the trial the vast majority of people were satisfied with orlistat. So, the actual use trial showed that people used orlistat in an appropriate way; they lost weight; and they were satisfied with their weight loss.

So, to conclude and summarize, the data show that people are able to identify when they are overweight. Both general and low literacy populations clearly understood the orlistat label. In the areas where self-selection was poor in the actual use trial and where it was considered a concern GSK has made changes to the label to improve self-selection, and has tested and validated those changes in additional studies. Further, GSK is developing programs to address these concerns. When consumers do use orlistat on their own, they use it properly; according to the

label; and with good safety and tolerability results. Finally, consumers reported losing weight and were satisfied with the product.

Thank you for your attention, and let me introduce Steve Burton who will discuss GSK's proposed consumer education and behavioral support programs.

Orlistat's Consumer Education and Behavioral Support Program

MR. BURTON: Thank you, Dr. Shiffman and good morning. You have heard about the science of orlistat and its potential for helping millions of people lose weight. The question I want to answer is how--how do we ensure that consumers actually experience the full potential, the full benefit of increased access to OTC orlistat?

We should recognize that achieving meaningful weight loss and consumer satisfaction in the real world will depend on more than simply product performance alone. Success will also depend on consumers having realistic expectations about what orlistat can do, as well as what they

need to do for themselves. Success will also depend on consumers getting support and the motivational tools to help them make the behavioral changes necessary for weight loss, again, in the real-world setting, and that is what we, at GSK, intend to provide, the appropriate messages and the appropriate tools to help people lose weight and make behavioral changes in an OTC setting.

Turning first to the messages that we will convey, because of the way that orlistat works orlistat communications will need to be candid, even to the point of being blunt. So, we will tell consumers that weight loss with orlistat is gradual and modest, and takes an effort on their part; that it will take effort to adopt a healthy eating plan and that you have to limit your fat intake to see efficacy and avoid the treatment effects that can accompany OTC orlistat. But here is the payoff: The orlistat program can be a powerful motivator to adopt a healthy eating plan and get more exercise, and if you do that orlistat can help you lose more weight than dieting alone. So, our message will

not be simply pop a pill and the weight is simply going to fall off. Our message is going to be that you can do it and orlistat can help.

Turning now to the resources that we will provide, OTC orlistat will be more than a package of pills. It will be a program that includes tools for changing behavior. The package will look like this. The medicine is on the right side and the six reference guides that are on the left. Consumers will also receive a carrying case for a day's supply of capsules. You can see that here above the medicine bottle on the upper right-hand corner.

The proposed brand name, pronounced Alli, conveys that the program is Alli with diet and exercise and GSK's role is to partner with the consumer who is committed to behavioral change in order to lose weight.

Here is a more detailed look at the support materials that will accompany the orlistat package with purchase. These guides are all pocket size so that you can carry them around with you and

they include a guide to starting the program; a 54-page handbook on how to use the product; a healthy eating and food shopping guide; a fat and calorie counter; and a daily journal because studies have shown that recording what you eat is very important in terms of helping people adopt and stay with a weight-loss plan. These materials have been reviewed by experts and were submitted to the FDA for their review, and they will also be available to consumers in Spanish.

In addition, consumers can also enroll in a free online behavioral support program that lasts for one full year. This program uses concepts from experts and established weight-loss guidelines to provide consumers with 24-hour individualized advice. Many studies and our own experience with the nicotine gum and the nicotine patch have shown that customized behavioral support is much more effective than generic self-help materials. So, based on what information consumers provide, literally millions--millions of unique versions of this program are possible, allowing consumers to

get weight-loss advice that is tailored to their own specific needs.

Let me explain the difference between the first half and the second half of the program. During the first six months we will help consumers lose weight with two lessons delivered on a weekly basis. These will cover topics like goal setting, proper use of the product and preparing a low fat eating plan. We will also monitor label heeding with this program.

During the second six months we will provide a customized exercise plan since studies show that exercise is the critical component in maintaining weight loss. This component of our program is unique and significant, and we will provide resources and follow-up for an additional six months after the product use has ended. We want people to hold on, as much as possible, to the weight loss that they have experienced during the first six months.

I would like to address the concern that OTC options might diminish the role of the

healthcare professional. If anything, we intend to increase it. As you have heard from Dr. Apovian, the reality, today at least, is that most people are not talking to their providers about weight loss. We discovered in the switch of the nicotine gum and nicotine patch to OTC status that doctors and patients were actually more likely to engage. They were more likely to talk to each other about smoking cessation options. Patients asked their doctors about how the new OTC products, and doctors used time efficient tools that we provided them to make sure that they very effectively counseled their patients on what new options were available.

So, we will equip doctors, nurses, pharmacies and dietitians with all the information that they are going to need to answer weight-loss questions and help their patients decide whether OTC orlistat is right for them.

In a moment Dr. Dent will talk about our post-marketing plans for orlistat but here I want to emphasize that we have the experience not only in making these commitments but also in following

through on them. After the switch of nicotine replacement therapy to OTC status we delivered on a number of commitments, importantly including targeting the right audience. In this case, it was smokers who were committed to becoming smoke free. With OTC orlistat we plan to choose advertising and advertising that targets adults. We also worked with the FDA to ensure that access was appropriate and that consumers were compliant with the label, and we monitored the actual use for six years based on concerns about misuse and abuse. We went on to publish these findings and, since misuse and abuse were not observed, GSK and the FDA eventually determined that these extra measures were no longer necessary.

In summary, GSK has the product, the program and the experience to help people change their behavior and lose weight. We are committing to promote gradual and modest weight loss that is a sensible alternative to the less regulated options that promise overnight results often without substantiation. Our goal is to help consumers

achieve meaningful weight loss in the short term and increase their chances of maintaining a healthy lifestyle long term.

Now Dr. Dent will return and talk about specific post-marketing plans for orlistat.

Summary and Commitments

DR. DENT: As the most comprehensively tested weight-loss drug ever, we believe orlistat is a really important tool that should be readily available to people who are trying to lose weight. However, we have identified some potential issues and we need to address these in the OTC environment.

Before we conclude the presentation today, I would like to discuss our proposals to address these concerns in specific populations. These proposals have not been reviewed or agreed with the FDA. They relate to two groups of people who might use orlistat, transplant patients taking cyclosporine and people on warfarin.

There are very few reports of an interaction between orlistat and warfarin or

orlistat and cyclosporine and the real risk may be theoretical. However, since this interaction could be medically significant, we feel that it is prudent to provide layers of safety net to minimize, if not eliminate, the risk of an untoward interaction. These safety nets will include enhancing the warning on the label; conducting new targeted educational outreach to pharmacists, educating them about the potential for the interaction; providing orlistat warning stickers to pharmacists to use when dispensing warfarin and cyclosporine; and, in addition, incorporating an orlistat warning in the patient information pamphlets printed by the pharmacist. We have already spoken to heads of major retain chains like Wal-Mart, CVS, Walgreens and Target and they are willing to support such a program.

With respect to cyclosporine specifically, we will work with transplant centers to ensure that the information about orlistat is included in the educational material that patients receive at discharge. We believe we have identified the most

significant potential risks and that we have successful safety nets in place to mitigate them.

In addition to our proposal to manage potential risks, we are committed to responsibly marketing orlistat to our target audience because for consumers to be successful in losing weight with orlistat, they have to use it properly, and for GlaxoSmithKline to be successful in marketing orlistat, we have to market it properly. This means not over-promising; it is a program, not a magic pill. Orlistat used in conjunction with a low fat diet results in gradual sensible weight loss. We must ensure that consumers understand that behavioral change is critical to success in losing weight. We will advertise appropriately targeting committed adults who are willing to follow a program.

So, let's review briefly what we have heard today. Orlistat is non-systemic. It is minimally absorbed. It does not affect the CNS system. It has no adverse cardiovascular effects. It is not addictive. It is not an appetite

suppressant; it is not a stimulant.

Orlistat is a tool that reduces the absorption of fat and calories. It is clinically proven to be both safe and effective, and people lose weight on orlistat in a sensible, gradual fashion. In addition, in an OTC environment orlistat can be safely used by consumers and they are satisfied with it.

Let's step back for one moment and recall why we are here. You heard today that there is an urgent unmet need for a safe product to help people lose weight. By 2008, it is estimated that three-quarters of the American people will be overweight or obese. Making orlistat available OTC will increase people's access to and utilization of a proven safe and effective weight-loss aid. I will fill a critical gap.

Thank you for the opportunity to present our data to you today. We are looking forward to answering your questions. Prof. Wood, if you would indulge me, could I go back just once more and address the question of vitamins?

DR. WOOD: Sure.

DR. DENT: I think I need to emphasize that when orlistat was first brought to the market the full impact of its effect on vitamins was not well understood. Subsequently we have gained a much better understanding, and the proposal to include multivitamin use with orlistat is very much a prudent measure. The actual effects of orlistat on vitamin levels in a very big clinical trial are rather small. If you would allow me, I would like to ask Dr. Hauptman, from Roche, just to review for you what happened in the Xenical four-year study to the levels of vitamins in unsupplemented people.

DR. HAUPTMAN: I will be very brief. As we said, in these studies what you saw is some data from before. They were four-year double-blind, placebo-controlled. Patients were taken off vitamin supplements four to eight weeks prior to entering and only if they had two consecutive values below the lower reference range they were to get a supplement. The data show that there were small but standardly significant decreases in many

of the vitamins over time, but these mean levels remained within the reference range and few patients were below.

I think the data that I will show you will really show what happens. Here, on this slide, we did several more vitamins than we did previously. Here we have 25-hydroxy vitamin D, as well as 125-vitamin D. When you look at it over time in the non-supplemented what you see is a small decrease that occurs generally by six months, and probably even by three months. Then it reaches a new steady state. And, there are very few differences over the rest of that four-year period. 25-hydroxy is important because that is the storage form for vitamin D; 125-dihydroxy vitamin D is the active form and, again, we see some small decreases but generally they parallel each other chronically over time.

DR. CARPENTER: I would like to comment on that if you could go back to the vitamin D slide. The normal range shown there for the 25-hydroxy vitamin D levels is not what is standardly accepted

today. I am reading those as nanomoles/meter units and although they are closer to what the U.S. units of nanograms/ml are, the lower limit of acceptability of that value today is in the 40-60 range of that scale. So, I would submit that those patients are borderline vitamin D deficient, unless there is some--you know, some glitch in the way the slide was labeled.

DR. HAUPTMAN: Two points, this was based on a reference range of obese Swedish subjects, and not based on the U.S. database, and so we actually came up with a reference range based on that, on people not on a diet. But what we do know about obese patients--if I could have slide 44--is that obese patients have differences in 25-hydroxy vitamin D levels.

This was a study done by Bell looking at what happens in 25-hydroxy vitamin D, 125 and PTH in the obese versus the non-obese population. We see a decrease in 25, a slight increase in 125, both significantly different in the non-obese, and an increase in PTH. So, although those levels that

we showed you are lower than the U.S. population they are not different than the obese population reference range. Nevertheless, it is also well accepted that obese people are less likely to get osteoporosis. I can show you some additional data on what happens on lower vitamin D levels in patients who may be compromised patients, if you want to discuss that in the discussion period.

So, just briefly to go back to our next vitamin slide, here we have both vitamin A and vitamin K1. We hadn't measured K1 previously. For vitamin A essentially there is no difference over this entire four-year period between orlistat and placebo. Again, even though the total reference range may be different than the standard reference range in the United States, we are comparing the orlistat group on diet and exercise versus the placebo group on an equivalent diet.

For vitamin K1, and there are two components of K. K2 comes from the gut bacteria, the other one comes from food. Again, you see this decrease that occurs, maximum effect by six months

and then a new steady state is reached over time.

Finally vitamin E, which is on the next slide--

DR. WOOD: Just before you leave that, you put a lot of effort into this interaction with warfarin, right? Why is that? Why does this drug interact with warfarin? It interacts because of the effects of vitamin K.

DR. DENT: It does not directly interact pharmacokinetically. You are correct, Prof. Wood, and we are concerned that it has a potential to interact with vitamin K. So we are really taking a very prudent approach in recommending that people--I beg your pardon, an additional consideration is that anybody who is already on warfarin and changes their dietary status ought to be in discussion with their physician anyway as they may require a modification in their warfarin dosing.

DR. WOOD: But we are making recommendations about warfarin because of the potential for the change in vitamin K absorption.

Right?

DR. DENT: We are making the recommendation for the change on the basis of the fact that they are changing their diet so they may be changing their vitamin K, and also they are changing their weight. So, as they change they really ought to be discussing that with their physician.

DR. WOOD: But you have not been overwhelmed by the vitamin K data yourself in terms of absolving yourselves from the recommendation about warfarin. Right?

DR. DENT: Well, we don't believe that there is a very large effect on vitamin K, as Dr. Hauptman just showed you. We think it is prudent that people should discuss their warfarin dosing with their physician.

DR. SCHAMBELAN: More importantly, did you monitor PT levels during your trials of people who were on warfarin? If so, what was the magnitude of the difference?

DR. WOOD: They did do it. That is a

coarse measure.

DR. SCHAMBELAN: More coarse than vitamin K levels?

DR. WOOD: Than some of the subsets, but that is actually in the FDA presentation I think.

DR. DENT: Would you like Dr. Hauptman to address that specifically?

DR. LEONARD-SEGAL: I guess that what I can say at this point is that you will hear more about this from FDA, but I think it is important for the committee to know that there are products over-the-counter now that have warfarin warnings because they are p450 products. Cimetidine is an example and miconazole containing vaginal antifungal products is an example. I think it may also be on the prolisac OTC label. I would have to double-check that. So, it is not foreign to the over-the-counter environment to have a warfarin warning on an over-the-counter drug--just for your background information.

DR. BENOWITZ: A follow-up on the warfarin question, it is my understanding that the drug

interaction study was done in 16 weeks. This slide shows a drop in warfarin at six months. Is a 16-week trial adequate to reflect this change that was seen at six months in vitamin K? I might imagine vitamin K depletion might take some time and might not be apparent in a shorter-term trial--or 16 days; the other trial was 16 days.

DR. DENT: I am sorry, your question is for the warfarin interaction study was 16 days duration--would that be long enough to see the effect?

DR. BENOWITZ: Yes, because the slide you showed on vitamin K showed a decline at six months, and I might imagine that it might take a while to see vitamin K depletion once you start to lose it.

DR. WOOD: Let's come back to that. Dr. Dent, can you wrap up what you wanted to say now so we can take a break?

DR. DENT: We are done.

DR. WOOD: You are?

DR. DENT: Yes, thank you.

DR. WOOD: In that case, we will stop and

then we will come back to your question after the break. We will be back here at 11:10, please.

[Brief recess]

DR. WOOD: Let's get started again. We are going to start with the FDA presentation. Dr. Golden?

FDA Presentation

Safety and Efficacy Review

DR. GOLDEN: Good morning, Chairman Wood, members of the committee. My name is Julie Golden and I am a medical officer in the Division of Metabolic and Endocrine Products. I will be discussing our perspective of some of the efficacy and safety issues in this application.

I will start with some background information. Next, I will discuss the studies that were reviewed for this application. I will present the efficacy of the 60 mg and 120 mg doses; how the findings fit into FDA's efficacy criteria; and discuss issues of treatment duration and lifestyle modification. Next, I will discuss some of the safety issues with orlistat and then I will finish

with some conclusions and issues that you may wish to consider in your deliberations.

So, first some background information. Dr. Colman discussed the definitions of overweight and obesity by the NIH guidelines and I won't repeat them. However, I will emphasize that the overweight population, that is, 25 to 29.9 kg/m

2,

is where a big focus of our discussion will be. I would like to also suggest that we divide the overweight population into low overweight and high overweight for the purposes of this presentation. This is because the studies supporting this NDA utilized these different populations in different studies and, in one sense, a question that we are posing to you relates to the efficacy and benefit in this low overweight population.

Let me start with reviewing the sponsor's proposal for nonprescription orlistat and comparing this to the prescription product. GlaxoSmithKline, the sponsor of the nonprescription product, acquired the marketing rights to the 60 mg dose from Roche, the sponsor of the 120 mg prescription

product. Glaxo also has a chart comparing the two products in their background package. This chart, which is somewhat different, is intended to emphasize the overlap between labels.

The proposed indication for the nonprescription product is the promotion of weight loss when used in conjunction with a reduced calorie and low fat diet. The prescription indication is obesity management including weight loss, wight maintenance and prevention of weight regain when used in conjunction with a reduced calorie diet. The sponsor has proposed a target population of overweight adults. This is in contrast to the regulatory or clinical definition of overweight as defined by BMI. Overweight in the nonprescription setting is to be defined by the consumer. As you will hear from Dr. Feibus, the actual use study demonstrated that subjects self-selecting as overweight fit into both the overweight population as well as the prescription population. The prescription population is those who are obese, as well as those with a BMI greater

than or equal to 27 kg/m2 with other risk factors. So, I would ask you to consider who you think the appropriate target population for this product is as we continue.

The sponsor has also proposed a six-month duration of therapy. Dr. Colman has presented some history of why the medical community and the Division treat obesity as a chronic condition, and I will present some longer-term data as well and would ask you to consider the appropriate duration of therapy.

Finally, the dose proposed is less than that of the prescription product, 60 mg, although individuals will be instructed to titrate the dose as tolerated. The efficacy and safety of the 60 mg and 120 mg doses will be considered.

Dr. Colman also discussed NIH's guidelines for the management of overweight and obesity, and this is also in your background package so I will just mention that FDA's criteria for prescription drug use mirror these guidelines. While weight loss in patients with BMIs less than 27 kg/m2 or

overweight but otherwise healthy individuals may be perceived as beneficial to the individual, the recommendation for drug therapy must consider the risk of any drug side effects and whether those side effects will counterbalance the benefits of weight loss. If the benefits of weight loss in a low risk population are modest or only cosmetic, then the safety concerns of drug therapy may no longer make pharmacotherapy a prudent treatment approach in this subgroup.

FDA's draft guidance for the clinical evaluation of prescription weight-control drugs considers a drug effective if at the end of one year of treatment the mean percent weight loss from baseline in the drug group minus the mean percent weight loss in the placebo group is greater than or equal to five percent, or the proportion of subjects who reach and maintain a loss of greater than or equal to five percent of baseline body weight is statistically greater in the drug group than in the placebo group. The prescription approval for orlistat was based on achievement of

the second criterion.

A five percent benchmark was chosen as the minimum amount of weight loss that is considered associated with certain meaningful clinical outcomes in obese patients such as improvements in lipids, blood pressure and glucose tolerance.

Before getting to the clinical studies, I would like to make a few comments regarding how orlistat works, specifically the pharmacodynamic and behavioral modification effect of the drug. Clinical pharmacology studies conducted by Roche for the approval of prescription orlistat demonstrated that orlistat 60 mg is associated with approximately 25 percent fecal fat excretion, and orlistat 120 mg is associated with approximately 30 percent fecal fat excretion. So, this means that essentially the more fat there is in the diet, the greater the drug effect. Someone consuming a diet of 40 percent fat will experience a higher proportion of daily calories being excreted than someone consuming 20 percent fat if both individuals have the same amount of daily caloric

intake.

Of course, not all of the weight loss achieved with orlistat may be attributable to the pharmacodynamic effect. There is some thought that non-compliance with a low fat diet leading to adverse gastrointestinal side effects may promote favorable dietary modification. This may, in and of itself, reduce weight but only if the individual does not compensate for the reduction in fat calories by increasing intake of carbohydrate or protein.

One might also conjecture that some people will avoid taking orlistat when they know they will be going out in a social situation or eating a high fat meal in order to avoid embarrassing GI effects. We know that three to five percent of subjects in the first four to six months of treatment discontinue orlistat due to GI side effects as compared on one percent of placebo-treated subjects.

In any event, clinical studies show that the incidence of orlistat related gastrointestinal

side effects is similar across different amounts of weight loss, indicating that the pharmacodynamic effect of the drug may have more of an impact on those who are less compliant with dietary change, and the effect of the diet may have more of an impact on those who are compliant with dietary change.

In support of the nonprescription NDA the sponsor provided analyses of three studies, the designs of which you have already heard so I will quickly review. Two of the studies were performed in support of the original prescription NDA, BM14149 and NM14161. These studies were pooled by the sponsor despite having different levels of lifestyle intervention.

Randomization occurred after a four-week placebo lead-in period, during which time subjects lost a mean of about 2.6 percent of their body weight. At day one subjects were randomized equally to placebo, orlistat 60 mg or 120 mg and then continued in this randomization for the duration of the study. Randomization was

stratified by whether the subjects lost greater than or less than two kilograms during the lead-in period.

The nonprescription efficacy time point was six months. The prescription efficacy time point for weight loss was one year, and the prescription efficacy time point for weight maintenance was two years.

A third study, NM17247, was a four-month study in the low overweight population, that is, BMI 25-28. This study did not have a lead-in period. Subjects were randomized to placebo or orlistat 60 mg for four months.

This table illustrates further details about these studies. There were about 200 subjects per group. You notice that the number of subjects in the four-month study was a little bit less than the number of subjects in the prescription studies. BMI range for BM14149 was 28-43 or higher overweight and obese; for NM14161 it was 30-43 or obese; and for NM17247 it was 25-28 or low overweight. All prescribed diets were hypocaloric

and were comprised of 30 percent fat. BM14149 utilized dietitians and had a more personalized dietary plan. Estimated total energy intake was calculated and then 600 calories were subtracted from this value. Study NM14161 had two prescribed levels of caloric intake, 1200 calories for those less than 90 kg and 1500 calories for those greater than 90 kg. Study NM17247 provided slightly more calories for men than women for each level of starting weight.

The educational program was clearly different between the two pooled studies from the prescription NDA. BM14149, as stated before, utilized dietitians and regular collection of food records was used to provide feedback. NM14161 occurred in the primary care physician offices where subjects were provided general encouragement but no specialized counseling. The program was designed to be self-instructional and videos were viewed by the participants several times during the study. The four-month study, NM14247, was designed to be self-instructional although it utilized the

study staff to provide encouragement and feedback based on returned food records.

This table demonstrates the rates of completion in the studies at the various time points. More orlistat-treated subjects completed the study than placebo-treated subjects, and these completion rates are pretty good for a weight-loss study.

This table demonstrates that in the prescription NDA pooled studies very few subjects were in the low overweight group at baseline. Therefore, only study NM17247 allows us to evaluate the efficacy of orlistat 60 mg in this low overweight population.

I started with the presentation of categorical weight loss as this was the criterion used to support regulatory approval for the prescription product. The first set of bars represents the six-month results for the pooled prescription studies in the high overweight and obese BMI ranges. As you can see, both orlistat doses are significantly greater than placebo in the

percentage of subjects with at least five percent weight loss, with approximately twice as many subjects reaching this benchmark in the orlistat-treated groups than in the placebo-treated group.

Because study NM17247 only went out to four months I have included the results of the pooled studies at the four-month time point as well for comparison. Again, in this group of subjects from the pooled studies with the BMI range 28-43 kg/m2 approximately twice as many subjects treated with orlistat achieved the five percent benchmark than those treated with placebo and these findings were statistically significant.

To contrast these findings, we see for the four-month study, NM17247, in subjects with the low overweight BMIs of 25-28 that subjects treated with orlistat 60 mg do not meet the benchmark of five percent to a statistically significantly greater degree than those treated with placebo.

DR. WOOD: Do you have any explanation for that? The difference between these studies is in

the placebo group really.

DR. GOLDEN: Right.

DR. WOOD: Yet, this is the study with the least intervention.

DR. GOLDEN: Well, I have a few comments if I can speculate about this placebo group. In terms of the dietary intervention, I would actually say that the level of intervention was probably somewhere in between the two prescription studies because while it was a self-instructional approach, subjects did complete food records, bring them back, and did get some feedback based on those food records from the study staff, whether it would be the primary care physicians or other people in the clinic. They were not dietitians though as in one of the prescription studies.

Another reason for this may be because there was no lead-in period. So, you know, both groups may be higher because they had those four weeks to attain that five percent. But that doesn't necessarily tell us anything about why this isn't that much higher than this one.

Again, this is just to speculate, but potentially a third reason may be the BMI. It may be that subjects with a lower BMI may be better able to diet; may be more active so just may do better on a dietary program than people in this obese population. Again, that is my own personal speculation.

This plot illustrates the full range of weight range by treatment group. The next slide will show you the values of placebo-subtracted weight loss. Again, the prescription studies were evaluated at six months and the nonprescription study was four months in duration. There was a greater weight change in all groups in the study with intensive dietary intervention as compared to the study with less dietary intervention.

These are the adjusted mean differences from placebo. You can see that in the low overweight population the placebo-subtracted weight loss was about 1.1 kg at four months. Weight change was higher in the higher weight populations after six months. The treatment effect was also

notably higher in the study with less dietary counseling. In this study also the treatment effect of the 120 mg dose was greater than the 60 mg dose and this was not the case in the study with intensive dietary intervention.

I will now present some data that addresses the issue of weight regain both in subjects that remained on orlistat for up to two years, and perhaps more relevant for this nonprescription proposal, what happens to individuals who are on the drug and then discontinue it. In all the studies out to two years that I will present subjects were on a hypocaloric weight-loss diet for the first year and then were switched over to a eucaloric or weight maintenance diet for the second year.

First I will show you what happened to the weight in the subjects in the pooled studies from the NDA when followed out for two years. These subjects remained in their treatment randomization for the duration of the study. I will then show you some data from a study done for the original

prescription NDA. The study was published in JAMA in 1999.

Subjects were randomized to placebo or orlistat for one year, then in the second year the subjects on placebo remained on placebo and the subjects on orlistat received either placebo or orlistat.

Here are the two-year data for studies BM14149 and NM14161. These graphs are from the FDA's statistical review in your background package. The Y axis is the weight change in kilograms from baseline. At 52 weeks the diet and educational program was changed to support weight maintenance rather than weight loss. The continuation of orlistat for two years clearly demonstrates drug efficacy over placebo in both studies although all groups, including the orlistat groups, experienced mean weight regain. Furthermore, the study with less dietary counseling, NM14161, experienced more weight regain in all groups as compared to the study with more intensive dietary counseling, BM14149.

This two-year study, published in JAMA in 1999, as I said, was based on a study conducted by Roche in support of the prescription NDA. The study design included a four-week placebo lead-in period after which time subjects were randomized to these groups. Subjects were either given placebo or orlistat 120 mg for one year, and then the orlistat groups were either given orlistat 120 mg, 60 mg or placebo for the second year. I will be focusing on subjects who were either on orlistat 120 mg or placebo for two years or on those subjects who were on orlistat 120 mg for the first year and then were switched over to placebo for the second year.

The first year subjects were on a weight-loss diet and the second year focused on weight maintenance. Dietary instruction was undertaken with the use of dietitians, food records and behavior modification sessions.

So, this is the figure from the JAMA article. Again, in the first four weeks all subjects participated in a four-week placebo

lead-in period. This line represents weight change over two years in the placebo-treated subjects. This line represents weight change over two years in subjects treated with orlistat 120 mg over two years. In the subjects that were treated with orlistat 120 mg and then switched over to placebo in the second year we can see that there was gradual weight gain over the second year, such that at the end of two years subjects were approximately at the same place the placebo subjects were. And, this was the best case scenario in which dietitians and behavioral modification were also likely a major factor in maintaining some amount of weight loss in this time period. In addition, these are completers data so the figure does not include the weight change of subjects who dropped out early.

Let me take this opportunity to stress that overweight and obesity are chronic conditions and, like drug treatment of other chronic conditions like hypertension or dyslipidemia, once you stop the drug you lose the benefits of the drug. In the case of weight-loss drugs, this means

lost weight is regained and improvements in co-morbidities reversed.

This brings me to a final point in efficacy, and that is the importance of lifestyle modification concurrent with pharmacotherapy. A study using sibutramine, the other FDA-approved drug for long-term weight loss, in this recent paper in the New England Journal of Medicine, is an example of this concept.

Briefly, this was a randomized, controlled trial of 224 obese adults who were assigned to one of four weight-loss treatments for one year: sibutramine plus intensive therapy; sibutramine plus brief therapy; intensive therapy alone; and sibutramine alone. In the drug therapy groups subjects met with a primary care provider eight times for about 10-15 minutes at each visit. In the intensive they groups subjects met with trained psychologists in a group setting 30 times for about 90 minutes at each visit. Drug therapy plus brief visits involved only a primary care provider but required subjects to complete food and activity

records and received feedback on these records.

These results demonstrate that subjects who received combined therapy lost more weight than subjects in the other three groups. Subjects treated with standard sibutramine plus brief therapy and those treated with lifestyle modification alone lost more weight than those who received sibutramine alone, underscoring the importance of lifestyle modification in combination with drug treatment. To quote the authors, they state that these findings provide strong support for recommendations that weight-loss medications be used only as an adjunct to a comprehensive program of diet, exercise and behavior therapy.

With that, we will turn our attention to safety. The primary data that the sponsor provided in support of safety were those studies that included an orlistat 60 mg arm. This included three studies from the original prescription NDA which the sponsor pooled. I will discuss these studies further in the next slide. The safety profile was also supported by study NM17247, the

four-month study in low overweight subjects and these supportive studies. BM14150 was a six-month dose-ranging study conducted for the original NDA. There were also two uncontrolled studies, a three-month actual use study, which you will be hearing more about from Dr. Feibus, and a four-week consumer use study.

Other safety data reviewed in support of this application included post-marketing data in the FDA Adverse Event Reporting System, or AERS, published literature and the FDA review of the original prescription orlistat NDA.

This table describes the three studies that were pooled for safety. I already discussed the study designs of studies BM14149 and NM14161 during the efficacy discussion. NM14302 was a year-long drug study conducted in subjects randomized after six months of dietary therapy. Treatment arms were placebo, orlistat 30 mg, 60 mg and 120 mg. In contrast to studies BM14149 and NM14161, subjects in study NM14302 received a daily multivitamin.

Fat-soluble vitamins and drug interactions are the safety issues of most concern with orlistat and I will be primarily focusing on these for this discussion. I will also briefly mention pancreatitis as it is an issue that is currently under review in the Division. Although gastrointestinal adverse events such as fatty and oily stool are common in subjects taking orlistat, I won't be focusing on these adverse events during this presentation because they are primarily tolerability concerns.

As you know, the fat-soluble vitamins A, D, E and K and beta-carotene depend upon dietary fat for absorption. The studies from the prescription NDA monitored vitamin concentrations and I will present some of the results for A, D, E and beta-carotene here. Vitamin K adequacy was monitored in these studies using prothrombin time as a surrogate and will be discussed under the context of warfarin use. There was no alteration in prothrombin time in subjects in the clinical studies.

I will start with a discussion of the mean change from the studies from the prescription NDA and then will summarize with a slide showing the percentage of subjects with values outside the normal range. Across all studies the mean values for fat-soluble vitamin concentrations were within the normal range.

These graphs from study BM14149 show change in vitamin concentrations at 24 and 52 weeks. I have significance testing at week 52 only. In this study mean change was significantly lower in D, E and beta-carotene in the orlistat groups as compared to the placebo groups.

The findings in study NM14161 were similar. Note that all groups in this study had a negative change in vitamin D as compared to the previous study although statistical significance was only seen for orlistat 120 mg at 52 weeks.

We also see similar findings in study NM14302 although these subjects were instructed to take a multivitamin. These results may minimize what might occur in the real world since people who

had two consecutive low values received a vitamin supplement. In fact, more subjects on orlistat in the two-year prescription studies required D, E and beta-carotene supplements than those on placebo.

This leads us to the next slide where we see the frequency of two consecutive plasma vitamin concentrations below the limit of the reference range, a more clinically relevant outcome compared with the group mean changes in vitamin concentrations shown on the previous slides. The orlistat 120 mg group had a higher proportion of subjects with low vitamin concentrations as compared to those on placebo, particularly for vitamins D, E and beta-carotene.

Because warfarin blocks the activity of vitamin K and therefore impairs coagulation, the impact of orlistat on prothrombin time in individuals who are on warfarin has been considered. Clinical pharmacology studies conducted by Roche demonstrate that orlistat does not alter warfarin pharmacokinetics. However, there have been post-marketing reports of both

prolonged prothrombin time and bleeding with concomitant drug use. The prescription label instructs individuals who are on warfarin to have their coagulation parameters measured frequently.

In the actual use trial, which you will be hearing more about from Dr. Feibus, out of 14 patients who were actually on warfarin seven initially failed to identify that orlistat was inappropriate for their use after reading the label.

A potentially serious complication of orlistat is its interaction with the immunosuppressive agent cyclosporine. Weight gain is common in organ transplantation and we know from a drug interaction study with orlistat and cyclosporine that the concomitant administration of both drugs will decrease cyclosporine concentrations. Moreover, there have been cases of decreased cyclosporine concentrations associated with orlistat administration in the FDA Adverse Event Reporting System as well as in the literature. Two cases of acute organ rejection as

a result of cyclosporine interaction with orlistat have been reported, one mild and one moderate. Neither case resulted in loss of the organ.

In the actual use trial in which two patients actually on cyclosporine were screened, one of these subjects failed to identify that orlistat was inappropriate for use after reading the label.

Finally, we would like to call your attention to the spontaneous post-marketing adverse events from the FDA AERS database with 30 U.S. reports of pancreatitis and orlistat over its marketing period, that is, since 1999. This is in contrast to one report with another prescription weight-loss drug, sibutramine, over its marketing period in the U.S., that is, since 1997.

Very roughly, we estimate the number of orlistat prescriptions to be about 1.5 to 1.7 times the number of sibutramine prescriptions in the U.S. At present, no definitive conclusions have been made with these post-marketing safety findings. However, controlled clinical trials out to four

years have shown no greater incidence of pancreatitis with orlistat compared to placebo. A plausible biological mechanism has not been established at this time and review of this issue is ongoing.

In conclusion, the first point I would like to make regarding efficacy relates to the dose of orlistat in the low overweight population. In the four-month study in subjects with a BMI in the range of 25-28 kg/m 2 weight loss was minimal, with a placebo-corrected, adjusted mean value of 1.1 kg or 2.4 lbs.

In addition, the study did not meet the primary prescription weight-loss drug efficacy criterion of more subjects on drug achieving at least five percent weight loss as compared to placebo. This criterion was met at four months in the prescription drug studies with a BMI in the high overweight and obese BMI range.

Given that the two prescription studies were longer and had differing degrees of lifestyle intervention, their findings inform issues related

to treatment duration and lifestyle intervention. First, it is noted that there was less of a treatment and dose effect in the study with intensive lifestyle modification although overall weight loss was greater in this study.

Second, data out to two years demonstrate a weight regain even in subjects taking orlistat and the less lifestyle intervention, the more weight regain. We do know that when weight is regained the benefits of weight loss are lost.

Furthermore, data from the JAMA paper that showed what happens to individuals who are originally on drug and then are switched to placebo after one year shows a progressive regain of weight once orlistat is discontinued.

The New England Journal paper in which subjects were placed on drug, lifestyle intervention or both highlighted the importance of incorporating a lifestyle program into a weight-loss program that includes a drug.

In terms of safety conclusions, clinical studies have shown that prolonged use of orlistat

without appropriate vitamin supplementation may lead to clinically important fat-soluble nutrient malabsorption. Vitamin D may particularly be a concern because deficiency of this nutrient is so common in the United States and is associated with the risk for osteoporosis and other chronic diseases. Furthermore, vitamin K malabsorption may be a problem for individuals on warfarin.

In terms of drug interactions, I discussed warfarin for which prothrombin time prolongation and bleeding have been reported and likely reflect vitamin K malabsorption and insufficiency. I also discussed cyclosporine, for which interaction with orlistat leading to decreased concentrations may, in the worst case scenario, result in transplanted organ rejection. Although there were very few subjects on either warfarin or cyclosporine in the actual use study, the preliminary findings raise concern that the messages regarding these drug interactions may not be effectively communicated.

Finally regarding pancreatitis, we have a situation where, on the one hand, there is no

signal of increased risk for this condition in patients from controlled clinical trials treated with orlistat for up to four years yet, on the other hand, we have an apparent increase in the number of spontaneous reports of pancreatitis in real-world users of the drug. At this point we have no obvious explanations for this disparity. Perhaps the increased number of spontaneous reports of pancreatitis represents confounding by prescribing patterns. Although our investigation of the spontaneous reports of pancreatitis has yet to be completed, it is reassuring that no increase in the risk for pancreatitis has been seen in large, long-term controlled trials of orlistat.

So, I would like to end my presentation with what I believe is question number six from the questions posed to the committee, that is, do you believe the potential benefits of nonprescription orlistat outweigh the risks?

Finally, I would like to thank the committee and acknowledge my colleagues who were a tremendous help in this review.

DR. WOOD: Let's move on to the other two FDA presentations. Dr. Weiss?

Label Comprehension Review

DR. WEISS: Good morning. My name is Susanna Weiss. I am a social science analyst in the Office of Nonprescription Products and I reviewed the label comprehension study.

I will begin with a brief overview of my presentation. First I will mention the regulation concerning label comprehension. Next, I will describe the purpose of label comprehension studies. Finally, I will describe the orlistat label comprehension study including the design, the population, questions and procedures, the results concerning the drug facts label, and the results regarding the materials included inside the package.

The regulation governing label comprehension says the following: Over-the-counter drug labels shall be written in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low

comprehension, under customary conditions of purchase and use. We interpret low comprehension as a reading level at or below 8th grade.

Let's take a look at the purpose of label comprehension studies. One of the primary objectives of label comprehension studies is to measure the consumer's understanding of key label information such as use of the product, warnings associated with the product, what to expect when using the product, directions for proper use and, finally, other information in the label.

Another primary objective of many label comprehension studies is to measure consumers' understanding of where to locate additional information included in the package. The orlistat package, for example, contains several guides and reference cards to help consumers better understand how to use the product.

Now let's turn to the orlistat label comprehension study. The inclusion and exclusion criteria were as follows: Male or female of any race or ethnicity, at least 18 years of age and

people who expressed an interest, meaning somewhat or very interested in weight loss. The gender breakdown of the study subjects was 36 percent male and 64 percent female in the general population and 39 percent male and 61 percent female in the low literacy group.

The study used two cohorts of individuals, a general population of 302 subjects, 18 percent of which qualified as low literate and were also counted in the low literacy group, and the low literacy group of 160 subjects, 54 of which were from the general population group and 106 of which were specifically recruited as low literate subjects.

Scenarios followed by open-ended questions were developed to test consumers' understanding of product labeling and to measure the respondents' ability to locate information in the tables of contents of various guides that were included inside the package.

This scenario sets up the following inquiry: Diane and her friend Bev are both

overweight and started taking orlistat at the same time. After taking orlistat for four weeks, Diane is frustrated since she has not lost the same amount of weight as Bev. Based on the package labeling, what, if anything, is the reason why Diane is not losing the same amount of weight as Bev?

Here we see the answer. The correct answer is contained in the section of the drug facts label subheaded "when using this product" where it says how much weight you lose will depend on how closely you follow the recommended diet and the orlistat program.

As part of the study protocol, an interviewing script was used to direct the questioning process. All of the participants were told that this was a test of the package labeling. They would not be questioned about previous knowledge or common sense but about what has been learned from reading the information in the package labeling. They should respond according to the information in the label, and they would be able to

view and read all the package labeling throughout the test. The study responses were coded as correct or acceptable or incorrect.

Now let's turn to the results. Twenty-seven scenarios and questions were used to test consumer comprehension of information in the drug facts label. The general population group achieved the following scores by answering questions correctly or acceptably, 95-100 percent on 11 scenarios; 90-94 percent on four; 82-89 percent on seven scenarios; 72-79 percent on three; 69 percent on one scenario and question; and 48 percent on one scenario and question. Taken as a whole, these results are actually very positive.

Now I am going to discuss the study results in more detail in the order in which the communication objectives are covered in the drug facts label. First the product use, then the warnings, then results concerning what to expect when using the product, and finally the directions for use.

This slide shows results concerning

comprehension of the product's intended use and target population. You can see that with regard to product use the results were excellent, but when it came to understanding that it is not okay to take orlistat if you are not overweight the scores were quite a bit lower, and I will explain some of the reasons for this later.

With regard to warnings, there was very high comprehension of all label warnings. Virtually the entire general population understood 12 of the 13 label warnings and 86 percent of the general population understood the remaining warning. Well over 90 percent of the low literacy group understood 10 of the 13 warnings and 74 percent to 86 percent understood the remaining three warnings. Taken as a whole, these are very positive results.

This table shows the correct response rates concerning warnings about cyclosporine were very high, 96 percent for the general population and 90 percent for the low literacy group.

For warnings about warfarin, kidney

stones, gallbladder problems and diabetes medication, on average roughly 50 percent of the subjects answered exactly according to the label instructions and roughly 50 percent took a cautious approach and opted to either ask a doctor or decided that it was, quote, not okay to take orlistat with any of these indications or concomitant medications. Again, these are positive results.

With regard to understanding what to expect when using the product, we can see that the correct response rates ranged from 72 percent to 95 percent for the general population and from 48 percent to 86 percent for the low literacy group.

As for directions, almost all the label directions were well understood by both cohorts. The general population scores ranged from 78 percent to 93 percent and the low literacy group scores ranged from 67 percent to 90 percent.

Only the label directions concerning multivitamin use were not particularly well understood by either group, and there were some

differences between the sponsor's and reviewers' coding of correct and acceptable answers. So, let's look at the issue of vitamin use more closely.

The instruction concerning multivitamin absorption specifically says the following, to ensure adequate vitamin absorption, you should take a multivitamin once a day, two hours before or after taking orlistat capsules.

This is the scenario and initial question that were used to test consumer understanding of the direction about multivitamin absorption. It says, Terry is overweight and would like to use orlistat for weight loss. She is concerned that she will not be able to absorb the vitamins in the food if she starts taking orlistat. Based on the package labeling, what, if anything, should Terry do about this concern?

These are the results for question 27. We can see that the sponsor has a combined total of correct and acceptable answers of 93 percent for the general population and 88 percent for the low

literacy group. However, if we look at the responses coded by the sponsor as acceptable, we can see that they are really default answers that have no relationship to the actual label instructions. For example, ask a doctor or a pharmacist; eat better foods or a more balanced diet; call the 800 number; or look in the user's guide or manual. None of these answers show that consumers understood the specific label instructions concerning the need and timing for taking a multivitamin. We can, therefore, reject these so-called acceptable answers and eliminate 24 percent from the general population total and 38 percent from the low literacy group total.

This leaves us with the following results, 69 percent of the general population and 50 percent of the low literacy group understood the need to take a daily multivitamin; 47 percent of the general population and 36 percent of the low literacy group understood not only the need to take a multivitamin but also grasp the importance of taking the multivitamin two hours before or two

hours after taking orlistat.

Now, because 160 people in the general population and 102 people in the low literacy group did not initially understand the proper timing for taking a multivitamin they were given a second opportunity to provide the correct answer. The scenario about Terry was repeated and a new question was posed to the study subjects. The new question, question 28, was more specific than question 27 and it asked, based on the package labeling, what is the recommended timing for taking a multivitamin to ensure adequate vitamin absorption?

This table reports the sponsor's calculation of results to question 28. As you can see, it shows that the sponsor's combined total of correct and acceptable responses for the general population was 79 percent and for the low literacy group it was 66 percent. However, as with the previous question, a variety of so-called acceptable answers are not appropriate. For example, two hours before and two hours after were

incomplete answers.

Neither the wording of the scenario nor the question provide the necessary words to complete the sentences. Responses such as six months, once a day and once a day for six months indicate that subjects were confusing the instructions for how often and for how long to take the multivitamin with the specific instruction to take the multivitamin two hours before or after taking orlistat. General answers such as before a meal or after you eat, or ask a doctor or pharmacist, or call the 800 number show no understanding of the label instruction and are little more than default responses.

If you eliminate 31 percent of the unacceptable answers in each group you are left with the following correct responses, 48 percent for the general population and 34 percent for the low literacy group. Ultimately then, if you combine the scores for the completely correct answer from question 27 with the scores for the correct answer from question 28, you can see that

after two opportunities to review the label information and respond accurately 73 percent of the general population subjects and 58 percent of the low literacy subjects understood the correct timing for taking the multivitamin.

Now let's turn to results concerning the instruction that orlistat is for overweight adults. I would like to preface my remarks by mentioning that the drug facts label used in the comprehension study did not include a specific warning telling non-overweight people not to use orlistat. After the completion of the label comprehension study such a warning was added to the label.

The scenario and question that were used to test this concept were as follows: Jane is 25 years old and not overweight. Jane is considering using orlistat. Based on the package labeling, is it okay or not okay for Jane to use orlistat?

As you can see, the scenario in question called for two decisions to be made in accordance to the label instructions, one about Jane's age and one about the fact that she is not overweight.

Results show that a little over 20 percent of the subjects in each group responded incorrectly that it would be okay for Jane to take orlistat.

Here are some examples of the verbatim incorrect responses. They indicate that consumers rationalized that since there was no specific warning in the label stating that non-overweight people should not take orlistat, then it would be okay to take the drug if a person is over 18 and healthy.

Another set of responses reflected the idea that orlistat would be good for maintaining desired weight. Here are some examples. I will let you read a few of them yourself. I can mention a couple: If she wants to maintain her weight, it is fine to use. If she uses it moderately, it will help her maintain her weight.

There was a variety of other interesting verbatim responses that rationalized why it would be okay to take orlistat and I will let you read a few of the examples.

Let's turn now to additional information

included in the package. At the time the label comprehension study was conducted the supplementary materials had not been completed. So, the test subjects were provided with a table of contents for those guides and they were asked to locate certain information in them.

This is the table of contents for the user's guide.

This is the at-home guide table of contents.

This is the away from home table of contents.

Here is an example of a scenario and question that were used to test the consumer's ability to locate certain information in the supplementary materials. The scenario says, Steve is overweight. He has been using orlistat. Steve is going out to dinner tonight but is not sure what would be best for him to order. The question says, based on the package labeling, where could Steve find information.

The accurate response is in the away from

home guide, which indicates that it covers dining out issues. Acceptable variations on that answer would be the dining out guide, or in the little restaurant guide, or in the calorie or in the calorie or fat counter cards.

Although correct response rates for the scenario and question 19 about dining out were low, as you can see--they are located at the very bottom there, there might be a fairly simple explanation for this and it is as follows: The working of the question that was read to the test subjects said, based on the package labeling, where could Steve find information? From the verbatim responses, it appears that many of the responders thought that the term package labeling meant the drug facts label that they had been reviewing in order to answer other questions in the test.

In spite of a few rather low scores, overall the correct response rates for the supplementary educational materials show about a 60/40 split between positive and negative scores.

I am going to skip the next slide because

we are short of time. So, what can we conclude from this label comprehension study? Well, first, there was very high comprehension of the label warnings and correct response rates concerning cyclosporine were in the 90th percentile for both the general population and the low literacy cohorts.

Next, almost all the label directions were well understood by the low literacy group and the general population group. Only the directions concerning multivitamin use were not particularly well understood by either group. This indicates that some modification of the drug facts label is needed to clarify and emphasize the instructions concerning taking multivitamins.

Finally, the lack of a warning on the drug facts label specifically telling consumers do not use this if you are not overweight confused some participants and led them to think that use by non-overweight individuals would be acceptable. As I mentioned earlier, after the completion of the label comprehension study the sponsor amended the

drug facts label to include the specific warning that states do not use if you are not overweight.

It may help consumers to make a more informed self-selection and purchase decision if there were some indication on the external packaging as to what constitutes being overweight. From the label comprehension study, it seems that many people have a variety of subjective opinions about this. Thank you.

DR. WOOD: Thank you. Let's go on to the last talk which is from Dr. Feibus.

Actual Use Study Review

DR. FEIBUS: Good morning. Mr. Chairman, members of the advisory committee, esteemed colleagues, ladies and gentlemen, my name is Karen Feibus. I am a medical reviewer in the Office of Nonprescription Products, and it is my pleasure to speak with you today about the actual use study submitted to the orlistat OTC application.

An actual use study attempts to simulate over-the-counter use of a product and, while the study does not provide perfect data, it does

provide important information about potential consumer behaviors. Generally there are few exclusion criteria in these studies, and those that do exist are usually based on safety concerns. There is a self-selection question that is asked, do people correctly choose the use or not use the product based on the label? Ideally, we like to see an actual use study conducted with the label that has already undergone extensive label comprehension testing and reflects the intended label for the product. In this case, because of the way drug development occurred, this study was conducted prior to the label comprehension study that Dr. Weiss just discussed.

These studies also ask a compliance question, do people dose and use the product based on label directions? Usually efficacy information from these studies is somewhat limited because of the open-label design, and it is uncontrolled and often it is not a primary study endpoint. The objectives of this study are usually product dependent.

So, what are the questions we would like to ask about this product? Who will use orlistat OTC? Do subjects correctly choose to use or not use orlistat OTC based on the label warnings and indications? Do subjects dose it correctly? Do subjects lose weight? Are there any safety concerns? Do subjects understand how to use a multivitamin correctly with this drug? Do non-overweight subjects choose to use it? And, are there any unexpected adverse events seen in the over-the-counter environment that may not have been seen when the drug was used in the prescription environment?

Just as a quick review, this was a 90-day study conducted through 18 pharmacies throughout the United States, each equipped with a certified scale. Recruitment was mostly through in-store advertising and newspaper advertising was used to supplement it when needed. Enrolled individuals were ages 18 and older and needed to be available to complete the telephone interview processes.

Subjects who had a "do not use" condition,

one listed in the "do not use" section of the drug facts label, were allowed to participate in the self-selection process but were not actually allowed to purchase drug. So, the self-selection process in this study went like this: Consumers were told to imagine that they were in a store, looking at a new over-the-counter medicine. They were told to take as much time as needed to review the label and were then asked the following question, do you think that this medicine is appropriate for you to use?

Once they answered this question, they were asked whether or not they would like to purchase the product and were told how much it would cost. The reasons for their answer were recorded, as well as their height and weight. Individuals who wanted to purchase orlistat were allowed to purchase between one and three bottles and also received the accompanying educational materials at that time.

Now, the educational materials for this study were somewhat different than those that

accompany the NDA and included the orlistat user guide, which was a 12-page guide that reviewed proper use of the drug; the indications for the drug; contraindications to its use; as well as teaching consumers some basic nutritional information, including how to use a nutritional facts label. These materials included a personal food diary where consumers could record their dietary intake and when they took orlistat; a pocket fat gram counter; a fact gram wheel; a portion size information card; and a 28-page binder called "the orlistat diet success planner" that contained very detailed information about how to construct meals, about how to eat out in a restaurant and how to alter their physical activity and exercise.

Data was primarily collected through scripted telephone interviews that used a computer-assisted device, and these interviews were conducted at about day 14, 30, 60 and 90 of the study, with a follow-up interview conducted at day 104. These interviews were conducted by trained

clinical interviewers and the material that was covered was rather expansive, including whether or not the consumer had started using the drug and, if not, when they intended to start using it; how they were taking it, including their dosing, the frequency of dosing; whether they were taking multivitamins; whether they were following a diet or exercising; if they were experiencing any new discomforts; or whether there were any changes in their medical conditions or other medications they were using; whether they had lost weight; and whether they were using the accompanying educational materials and referring back to the product's label. Interviews that had at least one answered question were included for analysis.

Information was also collected through the pharmacy visits. However, following enrollment, only one pharmacy visit was required for each enrolled individual and the time of this visit was not specified. The information collected included the amount of drug that was purchased; the day it was purchased; an objective weight measurement; as

well as adverse events being experienced by the individual.

I would like to make a few comments on design of the study to keep in mind while we talk about the results. The drug facts label and supplementary educational materials used in this study, while similar to the materials submitted with the NDA, do differ in some ways. There are elements of the drug fact label that differ in content or in location, and the actual educational materials that you were shown earlier were not actually used in this study and tested. Objective weight measurements, while performed intermittently through the study, were not collected on all orlistat users at the end of the study. Subject diaries, while available to the consumers, were not collected or analyzed, and some telephone interactions may have served to educate the subject during the course of the study and may have influenced how questions were answered as further interviews went on. There was no assessment of drug discontinuation, when consumers stopped using

drug. And, I just want to point out that this was a 90-day study as compared to the six-month duration of use on the proposed label.

So, let's talk about some results. There were 703 subjects screened, 681 of which were eligible. The 22 subjects who were excluded for protocol violations were all at one pharmacy site where it became evident at the end of the study that these 22 subjects may have been given information that would have inappropriately influenced their self-selection decisions. Therefore, these 22 subjects are not included in the self-selection decision data that I will present.

All of these eligible subjects were asked a self-selection question, whether this medication was appropriate for them to use, and 543 said yes, it was; 52 said no; and 86 said they didn't know or they were not sure. All of these individuals, regardless of their answer, took the REALM test for literacy and provided information about their demographics and health history. The 681 eligible

subjects were then asked the purchase question, would you like to purchase this medicine today? And, 339 said yes, they wanted to purchase; 261 said no; 66 weren't sure.

Inclusion and exclusion study criteria were then applied to the individuals who wanted to purchase drug and 49 did not meet criteria and were, therefore, excluded from purchasing and most of these individuals had a "do not use" condition; 28 ultimately chose not to purchase after initially saying that they wanted to; and 262 members of the eligible population did purchase. Now, the 22 individuals who were excluded for protocol violations also purchased drug but weren't included in the eligible population. So, ultimately there were 237 evaluable users.

So, who chose to use this product? Overall, the population who participated in the study was female, which is consistent with the controlled studies that were presented earlier. The mean age was about 45 years of age, the low end of that being 18 years of age up to 75 years of age

among users, while the age range was slightly broader among eligible subjects. There was a wide range of BMIs who enrolled in this study, anywhere from normal weight of 21 BMI up to morbidly obese BMI of 53. However, the majority of this population fell in the overweight and obese range, and you can see that the mean BMI was 32. Most of this population was Caucasian. Most were fairly well educated, with 85 percent of individuals having education beyond high school. Only 4.2 percent of the users tested as low literacy, which was half that of the low literacy population in the eligible group.

So, what constituted a correct self-election answer for this study? Subjects who had a condition that fell under the "do not use" portion of the drug facts label had to say "no, this medication is not appropriate for me to use" for them to answer the self-selection question appropriately. For individuals who had an "ask before use" exclusion, an exclusion that appeared in the "ask a doctor" before use or "ask a doctor

or pharmacist" before use, those individuals could say "no, this is not appropriate for me" or they could say "yes, it is but I need to ask my doctor first."

This slide shows a comparison of the warning elements of the drug facts label. The first column is the actual use study drug facts label warnings and the second column is the orlistat OTC NDA label warnings that were submitted to the application. As was pointed out earlier by the sponsor, some of these warnings are different. The ones that are highlighted in yellow are the same in both content and in location and the others differ in some way.

DR. WOOD: So, which is the proposed one?

DR. FEIBUS: The actual use study label is in the left-hand column. You can see that between the two labels--

DR. WOOD: No, I can see that, but which one are they actually proposing to use?

DR. FEIBUS: This is the set of warnings that actually appears on the NDA proposed label

that was submitted with the application. This label is identical to the label that was tested in the label comprehension study presented by Dr. Weiss, except that the "do not use if you are not overweight" warning was added following that label comprehension study based on the results of that study.

DR. WOOD: So, maybe the company should answer the question. Is the one on the right the one that is proposed?

DR. FEIBUS: This is the proposed label.

DR. DENT: [Not at microphone; inaudible].

DR. FEIBUS: So, let's look at the self-selection decision-making overall, and 681 eligible subjects made a self-selection decision. Of those, 465 individuals had some labeled exclusion. Of those with labeled exclusions, 107 self-selected correctly; 358 did not. Among the 216 individuals in the eligible population who had no labeled exclusions, 209 self-selected correctly, which means that they identified that this drug would be appropriate for them to use. The seven

who self-selected incorrectly said that the drug would be inappropriate for them to use. So overall, 316 of 681 eligible subjects made a correct self-selection decision, which is 46.4 percent of the population.

If we now break this down according to labeled contraindications, these are the four warnings that appear in the "do not use" section of the actual use study label. Among individuals who had one or more of these warnings, 35-50 percent made a correct self-selection decision. As you can see, two people were taking cyclosporine; 14 were taking warfarin; and there were 46 individuals on a diabetes medication.

Among individuals in this study who were using orlistat who had a condition that appears an "ask before use" warning section in the drug facts label, between 12 and 54 percent of these individuals made a correct self-selection decision. If you would like to focus on those warnings that remain on the proposed NDA label, those are the ones that are not crossed out and you can see that

it is still a similar decision range. The correct answers range between 12-40 percent on the label components that remain on the NDA label.

There are two NDA label warnings that have been added since the time of the actual use study. One is the "do not use if you are not overweight" warning and you have learned that that was added after the label comprehension study. There was also an "ask before use" if you have kidney stones warning that was added following the actual use study but prior to the label comprehension study, and that element did test well in the label comprehension study.

Of 631 eligible subjects, 284 purchased. Sixty percent of those who said they did not want to purchase, in addition to 30 percent who weren't sure if they wanted to purchase, those individuals cited cost as the primary reason for not purchasing. And, 17 percent of individuals who weren't sure about purchasing the drugs cited the need to speak with a healthcare provider first.

It is important to note that those who

were uncertain about purchasing the drug needed to make a decision on the day of enrollment and were not allowed to speak to their healthcare provider and later come back and purchase drug.

This slide looks at the user population compared to their baseline BMIs. As you can see, there were 18 individuals, which comprised eight percent of the user population, who were in the normal weight range. I would like to point out that only three of these individuals had a BMI under 22. Thirty-two percent of the user population was in the overweight BMI range and 60 percent were in the obese BMI range. When subjects were asked about perceptions of their height and weight, nobody in this study thought they were of normal height and weight.

Now let's look at the percent of subjects who made a correct use decision. This data is actually based on self reports that were gathered at the telephone interviews when subjects were asked whether or not they had spoken with their healthcare providers. Contact with their

healthcare providers was taken at face value. It was not confirmed with the healthcare providers themselves. As you can see, between zero percent of individuals and 50 percent of individuals with various "ask before use" warnings on the label made a correct use decision. I will let you take a second to just look at those various numbers.

Overall, subjects in this study dosed orlistat correctly, according to label directions, throughout the study. As you can see, nearly all subjects too the correct number of capsules per dose; took the correct number of doses per day; and took the correct number of capsules per day according to label directions. Nearly all individuals took orlistat with meals as directed.

With regards to multivitamin use, as was stated earlier, about 80 percent of users did use a multivitamin and almost all of these individuals were taking it at least daily. Unfortunately, only 38 percent of these individuals were taking a multivitamin according to the label direction to take it at least two hours before or two hours

after orlistat in order to enable the vitamins to be properly absorbed. This did increase to 53 percent at the end of the study and this may partially have been a learning pattern due to the reinforcement from the telephone interviews themselves.

It is important to note that the multivitamin instructions have migrated between labels. Originally, on the actual use study label the directions for multivitamin use were located in other information, down at the bottom of the drug facts label. For the proposed NDA label, these directions have been moved up to the directions for use section so they appear immediately under directions for how to use the drug. Those are the directions for use that were evaluated in the label comprehension study and when you looked at the two questions in the label comprehension study that evaluated this communication element, 73 percent answered it correctly and understood how to time the multivitamin with orlistat, which is an improvement over the figure seen here.

Now, there may be more than one factor contributing to understanding this element. One may be label comprehension and how this information is being conveyed but, in addition, the multivitamin is coming in its own container and contains its own directions for use and some multivitamins do contain instructions for how to take it with food and consumers may get confused if their multivitamin packet tells them to take it with food while the orlistat instructions are telling them not to take with their food and with their orlistat.

There are extensive educational materials included with this drug. Between 31 and 64 percent of users used these various materials at different times during the study. Of those who used the materials, between 77 and 86 percent of individuals found them useful. Of those who were using a diet, between 60-80 percent of subjects were following the diet during the course of the study. Unfortunately, this percentage declined as the study went on. Of those who were following the

diet, most individuals followed either a reduced rat and/or reduced calorie diet as recommended on the label.

Weight loss in this study was a secondary endpoint, and weight-loss information was collected in two ways. The weight-loss information collected through the self-reported way is through telephone interviews. Figures were only recorded for those individuals who actually lost weight and no information was recorded for those who did not lose weight or who gained weight. Therefore, the averaged weight information is somewhat skewed and I am not going to present it. The objective weight measurements that were collected at the pharmacy provide some information about how weight changed during the study. However, the information is limited because pharmacy visits were not required at a particular time.

This table presents weight change information that was collected between day 61-90 at pharmacy visits, but it only covers about 25 percent of the user population, or 60 subjects.

You can see that among those subjects who went for a pharmacy visit at that time, 42 percent did lose more than five percent of their body weight and five percent lost more than ten percent. This is after two to three months of drug use.

This slide shows the range of weight change. You can see that individuals gained as much as eight pounds and lost as much as 52 pounds. This range was much smaller among individuals in the normal weight range. It was somewhat broader for those in the overweight range and was the broadest among those who were obese.

Let's take a couple of minutes to talk about adverse events. The study population was 284 individuals. This included all of the purchasers who were in the eligible population as well as the 22 purchasers who were excluded for protocol violations. There were at least eight subjects and potentially as many as 26 subjects included in the safety population who did not use drug. There were two severe adverse events considered possibly related to drug use. One was an episode of

esophageal spasm and the other was an episode of abdominal pain that occurred in an individual with chronic anemia who was acutely anemic at the time of evaluation. Forty-three subjects experienced 65 adverse events that lead to early study discontinuation. Twelve of these events were non-gastrointestinal adverse events but were not serious, and 53 were gastrointestinal adverse events that overall reflect the adverse events that are often experienced with use of this product. These 53 events are encompassed in this list of common GI adverse events. The ones highlighted in yellow are the defecation-related adverse events that are often associated with the use of this product, and the percentages reflect the percent of individuals using the product who actually experienced this particular adverse event.

In conclusion, we asked some questions at the beginning of this study. Let's see what the answers are. Who will use orlistat OTC? Ninety-two percent of orlistat users were overweight or obese. Compared to the American

population, the study population under-represented consumers of low literacy and non-Caucasian ethnicity. However, this may or may not accurately reflect the individuals most likely to use this product in the consumer setting.

Do subjects correctly choose to use or not use orlistat OTC based on the label warnings and indications? As we mentioned, one of two subjects taking cyclosporine and seven of 14 on warfarin did incorrectly self-select that the medicine was appropriate for them to use. Overall, 46 percent of eligible subjects self-selected correctly and, as the sponsor mentioned earlier, they have conducted three further self-selection studies that focus on these issues that we have not reviewed as yet.

Do subjects dose orlistat correctly? Yes, subjects did dose orlistat correctly, and most subjects followed the recommended diet plan.

Do subjects lose weight while using orlistat? Well, the data is incomplete on the objective weight measurements. It does appear that

75 percent of subjects lost some weight and that 40 percent lost more than five percent body weight.

Other safety concerns--do subjects take a multivitamin correctly while using orlistat? In this study only 38-53 percent of users timed the multivitamin correctly with their orlistat, but we have seen that there have been some changes in labeling for multivitamin use and we have already seen some improvement in comprehension in the label comprehension study.

Do non-overweight subjects choose to use orlistat? And, 7.6 percent of users had a normal baseline BMI but there were no under-weight individuals who enrolled in this study.

Are there any unexpected adverse events that we saw with use in the simulated OTC environment? There were none.

I thank you very much for your time. I hope this information will help you with your deliberations and I hope you enjoy your lunch.

DR. WOOD: Thank you very much. It is now time for lunch. I have a note here that seating

has been reserved for the committee in the hotel restaurant on the first floor. In addition, anyone who wants to speak and has registered to speak at the open public hearing needs to register at the FDA registration desk outside the conference room. We will be back here at 1:15 to restart. Thanks.

[Whereupon, at 12:30 p.m., the proceedings were recessed for lunch, to reconvene at 1:15 p.m.]

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A F T E R N O O N P R O C E E D I N G S

DR. WOOD: Let's get started. We have to start the open public hearing at 1:30 but we have 15 minutes of discussion on the previous presentations before then. So, I will open that up to the committee for their questions and thoughts. Yes?

Questions and Answer Period

MS. COFFIN: I am curious, for the actual use study the majority of the people stated that cost was the major issue why they didn't purchase the drug. What were the other major issues?

DR. DENT: [Not at microphone; inaudible].

MS. COFFIN: Was that about 50 percent, 70 percent, 80 percent who cited cost?

DR. DENT: [Not at microphone; inaudible].

MS. COFFIN: Were there other decisions besides cost that showed up more often?

DR. DENT: [Not at microphone; inaudible].

MS. COFFIN: Thank you.

DR. WOOD: Dr. Woolf?

DR. WOOLF: I am a bit perplexed. I think

we all agree that obesity is a chronic disease. The prescription drug is for chronic use and the company is proposing six-month use of the drug and then the patient, presumably, will have learned enough from the various educational tools to be able to do this on their own, yet we have data that we were shown by Dr. Golden, from JAMA and the New England Journal, that despite more intensive patient education the patients who came off active drug lost weight. So, what is the rationale for a six-month trial of a drug and then patients are going off on their own?

DR. DENT: [Not at microphone; inaudible]...the trajectory of weight loss for those people was such that their maximum amount of weight loss was at six months. Then we are putting in place a behavioral program that will support them to keep that weight off. People probably will not continue to buy a product if they don't continue to lose weight. So, we are providing them with the opportunity to lose the weight and then a program that will support them in keeping that

weight off.

DR. WOOLF: That sort of gets back to my question from earlier in the morning. How much behavior modification is enough, and for how long, and how intense? Dr. Foster is the one to answer that.

DR. FOSTER: Let me first, if I could, address a little bit the first question, and that is why six months? I think the answer is, as Dr. Dent suggested, that that is where you get the maximum benefit for weight loss. But, in addition, that is what in fact the NIH guidelines say on page two of the executive summary. They indicate that obesity, despite being a chronic condition, should be treated in a step-wise fashion and they specifically said that the first six months should be dedicated to weight loss; after that weight maintenance of some undefined period; and then a reevaluation with a primary care physician. So, that is the initial reason.

In short, you can't get to this real thorny dilemma which the field hasn't fully

reconciled about how to keep weight off until you have lost weight. So, the indication that GSK is seeing is for weight loss and that is why six months.

To your question about what is the sufficient or minimal dose for behavioral treatment, that question hasn't been answered. What has been answered elegantly by Tom Wadden, Bob Berkowitz and others is that some behavior therapy is better than none and a lot of behavior therapy is better than some. So, I think what the attempt of GSK to do is to have a considerable amount of behavioral support material right with the purchase of the product and, in addition, to do a full year of behavioral support trying to replicate what happens in the clinic, specifically finding an engaging way in a web-based program for people to record their food intake; to limit their cues to overeating and inactivity.

The behavioral principles and practices to get people to lose weight are well-known and well documented. It is really can you do that,

decreasing some of the barriers of clinic-based treatment? I believe, and I think GSK believes, that if we can decrease some of those barriers in terms of the web base and, in addition tailor it, we will provide a comprehensive behavioral program in an OTC setting.

DR. WOOLF: Has this been field tested?

DR. FOSTER: It has not been field tested and the rationale, again, is that, sad to say, we haven't learned much in the last decade or two about what is necessary from a behavioral weight control perspective. It is well documented and it is very effective over a six-month period. So, the challenge then is to repeat those principles and practices, again keeping detailed records of intake and activity which I think is easier to do, and data would show is easier to do, in a web-based environment where patients can get instantaneous feedback rather than a clinic-based environment where they may not get feedback for a week--limiting cues, increasing physical activity.

So, the rationale is this package, this

behavioral package that has been well tested and well evaluated. The next step is to make it useful on the web and some of the data for that has been tested at Brown University and the University of Vermont, showing that you can get a better response on an internet-based program if you make it behaviorally specific. That is, give people specific behavioral tests to do on a week to week basis rather than saying just go and surf the web; there is a lot of good information about weight control.

So, those two pieces of data make me confident that we can replicate what has been done in the clinic, or at least model it on what we know works.

DR. WOOD: Dr. Woolf, are you satisfied?

DR. DENT: [Not at microphone; inaudible].

DR. WOOD: Why don't you come up to the podium and answer it there? The sound guy seems to be having a lot of trouble getting the sound right.

DR. DENT: I am sorry. While we haven't obviously yet tested this program because we don't

have the product on the market, we do have experience from smoking cessation with Nicorette where a behavioral support program was a part of it, was actually tested in the real world, and was demonstrated to increase quit rates. If you would like to see that data I will ask Mr. Burton to come and show it to you.

DR. WOOD: No, we will pass on that and come back to it if we need to. Ruth?

DR. PARKER: I had two questions. One related to whether or not, since we haven't actually seen these education materials except on the PowerPoint, they are available and we can see them. I would like to see actually the whole packet of materials if they are available for us to look at. But the concept of BMI, though not intuitively obvious to most people, is one that we use a lot when we describe obesity as a medical condition. I wonder if in your health education materials you discuss that concept, and if we have any idea how well people in real use can grab that concept and use it in a meaningful way, and whether

or not that is something that is included in your materials.

DR. SHIFFMAN: Your question was since the scientific and medical community use BMI, why not have consumers use BMI and kind of teach them, if you will, how to do it? In fact, early in the research program precisely that was tried. There was testing where consumers were shown in several different ways how to figure out their BMI. If I can have the slide that shows the charts? I will tell you about the design of the study in a moment but these are examples and I think you have seen charts like this used for consumer use. What the study showed was that despite what seemed to us to be the clarity of the expression--if I can have the next slide--across four different ways of showing this, less than 45 percent of consumers, even when they had a chart with BMI on it, could do it accurately.

So, it was felt that making BMI a basis for deciding where you belong wasn't working. I emphasize, conversely, that, as I have shown you,

when we asked people simply to say whether they were overweight the study showed that their self-perception was actually quite good in relation to our calculation of BMI. So, that is why BMI, although it is discussed in the materials, isn't prominent as a way to make this decision. People seem able to make it quite well--in fact better--just by saying they are overweight.

DR. PARKER: Just another question regarding people's ability to understand, if you take a medicine tid or three times a day and you are supposed to take a vitamin two hours before or after taking a medicine that you take three times a day, what time do you take the vitamin? I am not sure.

DR. DENT: The intent is to take the vitamin literally two hours after. What we observed in the actual use study was that about 75 percent of people did take vitamins but not everybody took them two hours before or two hours after.

To put that in context in terms of safety,

we feel that there is not a negative safety consequence of taking the vitamin with the meal because 70 percent of the fat-soluble vitamin will still be absorbed. So, to answer your question very specifically, you should take it two hours before or two hours after according to the directions. If you take it with the meal you will still get 70 percent of the vitamins that are in that supplement absorbed--fat soluble. All of the water-soluble vitamins will be completely absorbed.

DR. WOOD: Let's take a pause and we are going to go to the open public hearing and then we will come back to other questions.

There are a couple of things we have to read first. Let me first of all begin by saying that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee, FDA believes that it is important to understand the context of an individual's presentation.

For that reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its products and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Each of you I think has a number and we will call on you by number. Each speaker will get six minutes to speak. At the end of the six minutes the microphone will be switched off and only your lips will keep moving--

[Laughter]

--so it is probably best to vacate the podium at that point. The first speaker is Dr. Wolfe.

Open Public Hearing

DR. WOLFE: Thank you. I paid for my subway ride up here and, to my knowledge, I don't have any financial conflicts of interest.

I am just going to go through some principles that we have previously used in terms of considering whether something should be switched from preclinical to over-the-counter. First is the possibility of self-diagnosis. The actual use trial demonstrated that a significant proportion of people choosing orlistat were not very overweight. In two age groups, for example, 16 percent of women had starting BMIs of less than 25.3 and 26.4 respectively. Almost a third of women had BMIs of less than 30.

Continuing on that, current research on cardiovascular risk clearly stresses assessment of global risk rather than focusing simply on treating just one possible risk factor. This explains the

current FDA-approved labeling on prescription orlistat, quote, long-term effects of orlistat on morbidity or mortality associated with obesity have not been established, end quote. The need to consider all factors, including hypertension, diabetes, smoking, family history and others, is one of the major arguments against OTC availability of antihypertensive, cholesterol lowering, diabetes and weight reduction drugs.

In explaining why they had not included data on blood pressure and serum lipids in the integrated safety summary, Glaxo said, quote, mainly because the OTC indication is to promote weight loss and all other benefits achieved from orlistat would be most properly handled under the supervision of a physician.

FDA responded to that by saying that the company seems to be saying that overweight individuals with weight-related co-morbidities such as these are inappropriate candidates for OTC orlistat because weight loss in such patients would require management by a physician to ensure that

all such changes would favorably alter cardiovascular risk, overall risk. Dr. Golden further stated that it is difficult to imagine the proposed dichotomization of the target population to mildly to moderate overweight adults with and without weight-related co-morbidities as succeeding in the real world.

The second variable is a self-limited or chronic condition. This is relevant to treatment duration, the evolution of the disease and the occurrence of adverse reactions that may require physician monitoring. In the case of OTC orlistat, the evolution or co-existence of diabetes, hypertension or the need for frequent long-term INR monitoring to see how thin the blood is if on warfarin are serious problems.

In the actual use study 68 percent of eligible subjects had one or more labeled exclusions, including 24.4 percent with hypertension, 6.8 percent taking diabetes medications and 2.1 percent taking warfarin. You have seen these before. I show them to you

briefly. Of 247 subjects with conditional labeling exclusions, only 32 percent correctly chose not to use or said they would consult a health professional first.

Benefit/risk ratio--this is related to the first two points because the difficulty of continued evaluation of benefit and risk by the patient without any input from the physician, arguably, can significantly alter the ratio over time and hamper the ability to keep it favorable for the patient. A risk tolerable under physician supervision may not be so with OTC use. The time-related increase in weight also alters the benefit/risk ratio, decreasing benefit while continuing risk, as shown in the next slide, going back up towards normal.

The fourth category has to do with adverse drug reactions or interactions. There may be adverse reactions or interactions that may not be fully known to the patient or physician. This presents even more cause for concern than the already troublesome situation involving

prescription only drugs. A good example of this are people using warfarin or cyclosporine, as does the documented inhibition of fat-soluble absorption of vitamins.

A few other OTC drugs, as pointed out I am sure this morning, have warnings about concomitant warfarin use but this problem is compounded with orlistat because the drug also decreases the absorption of fat-soluble vitamin K whose, quote, deficiency induced by warfarin is the mechanism by which warfarin inhibits blood clotting. Although GSK cites a study that finds no clinically significant decrease in blood vitamin K levels, the study actually shows a statistically significant decrease, still within the normal range but, of course, this was not combined with warfarin.

Long-term data from prescription use--problems that have arisen and been documented during prescription form are likely, if not certain, to be more common and more serious in the OTC version. There are 39 cases of increased INR abnormal blood thinning in orlistat users,

including 29 taking warfarin; one with vitamin K deficiency not using warfarin; one death; ten hospitalizations, four with life-threatening reactions; and reports by FDA of several others with bleeding episodes. More of these will inevitably occur with OTC use because 50 percent of the 14 warfarin users chose to use OTC orlistat and may not have told their physicians and, thereby, get weekly monitoring as recommended in a recent study. For the first four weeks, someone who is getting Coumadin should have weekly monitoring.

Conclusions--the switch of orlistat to OTC status would be a serious, dangerous mistake in light of its marginal benefits, frequent coexistence of other diseases, common bothersome GI adverse reactions, significant inhibition of absorption of fat-soluble vitamins and problematic use in the millions of people who are using warfarin or, less commonly, cyclosporine. Last year there were 23 million prescriptions filled for warfarin.

Physicians are increasingly rejecting the

prescribing or orlistat, decreasing from 2.6 million to one million in 2004.

DR. WOOD: Okay. Speaker number two?

DR. SIMENSON: Thank you for the opportunity today to present the views of the American Pharmacists Association. I am Steve Simenson, trustee elect to the APhA board of trustees, and president of Goodrich Pharmacy in Aonka, Minnesota.

In the interest of full disclosure, two years ago I participated in the actual use study and examined the provision of orlistat over-the-counter. The research study consisted of enrolling patients, providing orlistat over-the-counter, monitoring self-selection, medication use, patient behavior and weight loss. However, neither I nor the Association received funding to participate in today's meeting and the views I am presenting are solely those of the Association and its membership.

APhA supports the transition of suitable prescription drug products to OTC status when

supported by studies assessing the safety, efficacy and appropriateness of such drug products used for OTC switches, and we don't have a specific recommended position today. We rarely take positions on specific product switches.

But we do have an opinion and information to share and request that you consider these comments in your deliberations. Decisions to classify products as either prescription or OTC are best made by the FDA in consultation with the product sponsor, with the ultimate decision based on evidence of safety and effectiveness. However, the decision must involve more than a review of the clinical research information. It must also include an examination of the risks and benefits associated with increased access; the environment surrounding the use of the product; the disease and condition at issue; and the real-world use of the product in the OTC environment; and a review of the existing therapies in the self-care market.

In preparation for this meeting, I did a brief search of products in the marketplace and

found over 70 dietary supplements that claimed to aid weight loss. I would like you to note that I don't carry any of these products in my pharmacy. The products are problematic because they are promoted through unregulated claims; promise miracle treatments; lack adequate directions and warnings; and contain potentially risky ingredients. Unfortunately, these existing options raise questions of safety, effectiveness and quality.

Because of these concerns, the relative safety of the product under consideration today may increase and shift the risk/benefit analysis in favor of OTC availability. Pharmacists are in a good position to work with consumers if orlistat is made OTC. A large number of OTC products are purchased at a pharmacy, placing pharmacists in the ideal position to help consumers at the point of decision-making and purchase.

A recent survey found that consumers frequently turn to a pharmacist for advice. Forty percent ask a pharmacist for advice before

purchasing an OTC for the first time. The survey also found that when consumers approach a pharmacist it is frequently to discuss an OTC, obtain a product recommendation, discuss a medical condition, or obtain information on how to take a medication. If orlistat is approved for OTC use, pharmacists will continue to serve as this resource for consumers. We can ensure that the patients are appropriate self-treatment candidates; assist with product selection; and refer patients to a physician when necessary.

We also work with patients to ensure that they understand how to use the product and can monitor for drug interactions and for the development of adverse effects. It is important to note, however, that mass marketers without pharmacies are gaining a larger share of the OTC market. In these environments consumers make OTC decisions without the assistance of a healthcare professional.

The question that the agency must focus on is whether orlistat can be used appropriately and

safely without the intervention of a healthcare provider. If the advisory committee decides that consumers can use orlistat without professional guidance, the agency has several options for approving the product as an OTC. The agency can approve the product with traditional OTC status or, if the FDA and product sponsor determine that consumers would benefit from the opportunity to interact with a pharmacist, the agency and product sponsor should consider another option, that of limiting distribution of the product to outlets with a pharmacy. This pharmacy care OTC approach would provide patients with access to the medication without a prescription while ensuring that patients have access to consultation with a pharmacist if they so choose.

Like other OTCs, pharmacy care OTCs would be available in pharmacies on the open shelf with other OTC medications but, by limiting them to outlets with a pharmacy it facilitates voluntary interaction between consumers and pharmacists.

To conclude, I would like to reiterate our

recommendation that the agency consider the real-world use of orlistat in the OTC environment with the risks and benefits increasing the access and the ability of consumers to appropriately self-select and use the product. Should the agency approve the application to move orlistat to OTC status, pharmacists will work proactively with consumers to ensure that they understand when the use of the product is appropriate; provide counseling on the product use; recommend and reinforce behavior and lifestyle modifications; evaluate nutritional needs, including vitamin need; monitor progress and refer patients to additional resources when appropriate. Thank you.

DR. WOOD: Thank you very much. Speaker number three is Deborah Fisher.

MS. FISHER: Hello! My name is Deborah Fisher. I think I am here to represent "John Q. Public" as opposed to any medical professional. I happen to be a registered nurse in the Baltimore area and I also have a four-year degree in health education but basically I am representing myself as

somebody who has struggled with a weight problem throughout their entire life.

I am here today because I feel very strongly that we need a new solution to the problem of losing weight and keeping it off. I was put on my first diet, when I was seven years old, by my pediatrician. I am now 52 years old and I have been dieting for 45 years unsuccessfully. I don't look so bad today because just recently I got my body mass index under 30; 30 and above is obese. I have 24 pounds that I must lose before I reach a body mass index under 25 pounds, which is considered a healthy weight. So, the battle goes on.

Eat less; move more. It sounds pretty simple, doesn't it? Well, as my kids would say, "not." How many of you saw the article in "The Washington Post" magazine business section on Sunday? Any of you saw this? "Why America has to be Fat?" It is very interesting reading. I strongly recommend that you read it. Basically, there is an industry out there, a huge industry

that is making us fat and there is a huge industry out there that is trying to make us thin. I think the fat industry is winning.

After I decided I was going to speak at this public forum I picked up my December edition of "Health" magazine which I have gotten for years but I looked at with a different perspective. I was looking at the weight loss articles and there were many; there were 13. "Drink milk; lose weight." "Walk your way to weight loss." "Blast away the pounds." "Drinking water is essential to weight loss." "You want bacon and eggs; skip the bacon; use a bacon spritz." My favorite one was "Mom, do you want to get your weight back? Try Everslim, formulated by doctors." Well, my goodness, if it is formulated by doctors it has to be good! And there were more.

In terms of my own personal history, I don't know if any of you out there are old enough to remember Metrical, the first liquid weight loss meal replacement. It was the precursor of Slim-Fast. I don't know if any of you remember the

medication Aids, a little caramel you took with hot tea before you had your meal. It lost its marketing share when a terrible illness came out with a similar name. I have tried the cabbage diet. I have tried the grapefruit diet. I tried Dr. Erwin Stillwin's quick weight loss diet, a precursor to the Atkin's diet. I have tried Weight Watchers. I have tried Weight Watchers again and again and again--and I could go on.

Obesity is becoming the number one killer in America. Take a look at the association between obesity and type 2 diabetes. I challenge every one of you in this room to go to an outpatient chronic dialysis center and take a look at the patients that come every day for hours for kidney dialysis. You are going to see blind patients. You are going to see patients in congestive heart failure. You are going to see patients who are obese and have amputations and, of course, these patients have kidney failure. And this is the result for many of them from being obese.

We need help. We need safe help. There

is a multimillion dollar industry out there selling over-the-counter weight-loss products that are unregulated, untested and unsafe, and we are buying them and we are swallowing them in massive quantities. We heard about the deaths from Ephedra. Well, there are over-the-counter drugs out there that contain massive doses of caffeine, chromium and bitter orange which is purported to have a chemical similar to Ephedra. And we are taking those medications.

FDA, you have been wonderful and responsive in allowing formally prescription medications to be sold over-the-counter--pain management medications, medications for smoking cessation, medications for acid reflux, allergies, to name a few. I believe that now is the time for the FDA to step in and approve a product that has been tested as proven safe and effective and will live up to its name. We are literally dying for something like this.

I am not alone in this battle, and I ask the FDA to please consider this medication to allow

us to have an additional tool which can help us. Thank you.

DR. WOOD: Thank you. The next speaker is number four, Laurie Tansman.

DR. TANSMAN: Thank you. First, my comments reflect my own professional opinion, not of my medical center, and I have no financial conflicts of interest.

I am going to be addressing the issues that are bolded on this slide. First, the concern of vitamin malabsorption. To address this concern, the FDA should require that the fat-soluble vitamins be added to orlistat, just the way the FDA required that these vitamins be added to food products containing the fat substitute Olestra. How this will be compounded into orlistat for appropriate time release will need to be addressed by GSK.

Second, will lifestyle changes such as diet and exercise be disregarded? These are the well-known cornerstones of weight-loss treatment which were discussed today, and even in the Xenical

patient education material the section on reduced calorie diet is bolded. Of course, as we heard today, the over-the-counter version of orlistat will be marketed to emphasize the importance of diet and exercise too.

But in this quote from Dr. Robert Bonow in addressing concerns about statins being approved for OTC, the same concerns can be addressed regarding approval of orlistat for OTC, namely, human nature. People who ought to be dieting and exercising are going to feel that since they are taking the pill they can now continue habits that are unhealthy and I can tell you that, as a clinician, I see this all the time and hear it daily.

Third, how will over-the-counter orlistat impact on the obesity epidemic? In the press release from GSK in July, 2004 it was stated while a healthy diet and exercise remain core treatment approaches, they have not halted the epidemic. You know why these approaches may not have halted this epidemic. Do we provide the opportunity for a

person to realize appropriate dietary and exercise changes with professional health? The answer is no.

On the website of this well-known weight control center at St. Luke's Roosevelt Hospital in New York City it states, insurance reimbursement varies depending on your health plan. Physician visits are usually covered but nutrition classes and exercise sessions most often are not.

From the Xenical website, it makes one wonder just how serious the American healthcare system is about addressing obesity today if a prescription medication cannot have insurance reimbursement.

I am just going to read this to quote Morgan Downy who is actually speaking after me today, he said once in a publication that Medicaid and other healthcare plans cover prescriptions of Viagra for male ED but do not cover many forms of obesity treatment. Few would argue that male ED is as serious a threat to obesity. If we are going to get serious about weight loss, then we have to

address the issue of consistent insurance reimbursement for dietary and exercise intervention, as well as for prescription weight-control medications. Until the insurance industry gets serious about weight loss we cannot begin to see a statistically significant decline in the obesity epidemic.

Approving orlistat for OTC rather than fighting for insurance reimbursement may have a negative impact on obtaining reimbursement for the core treatment approaches to weight loss. In fact, approving orlistat for OTC diminishes the seriousness of how we approach the treatment of obesity. Obesity deserves to be treated with the same seriousness as other chronic medical illnesses. As you well know, it wasn't until April, 2002 that the IRS first ruled that obesity is medically accepted to be a disease in its own right, and that medically valid weight-loss treatments not covered by insurance could be taken as a tax deduction.

If we are going to get serious about

addressing the girth of this nation, then insurance reimbursement for recognized treatment modalities is a must and that is where we need to focus our efforts. Thank you.

DR. WOOD: Thank you. The next speaker is Morgan Downey, number five.

MR. DOWNEY: Good afternoon and thank you. I am Morgan Downey, executive director of the American Obesity Association. We are a non-profit, tax exempt educational and advocacy organization. We have numerous conflicts of interest. In addition to receiving some funding from the sponsor, GlaxoSmithKline, we are supported by lay members, professional members and the following companies, Abbott Laboratories, Amlin, Bristol-Myer Squibb, Eli Lilly and Co., Inamed Corporation, Johnson & Johnson, Pfizer, Roche, Sanofi-Aventis, Weight Watchers International, Jenny Craig, Ethicon, Endosurgery, Slim-Fast, Wellspring Camps, American Society of Bariatric Surgeons, American Society for Bariatric Physicians.

I would like at the outset of my statement

to point out an issue that came up this morning that I was surprised was not clarified. This goes to the safety issue with cyclosporine. I think it is important to point out that persons who are obese are not eligible for organ transplantation. They are not eligible as donors or as recipients. We had this information anecdotally. I was able this summer to confirm it with the Department of Health and Human Services, Office of Organ Transplantation which confirmed their understanding of the protocols followed at transplantation centers.

Obesity is the most prevalent fatal, relapsing chronic disease of the 21st century. It affects every racial, ethnic gender and age group in the United States. It is increasing at just under one percent a year, an unprecedented rate for a chronic disease. No other condition--not cancer, heart disease or HIV AIDS--compares to obesity's prevalence, mortality, morbidity, disability, stigma and discrimination. Prevention of weight gain when one is at a normal weight or overweight

has been recognized by the Surgeon General and others as a major national public health goal and as part of Healthy People 2010.

Obesity has been associated with numerous adverse conditions affecting every body organ, including type 2 diabetes, stroke, coronary heart disease, heart failure, sudden death, hypertension, high triglyceredemia, hypocholestemia, osteoarthritis of the knees and hips, several cancers, obstructive sleep apnea, gallstone, GERD, fatty liver disease, urinary stress incontinence, PCOS, reproductive dysfunctions, miscarriages, birth defects and end stage renal disease. It is associated with increased mortality and reduction in the years of life lived without disability. In addition, it is often accompanied by painful emotional distress, stigmatization and employment discrimination.

We support the conversion of orlistat to an OTC status for the following reasons: One, orlistat has been evaluated in over 100 clinical trials involving over 300,000 subjects in four-year

controlled clinical trials. Orlistat prescription dosage is approved in over 145 countries, including six in which it is available over-the-counter.

Numerous studies have shown prescription orlistat is effective in weight loss and improvement in lipids, glucose, hemoglobin A1c, blood pressure, dyslipidemia and hyperglycemia. In diabetics, prescription orlistat has been shown to improve insulin resistance, glycemic control and reduction in the use of diabetes medications. These benefits seem likely to continue at lower dosages.

Orlistat, since its approval, has not shown significant unintended adverse health effects which are non-serious, transient, predictable and manageable. Numerous governmental and professional treatment guidelines and technology assessments support the use of orlistat for weight loss, including the guidelines of the NIH and technology assessments from the Agency for Healthcare Quality and Research.

The over-the-counter weight management

category has no approved FDA product. Most of the over-the-counter dietary supplements purporting to cause weight loss have little to no research behind them and are not subject to any independent review and approval.

Frankly, I was stunned this morning that the FDA did not brief the committee better about the extent of the dietary supplement market. Yesterday, not a half block from here, I went and purchased this item. It is advertised as an exclusive hunger-satisfying formula; safely reduces hunger; reduces body fat. This is called Diet Fuel. It says lose weight; gain energy--totally unregulated. There are dozens of these products on the shelves of the nation's pharmacies; not one approved FDA medication. Many of these OTC products for weight loss are subject to FDA or Federal Trade Commission enforcement actions for false and misleading advertising. Just a week ago the FDA issued warning letters for two unapproved dietary supplements.

Having an easily accessible, affordable,

effective weight-loss product available over-the-counter will be important to the uninsured population and the under-insured population which tend to be of lower socioeconomic status, female and minority. Thank you for your time.

DR. WOOD: Thank you. The next speaker is number six, Dr. Robert Berkowitz.

DR. BERKOWITZ: Good afternoon. I am Robert Berkowitz, representing NAASO, the Obesity Society. NAASO has received an unrestricted financial contribution from Roche Laboratories, which manufactures orlistat, and from GlaxoSmithKline, which seeks OTC use of the product. Both companies have supported the Society's annual professional scientific meeting and other educational related activities, including research.

NAASO's public affairs committee reviewed the scientific literature and briefing materials, prepared this statement and declares no conflicts of interest with Roche Laboratories or GlaxoSmithKline in general or this application

specifically. NAASO's public affairs committee developed this statement independently from, and without input from the NAASO officers or administration.

NAASO has 2000 members and we are committed to improving the understanding of causes, consequences and management of obesity. In considering the present OTC application, the Society's public affairs committee assembled a panel of scientists and practitioners to review the publicly available information presented by GlaxoSmithKline and the peer-reviewed scientific literature previously published on orlistat. This evidence was reviewed in consideration of orlistat's approval as an OTC medication, quote, as a weight-loss aid and to promote weight loss in overweight adults when used with a reduced calorie, hypocaloric low fat diet, unquote.

NAASO, the Obesity Society, is in principle supportive of the development and approval of OTC weight management products that have proven safe and effective in rigorous

scientific clinical trials and/or in post-marketing surveillance of ethical pharmaceuticals as prescribed by physicians and other licensed practitioners. The position of NAASO, thus, is to support the application of GlaxoSmithKline to the joint meeting for the approval of orlistat OTC as outlined in the briefing document, dated January 23, 2006.

It is important to note that a five percent to ten percent weight loss has significant health benefits, as shown in the diabetes prevention program research group's publication. This is the amount of weight loss expected from adjunctive use of orlistat when used with a reduced calorie or hypocaloric low fat diet. This is in distinction to numerous currently available over-the-counter products that have no effectiveness or safety scientific publications.

Our committee's view is that orlistat has a strong safety record, with no serious adverse events attributable to the drug since its introduction in the United States in 1999. There

are, however, potential safety issues. While NAASO believes that orlistat has a strong safety record, panel members thought that several issues should be carefully addressed in considering OTC use of the product.

The first relates to the lipid-soluble vitamin depletion and interference with the absorption of selected drugs. There is a major need for multivitamin supplement of fat-soluble vitamins while taking orlistat over-the-counter. Orlistat also may interfere with the absorption of lipid-soluble drugs--as noted earlier--cyclosporine and warfarin. It is important that any over-the-counter bottle clearly note these concerns. Labeling should also strongly recommend that multivitamin supplements be taken with orlistat. We recommend that these be noted on the bottle under a precautionary note.

We are concerned also about potential for misuse as an over-the-counter drug. There is concern that this availability may potentially lead to misuse by people who suffer from eating

disorders such as anorexia nervosa or bulimia nervosa. Furthermore, orlistat over-the-counter is only recommended as an adjunct to lifestyle modification such as individuals engaged in an active weight-loss program that focuses on healthy diet, caloric restriction and increased physical activity.

Regarding age limitations of orlistat use, there is available research suggesting that orlistat use must be limited to persons aged 14 years and older. Research indicates that trials have been conducted with adolescents and there were no serious problems. This research found that orlistat in combination with diet and exercise and behavior modification improves weight management in obese adolescents. We are concerned that normal and/or anorectic or bulimic adolescents may misuse this drug. The orlistat package limits orlistat use to overweight adults 18 or older. However, there are no controls to limit usage to this age, and such limitations ought to be recommended.

In summary, NAASO, the Obesity Society,

endorses the approval of orlistat as an over-the-counter drug. Thank you very much.

DR. WOOD: Thank you. The next speaker is Dr. Nathaniel Clark, number seven.

DR. CLARK: Good afternoon. I have no personal conflicts in regard to GlaxoSmithKline. The American Diabetes Association accepts money and grants from GSK, as we do from all companies essentially and equipment companies in the area of diabetes.

My name is Nathaniel Clark and I am a pediatric and adult endocrinologist, and the national vice president for clinical affairs for the American Diabetes Association. I am also a registered dietitian.

The mission of the American Diabetes Association is to prevent and cure diabetes and to improve the lives of all those affected by it. Overweight obesity is both a major risk factor for diabetes and significantly complicates diabetes management in those with it. Due to our interest in overweight obesity, we have recently established

Shaping America's Health, the association for weight maintenance and obesity prevention, and I speak today on behalf of both the American Diabetes Association and Shaping America's Health.

It is estimated that greater than 120 million adults, nearly two-thirds, are overweight or obese and the increases seen over time are dramatic. Overweight obesity substantially raises the risk and morbidity for type 2 diabetes, hypertension and dyslipidemia, all major risk factors for cardiovascular disease, stroke, as well as several other medical conditions.

Even a modest five percent weight loss can have a significant clinical impact on the levels of cholesterol, blood pressure, triglycerides, hemoglobin A1c and, of course, the risk of developing type 2 diabetes. Current estimates suggest that more than 20 million Americans have diabetes and 41 million have pre-diabetes. The significant increase in both these conditions is closely linked to the dramatic rise in overweight obesity.

On a more positive note, in both the Finnish diabetes prevention study and the diabetes prevention program trial weight loss of five to seven percent and modest increases in physical activity resulted in greater than 50 percent reduction in the development of diabetes in those with pre-diabetes felt to be at high risk. It is estimated that one in three American adults is attempting weight reduction, much of which is self-driven and not medically supervised.

While lifestyle change, decreased caloric intake and increased caloric expenditure should always be the primary treatment approach, weight-loss medications can be an important adjunct to these approaches in those who meet established criteria. As with any over-the-counter product, careful review and consideration must be given to product labeling so that consumers are fully informed about the product's risks and benefits, particularly if they are part of a population that would be considered at high risk of experiencing significant side effects as a result of their other

health conditions.

In closing, having a safe and effective medication for weight loss available as an over-the-counter product, in conjunction with important lifestyle behavioral changes, would provide an important addition in the treatment of this condition. Thank you very much for your consideration of this application.

DR. WOOD: Thank you. The next speaker is number eight, Jennifer Weber.

MS. WEBER: Good afternoon. My name is Jennifer Weber and I am the manager of National Nutrition Policy for the American Dietetic Association, which I will abbreviate ADA. I am a registered dietitian and a public health specialist. I do not have a financial agreement with GlaxoSmithKline.

Instead, I am here representing ADA's nearly 65,000 food and nutrition professionals who are working to improve the health status of Americans through proper nutrition. ADA members work in nearly every aspect of food, food safety,

nutrition and health.

Since dietetics is the only nutrition science that directly connects food to nutrition and health, dietitians are uniquely trained in ways to help the public integrate nutrition into healthier choices and lifestyles. ADA has a long-term commitment to health literacy and nutrition education.

Helping people attain and maintain a healthy weight is a major focus of ADA and its members. We know that obesity is a complex, multifactorial chronic disease state involving interactions between genetics, physiological, metabolic and environmental influences. The nature and depth of work required to effectively intervene on an individual or community basis will require resources beyond those routinely provided today.

Both public and private initiatives are necessary to combat factors contributing to the increase of obesity rates. Furthermore, strategies for more treatment and prevention are needed. ADA recommends a framework that includes

multi-disciplinary health initiatives with registered dietitians providing their particular knowledge and skills to help people make the necessary changes in diet, combined with activity, to achieve health diets and healthy weights. Interventions must be carefully targeted and chosen based on generally accepted, peer-reviewed scientific research.

Obesity is such a complex chronic disease that it requires the expertise of a multi-disciplinary team over an extended period to effectively address it. Registered dietitians and diet technicians, physicians, nurses, psychologists, exercise physiologists, pharmacists and others working collaboratively have the best opportunity to identify and treat, support and educate people so they can be successful in addressing overweight at all stages of their life span.

Two, programs integrating both nutrition and physical activity that support the individual to be able to make wise lifestyle choices.

Three, greater funding for basic, translational and outcomes research on overweight and obesity and, four, continued, current and adequate monitoring and data collection of food intake, eating behavior and health status as needed to assess the incidence of obesity, identify at risk populations and define contributing factors to increases prevalence of overweight and obesity, and to design and offer successful interventions.

Approving orlistat for over-the-counter sales provides the public an important additional resource to successfully lose weight. At this time, no OTC anti-obesity agents similarly scientifically tested and approved by FDA are available to consumers, although a number of commercial food and supplement products without similar safety and efficacy testing and approval are.

ADA urges that, if approved for OTC sales, the orlistat label include a statement to advise consumers that the drug works best when combined with a reduced calorie, low fat food plan and

increased activity, and that safety and efficacy may be enhanced by seeing and following the advice of qualified health professionals, including the registered dietitians. Registered dietitians are best able to assist individuals in making the required changes for optimal drug compliance and results.

To summarize, helping people attain and maintain a healthy weight requires multiple strategies and resources. Few conditions are so difficult for an individual or society to successfully address. Finding the resources that work, making them available in concert with appropriate supportive services and offering them responsibly to the public is our hope for overcoming the epidemic of obesity one person at a time. Thank you.

DR. WOOD: Thank you very much. The next speaker is number nine, and John Foreyt.

DR. FOREYT: Good afternoon. My name is John Foreyt. I am with Baylor College of Medicine, Behavioral Medicine Research Center. We do have

conflicts. We have been funded by Roche for a number of clinical trials. I am one of the authors on the JAMA 1999 paper that was two years with the 60 mg during the second year. But what I say is my own. I mean, nobody told me what to say.

I believe that the best way to really manage weight is a healthy diet and good exercise program, period. Use behavior modification to support that; self-monitoring; stimulus control; cognitive restructuring and social support. That is the way to go. Unfortunately, you know, if it were that easy--if lifestyle modification was easy everybody would be skinny. Everyone is not. Two-thirds of us are overweight. We are gaining one percentage point a year in terms of overweight and obesity. By 2040 the entire population of the U.S. will be overweight assuming present trends continue--present company excluded but everybody else.

But the bottom line really is that we need all the help we can get. If we then have a safe, effective drug like orlistat, a tool, why not? To

me, it is a no-brainer. What people are doing out there, as all of you know, is they are buying these idiotic diets. They are buying these stupid pills that Morgan showed you that you can buy in any health food store. We need something that really is safe and effective. Orlistat has been tested--you saw the studies--more than any other obesity drug in the world.

We find that in addition to its work as a fat blocker, from a behavior modification point of view it really works as a way to avoid a high fat diet. The patients that we have seen that have lost 100 pounds on orlistat really use it also as a behavior modifier tool. That is, they say I am going to stay away from this high fat diet to help me to not have these treatment effects. So, it works in both ways, as a fat blocker and a behavior modifier tool.

I believe, again, all of us need all the help we can get. I think orlistat has been shown to be safe. It is effective and, you know, to me it is a no-brainer; get on with it. We need this

stuff so I really urge approval of this drug.

Thank you.

DR. WOOD: Thank you. The last speaker is Valentine Burroughs, who is number ten.

DR. BURROUGHS: Thank you. I have no conflicts. The NMA paid my way here out of our concern for obesity and overweight of the African American community.

Good afternoon. My name is Dr. Valentine Burroughs. I am the chief medical officer and chairman of the Department of Medicine at North General Hospital, in New York City, right in east Harlem, at the epicenter for the obesity epidemic in New York State.

I am here representing the National Medical Association, based in Washington, D.C. The NMA is the oldest and largest African American professional association, comprised of some 30,000 African American physicians with over 120 affiliates nationwide. The National Medical Association is focusing on eliminating health disparities and improving health outcomes for

people of color, and over the next five years one of our areas of concentration is addressing the emergent problem of overweight and obesity among African Americans.

There are an estimated 120 million, or 64 percent of Americans who are overweight or obese. Of course, the correlation between obesity and overweight and the risk of developing serious and often disabling medical conditions cannot be ignored. Adult African American women had age-adjusted obesity rates of 48.8 percent compared to 30.7 percent of adult white women according to the CDC data for 1999 to 2002. That same data indicate that African American adolescents are much higher in terms of rates of overweight than white children in the same age groups during the same time frame.

As the data show, overweight and obesity is a real problem that must be effectively and proactively addressed and, clearly, those suffering with benefit from affordable, accessible treatments that have been extensively studied and shown to be

safe and effective. There is a clear need for additional tools to combat overweight and obesity. Specialized clinics and a variety of treatment facilities offer a choice for those who have access to such intensive treatment options. But for those of the population who don't the options are limited.

We hope that this advisory committee and the administration will take into consideration that there are millions of people who try to lose weight unsuccessfully, often using nonprescription supplements for which there is limited clinical data supporting safety or efficacy.

The National Medical Association recommends the approval of well-supported, clinically proven weight-loss treatments that may benefit millions who truly need the help. The National Medical Association's focus on overweight and obesity that disproportionately affects our patient population reflects our mission and our continued historical commitment to improve health outcomes for all people, especially people of

color, to achieve parity in healthcare.

As a practicing physician and endocrinologist faced with the overweight and obesity problem on a daily basis, over the years I have been ashamed of my success, or lack thereof, in helping patients who suffer from this very difficult disease. The overwhelming burden that society places on individuals who suffer from obesity is really a contradiction relative to the attitude of the American marketplace in providing suboptimal choices to promote good health and nutrition.

To fight obesity we need all of the help that we can get, particularly safe help. I want to thank you for your careful consideration of this vitally important adjunct to the battle against weight loss. Thank you.

DR. WOOD: Thank you very much. We actually have one more speaker who has announced he would like to speak, Alex Perez.

MR. PEREZ: Good afternoon. My transportation and my lodging was paid for by

HealthSTAR. My name is Alex Perez. I am from Houston, Texas. I want to share with everyone at the advisory committee meeting how orlistat has helped me get back to a healthy weight.

For years I struggled with my weight because I didn't know exactly how to eat right. I thought I was eating healthy food when I ate Caesar salads, Greek salads. I developed high blood pressure, diabetes and high cholesterol. My doctor told me that I had to do something so he enrolled me in a diabetes study at the Baylor College of Medicine and put me on Xenical. I started following the healthy diet and learned ways to change my relationship with food.

As a result, I lost 40 pounds. I feel great. My blood pressure has improved. My diabetes is under control and my cholesterol is lower. But most importantly, I have learned how to eat right. I know that other people like me can benefit from the drug and I think it needs to be made available to the public. Thank you for giving me the time to speak about my experience at this

meeting.

DR. WOOD: Thank you very much. That concludes the open public hearing. Let's return to the committee's questions and discussions. There were some hangover questions from before. Neal?

Committee Discussion/Questions

DR. BENOWITZ: Before I talk about that, I have a number of safety questions. I would like to get back to the question I asked this morning and the one that Paul talked about before which relates to the Davidson 1999 study, which seems to me to be one of the most important bits of data. The sponsor, unfortunately, didn't show us that but that, as you recall, it was a two-year study where people underwent behavioral modification with dietitians, food diaries and counseling. After one year people who had taken orlistat were switched to placebo. There was also a full placebo group for two years. In the second year the placebo group did not gain very much weight. So, it seemed to me that what they lost in the first year by just diet and exercise was pretty much--there was a small

amount of weight gain but they maintained most of it. The orlistat group regained every bit of excess weight that they had lost in the first year so by year two they were exactly the same as placebo.

So, there is no question that orlistat is effective when you are taking it. But I would just like to have some more reassurance from the sponsor that what they are planning--the six-month therapy and a behavioral package will be any different than the Davidson study which involved extensive counseling and which showed no benefit at all at two years.

I think this may still be controversial but I have read studies that when you lose weight and gain weight repetitively that may have adverse health effects. So, I am concerned that this, while in the short term may be useful, may not provide long-term benefit. I would just like the sponsor to try to reassure me.

DR. WOOD: So, the question is what is the relationship between short-term use of this drug

versus long-term reduction in weight?

DR. BENOWITZ: Is there any prospect that six-month treatment is going to produce long-term benefit?

DR. DENT: First of all, I would just like to clarify that I did not know that the last speaker was going to speak and they indicated that their travel was paid by HealthSTAR. You should all be clear that HealthSTAR is a communications firm that has been helping GlaxoSmithKline with this project. I apologize for that.

I would like to ask Dr. Hauptman to first address the issue of the study and then we will move to addressing the question of rate weight loss and regain. The reason that data weren't presented is because there was no 60 mg dose in the one-year weight loss period.

But very important, I don't think that the reviewer who presented it--and we don't have a slide but we could put up their slide, if you want--didn't really present what happened in the second year. After the first year, after patients

lost weight the entire study design really switched to maintaining their weight. We reevaluated their dietary requirements based on the new body weight. If they actually increased weight they were told not to go back and try to lose weight but try to maintain whatever weight they were on.

The third point is that you can't use that study as an example of what happens when you stop the drug because patients were placebo controlled. So, these patients who were on orlistat the first year assumed that they were taking the same treatment the second year and, therefore, it is not the same thing as losing weight and now saying you have to use new strategies to maintain that weight. So, those design concerns are very important to understand.

The fourth point for that study was that the placebo group lost weight and regained it at the same percentage based on what their maximum weight loss was. They regained it. They didn't spend a great deal of time on that but I can tell you that is exactly what it did. So, that is not a

good example of what happens because the patients still thought they were getting all the same treatments, which is different than if you actually now lost the weight, which you have to before you can have an attempt to maintain it.

DR. WOOD: I think what Dr. Benowitz is trying to get at is after you have lost weight on six months of this drug, what are the chances and what are your data that that weight loss is maintained? I think the answer is you don't have data.

DR. HAUPTMAN: You are right. We never did a clinical study.

DR. WOOD: So, the answer is we don't know if there is evidence that you maintain your weight loss after six months, which probably doesn't reassure Neal. Is that right, Neal?

DR. BENOWITZ: I have to say I think it is a shame that the example of nicotine over-the-counter wasn't followed where efficacy trials were done with the over-the-counter package. The package proposed here may be very effective,

but we don't know and I really wish we had some evidence that it worked.

DR. DENT: Could I ask Dr. Foster to address that?

DR. WOOD: Let's not keep on having people jump up and down or we will never get through. Dr. Carpenter?

DR. CARPENTER: Yes, I had a brief question related to some of the materials that were provided in the handouts sent to the committee. This had to do with a pharmacy mechanism by which under-aged potential purchasers of over-the-counter orlistat would be prevented from doing that because of some bar coding or something to that effect. I was not aware of such a system and wanted to know if such a system was in place for other over-the-counter medications and how effective that is in a setting where one is trying to restrict sales to those under 18. I think it was in some of the sponsor's materials.

DR. WOOD: The sponsor can probably answer that with the nicotine experience.

DR. DENT: When nicotine was approved there was a system for age verification and it was effective, as was demonstrated and agreed with the FDA.

DR. GOLDSTEIN: Alastair?

DR. WOOD: Yes?

DR. GOLDSTEIN: Two questions, number one, does the sponsor have any outcome--we have heard a lot about vitamins today. Does the sponsor have any data on outcomes in those given orlistat and vitamin-related matters?

DR. DENT: Yes, indeed, there is a large body of data from the Xendos study which includes outcome data. Dr. Hauptman?

DR. HAUPTMAN: One of the key things that we wanted to determine was are there biological consequences to the small changes in vitamins that we see. So, as part of the Xendos data, we did measure to look at biologic markers of change in bone. One of the key concerns obviously is if you have decreased vitamin D you could have decreased calcium causing secondary hyperparathyroidism, then

producing decreasing bone mass, increased bone turnover.

Can I have the slide on, please? In the Xendos study what we did was, we looked at calcium. We looked at those patients who had low calcium, high parathyroid, high osteocalcin, and high urine anterior peptides as markers of changes that could occur with bone. We looked at it by year by treatment group.

If you look at the data for the first year, very few patients have low calcium levels, 0.2 to 0.1 percent, very similar between orlistat and placebo. If you look then at those patients that had elevated parathyroid hormone which could be a consequence of low calcium, if it was there, again, 0.4 on placebo, 0.1 on orlistat and, again, no differences in terms of osteocalcin or urinary anterior peptide.

We did that for each year subsequently through four years where we see that at the end of four years of treatment those patients on orlistat or placebo had very small numbers of patients with

low calciums or high parathyroid hormones and really no effects that we saw on bone.

But we also did DEXA measurements in a subgroup of patients. Slide on. At two of the sites we did DEXA measurements, and these are patients that actually continued and finished four full years of treatment and, again, we looked at bone mineral density over the entire time and we see, again, no difference if you look at the mean or the median value over time. These were in Sweden. This was total bone mineral density.

There is some other data that we have which I think would be useful in terms of changes. Could I have slide 43, please? In the original NDA we also thought it was important to look at the patients who were postmenopausal who were not receiving estrogen treatment--slide on, please--to see if they had differences over two years of treatment. Here you can see that in this subgroup of patients we have similar values for 25-hydroxy vitamin D. The two-year change from baseline was not significantly different. It was about the same

in both groups. The incidence of patients who had two consecutive low values and these were patients who, you know, were considered supplementing, also had no significant difference. Slide off, please.

We have additional data in different subgroups, but essentially what we found was that the small decreases in vitamins that we saw, although statistically significant, didn't really reach the level of clinical significance. Remember, these are all patients who didn't get any vitamin supplementation so probably 98 percent of patients in our four-year studies had no vitamin supplements, yet still had no evidence of abnormal bone marker changes or DEXA changes.

DR. DENT: Maybe somebody could go and ask the hotel if they would switch off the sound system in this room.

DR. WOOD: The issue here, as I see it, is you either want to undercut the data on the need for vitamins or you don't but you can't have it both ways. You either think that people should take vitamins, in which case you have to develop a

system to make sure they should; or, you don't think they should take vitamins, in which case you shouldn't have proposed it in the first place. You can't do both simultaneously. You can't stand here and say you don't need to take the vitamins but we are saying you do and, at the same time, say, well, you don't really need to take the vitamins so don't bother about that. It has to be one or the other, guys. Make up your minds.

DR. DENT: Prof. Wood, we think that it is appropriate for people to take vitamins and we will certainly work with the FDA to make sure that we have appropriate labeling and that people follow that.

DR. WOOD: So, it is not your position, as we just heard, that that doesn't matter?

DR. DENT: We think that it is appropriate for people on orlistat to take vitamins. We don't think that it will cause a significant health effect but it would be sensible for people to do.

DR. WOOD: So, we need to make sure that that happens properly. Terry?

DR. BLASCHKE: I wanted to just follow-up on Neal's second question that I don't think really got an answer, and that has to do with the risks or the benefits of essentially the up and down recycling of weight that occurs in obese individuals. That is, they lose weight; they gain weight; they lose weight. Neal raised the question as to whether there is any information about whether or not that could be harmful. I would raise it in the other direction as well, could it be helpful? An integrated issue is, is some weight loss part of the time better than no weight loss any of the time? I just wonder if there are any data addressing those questions.

DR. DENT: Thank you. Dr. Benowitz, apologies, you did ask that question and I lost it; my fault. Dr. Apovian, would you like to address that question?

DR. APOVIAN: So, the question was what are the effects of weight cycling? Is it detrimental to long-term health or could it actually be beneficial? First of all, a 1993 task

force on weight cycling concluded that there are no detrimental effects to be seen in the literature from weight cycling, and the authors concluded that people should not be dissuaded from trying to lose weight. That is the first point.

The second point is that in my talk today I mentioned that Americans are gaining weight. I talked about the Framingham heart study that showed that people who started out with normal weight, one in two eventually became overweight over 30 years and a proportion of normal weight persons actually went on to obesity. Theoretically, if those people were trying to lose weight and weight cycled throughout that period of time, they could potentially have ended up at a lower weight than if they had done nothing and continued to gain weight and gone on to become overweight or obese. So, I would argue that weight cycling can actually be beneficial in the long term.

Slide on, please. I just want to show this slide. This is from a weight-loss trial with sibutramine and it shows that there were times

during the trial when patients on sibutramine were then placed on placebo. As you can see, those patients who were on sibutramine--it is called intermittent sibutramine therapy--then went off the drug and started to regain weight. But then, when placed back on intensive treatment with sibutramine, they then lost weight. The whole time they did better in the end than those patients who were on placebo through the entire period.

So, this basically proves my point that if you try to lose weight but then start to regain and then go on another intensive program, you will end up being better off than if you really didn't try at all during that period of time.

DR. DENT: Thank you.

DR. WOOD: Neal?

DR. BENOWITZ: Just a follow-up on the vitamin question, is it true that to absorb fat-soluble vitamins you need to have fat? If not, if you take it at a time when there is no fat in the GI tract, will you absorb them?

DR. DENT: I think the answer is quite the

reverse. If you have unabsorbed fat in the GI tract, that will decrease the absorption of fat-soluble vitamins but generally if you take fat-soluble vitamins when you don't have high levels of fat they will still be absorbed.

DR. WOOD: Ernest?

DR. CLYBURN: Yes, in the 16-week trial there was a statistical significance only for about three percent weight loss and this was in an overweight population. Are there any data that three percent weight loss with a BMI of 25-28 confers any benefit?

DR. DENT: First of all, I would just like to emphasize that it was only a four-month period, and the purpose of that trial was to look at the pattern of weight loss that would occur in overweight individuals and to see whether that mirrored what was seen in the other clinical trials where you had a range of obese--mostly obese people. What we observed from that trial was that, in fact, the pattern of weight loss was similar.

To answer the question in terms of the

benefits of that, Dr. Bansal, would you like to address that?

DR. WOOD: While she is coming up, I think in fairness, weight loss is an approvable indication in itself. So, you don't actually have to establish that there is a relationship to some other benefit. Right?

DR. DENT: That is correct.

DR. BANSAL: That is correct. Can I get the slide from my core please, C-44? It may have been renumbered to C-45, the slide I showed earlier on the risk factor improvement.

DR. DENT: You want the risk factors?

DR. BANSAL: Yes, I would like to start with the risk factors. No, no, no, next slide, please, the one on the risk factor improvement. Thank you.

In looking at the weight loss that was presented earlier with the four-month study, we did see significant improvements in some of the risk factors--systolic, diastolic blood pressure, LDL and total cholesterol. Slide off, please. EF-20,

please.

In looking at the weight loss seen in this four-month study compared to what we saw in the six-month studies--slide on, please--earlier I had presented the mean weight loss you see in the obese population, about five percent, very similar to what you see in the overweight population. To your point about the categorical analysis, I would like to also talk a little more about that. EF-23, please.

What we tried to do is to look at the percent of people in the six-month studies in the obese population and see what percent of those lost three percent at four months and went on to lose five percent at six months as a way to predict what percent of people who lose three percent at four months go on to lose five percent at six months.

What we found was that for those people who lost at least three percent of their weight at four months in the six-month studies, the majority of them went on to lose five percent at six months. In the FDA review there was another analysis that

was done looking at the predictability of the four-month data to the six-month data. If we could put that slide on, please?

Here what we see is a very tight correlation coefficient showing that what you see at four months is very predictive or what you would see at six months. So, I would like to emphasize that that study was not designed or powered to achieve the categorical analysis. It was designed and powered to look at significant mean percent weight losses at four months compared to placebo and not to look at the categorical analysis. So, we had not achieved it because we had not set out to achieve it. But in looking at this predictability, it is highly expected that we would have achieved that endpoint.

DR. WOOD: Mary?

DR. TINETTI: My question is actually related to that, sort of taking it to the next step. I think we are convinced that you have shown us that there is a statistically significant change in weight and that that translates into changes in

these risk factors. But the clinical benefit is I think what we are particularly interested in and my question is, assuming that we have the two-three kilogram weight loss, which is probably what we can expect from the data that you have shown us at six months looking at the slide that Dr. Apovian showed, that means that the systolic blood pressure will change by about 1.2 to 1.5 mmHg--

[Audio interruption]

DR. WOOD: That was the sound guy getting shot!

[Laughter]

DR. TINETTI: --the LDL cholesterol, for example,, by about 2 mm/dl. Do we have any data that those translate into clinically relevant outcomes such as strokes, MIs? And, to address Alastair's point, although that may not necessarily be a bar that we have to show, this is benefit versus harms so this speaks to that side of the equation. So, is there any evidence that these levels of changes translate into stroke prevention, MI prevention?

DR. DENT: Dr. Foster?

DR. FOSTER: The answer for orlistat specifically is no, but the answer for the whole field is no as well. One of the problems in the obesity field right now is that there is not a single long-term trial that has looked at hard outcomes in terms--

DR. TINETTI: That is not my question.

DR. FOSTER: Okay, what is the question?

DR. TINETTI: You have shown us data to show how much change you can expect in these risk factors with the amount of weight loss that you expect with this product. You have also shown us epidemiologic data that relate to weight loss and a change in these risk factors. My question to you is are there any even epidemiologic data to show that this amount of risk factor change--a millimeter of mercury or two of blood pressure and maybe 3 mm/dl in LDL--translate into prevention of stroke or MI? That is the question.

DR. FOSTER: In the context of weight loss, I am not aware of any such data.

DR. WOOD: No, I think what Mary is asking you is in the Framingham data for example--

DR. TINETTI: Right.

DR. WOOD: --what would you expect to see in Framingham from a 1.2 mm reduction in blood pressure? That is what you are getting at, right?

DR. TINETTI: Exactly, and how much stroke prevention and MI prevention, for example, with these kinds of changes in risk factors.

DR. FOSTER: I am not aware of any data separate from weight loss.

DR. PARKS: Could I add something regarding the cholesterol reduction? Not necessarily for weight-loss drugs but certainly from clinical trial data, particularly the statins, you are asking whether or not we have some benchmark with respect to degree of LDL or total cholesterol reduction and degree of risk reduction.

If you look at data from AFCAPS, which is a primary prevention study with lovastatin, if you look at a secondary prevention study, let's say with simvastatin, typically across the board for

all these statin trials your risk reduction is about 30-35 percent, but the amount of cholesterol that you have to--these studies have shown that percent reduction is clearly in the range of about 30 percent reduction--much, much more than what you are seeing with orlistat.

DR. WOOD: Wayne?

DR. SNODGRASS: Again, I want to extend this benefit/risk consideration a little further. You presented data in the actual use study that only about 46 percent self-selected correctly. I think the efficacy data would say somewhere around 40 percent lost greater than five percent of their body weight.

My question really has two parts. One is do you have an estimate of the numbers of persons in the United States over the age of 18 who would meet the proposed criteria for use, say, on an annual basis? In addition to that, do you have an estimate of the number of persons who might purchase the product?

MR. BURTON: There are two components to

your question, estimate of the number in the U.S. who might... [not at microphone; inaudible].

DR. SNODGRASS: Criteria for use.

MR. BURTON: [Not at microphone; inaudible].

DR. WOOD: Turn your mike on.

MR. BURTON: The number of people who might meet the criteria in terms of the proposed use; and what was your second? I am sorry, Dr. Snodgrass, what was your second question?

DR. SNODGRASS: The second question is the number of persons estimated who might purchase it.

MR. BURTON: I think one of the principles that we talked about before is that Alli is certainly not going to be for everybody. We have been very up front in all of our communication with consumers about how Alli is based on gradual and modest weight loss. We have also been very up front in our concept tests where we have been very clear with consumers about treatment effects and what they can do to manage them.

So, with that very up front disclosure, in

the studies that we have done we estimate roughly five to six million new people each year would be using Alli, and we think that is probably the right place to be if we are going to get a committed consumer.

DR. SNODGRASS: So, that answers the question about the total number per year you are estimating would purchase it. Of that five to six million, how many would meet the criteria?

DR. DENT: Dr. Shiffman?

DR. SHIFFMAN: The 46 percent that you heard is based on a lot of the conditions that are no longer on the label. So, if we can have the slide on I will see if I can walk you through that.

In all, 18 percent of the people who presented for the actual use trial had a condition which is present on the current proposed label. Importantly, you can see that for the conditions that have attracted the most concern, cyclosporine use and warfarin, it was a little under three percent. So, the percent of people who are attracted to a product like this who have a labeled

condition of concern is nowhere near 46 percent; it is on the order of perhaps three percent.

DR. SNODGRASS: I guess it is not clear to me. The answer I got is that it is five to six million people that you are estimating in total would probably purchase this per year. But my question is really of that, are you telling me that 100 percent of them entirely meet so-called inclusion criteria?

DR. SHIFFMAN: Put that on, please, again. No, that is what is on here. In other words, using the actual use trial as a projection of who might be interested in orlistat, of the 681 people who showed up saying I might be interested in this product, 18 percent had any condition that is still listed on the current proposed label and a little under three percent were either using warfarin or cyclosporine.

So, this is a projection based on this sample of the percent of people--well, let me put it the converse way, that is, I think you saw in my presentation that 87 percent of the whole sample

were eligible to use orlistat--either had the conditions and made the right decision, or didn't have a condition which would have raised any limitation on their use of orlistat.

DR. SNODGRASS: Thank you.

DR. WOOD: Dr. Follmann?

DR. FOLLMANN: I have a couple of questions. The first series of questions has to do with analysis of study NM17247 where, according to the FDA analysis, we get a treatment effect of about 1.1 kg. This is in contrast to the other longer-term studies in heavier people where the treatment effect was about 2 kg. So, I am trying to understand what the reason for the difference would be. There were some suggestions made earlier including that maybe treatment effect varies with BMI. And, analyses by both you and the FDA have shown that it doesn't seem very plausible; that the treatment effect does seem constant as a function of BMI.

A couple of specific questions I have then are, the two studies where you had a larger

treatment effect you had a four-week run-in. I was curious as to what the purpose of that run-in was. In some studies where I have been involved where you have run-ins you will exclude people who sort of failed the run-in period; randomize only the successful people and then, you know, presumably you would get a larger treatment effect. So, I would like a little more detail about the run-in on the two studies. What was its purpose? What did it do?

DR. DENT: Could I ask Dr. Hauptman to address that question, please?

DR. HAUPTMAN: Since I designed the studies I can probably come up with an answer. The answer was that we were stratifying based on the amount of weight. It is well known that if you are successful in losing weight in a short-term period you will be successful in losing weight in a long-term period. If you are not a good loser in the first four weeks of treatment, you won't be a good loser at the end of treatment. No patients were excluded because they didn't lose weight. It

was really just to stratify because you could understand the situation where you have an imbalance. In groups that were on orlistat you have a predominance of good losers in the lead-in period who then will lose a lot of weight at the end of the trial and a lot of poor losers on placebo who will lose a little bit at the end of the trial so it will exaggerate the effect, or just the opposite. So, this is purely a stratification and these patients were not excluded regardless of if they lost weight, gained weight or did nothing.

DR. FOLLMANN: So, if no one was excluded would you say this is evidence that it helps to have four weeks of diet and exercise before getting Alli?

DR. HAUPTMAN: No, absolutely not. The data from our Xendos study had no lead-in period and it shows virtually the same results over time at the six-month period. And, we have other studies where we have no lead-in period as well. So, there is really no reason--at the time that you want to start treatment you can start your diet,

your exercise and orlistat at the same time and, at the end of the day, those patients who are on orlistat will lose more weight than those people who are on other active treatments.

DR. FOLLMANN: So, you don't think the run-in is a plausible reason why there is such a difference in the treatment effect between the two types of studies?

DR. HAUPTMAN: Not in that study, no, I don't think so.

DR. FOLLMANN: Could you go into a little more detail about the counseling that was done in the NM17247 and how that differed from the other studies? Maybe that will shed light on the difference.

DR. DENT: Dr. Bansal, the difference in counseling?

DR. BANSAL: The reason I think the treatment difference seems like it is different from the other studies is that we are looking at the absolute kilogram difference. But, if you recall, the initial body weight in these studies

with the overweight population and the obese population is different in that the mean initial weight in NM17247 was about 72 kg. The mean initial weight in the obese population was about 100 kg. So, you need to look at the mean percent weight loss, not at the absolute percent weight loss, as a way to compare the trials and in that you do see a similar percent weight loss from mean baseline weight and that is about five percent.

In addressing your question on the levels of dietary intervention involved in our clinical program--slide on, please--you are specifically asking about this study, NM17247, and basically that was a study with the least dietary intervention and there seems to be a bit of a difference, but that was a study which was intentionally done to mimic an OTC environment. Subjects were given written materials to take back with them after their study visits. They did come back with the diaries completed. Those diaries were checked for compliance to see if they were completed and subjects were using them, but they

were never given any kind of nutritional feedback whatsoever once those diaries were reviewed. They were simply used as a tool of compliance and not as a tool of providing any kind of specific dietary feedback, mainly because that study did not have any experts in the area of providing dietary intervention. There were no nutritional experts or dietary experts of any sort in this study or in NM14161. I hope that answers your question.

DR. FOLLMANN: The other questions I have are to do with cyclosporine. In the documents we saw there were I think two people who were using cyclosporine and one chose to use orlistat so, you did more studies, which I think is to your credit, and you got about 50 people who were on cyclosporine and asked them questions. In that, surprisingly to me, ten percent of the people on cyclosporine said they would still use or take orlistat.

That makes me a little more concerned about what the effect of taking cyclosporine with orlistat would be in transplant patients, and have

there been studies done which look at how it affects the absorption or the amount of cyclosporine in the blood and whether that can be linked to a risk of rejection?

DR. DENT: There are two components to your question. The first one is with respect to absorption and, yes, a pharmacokinetic study has been done or conducted in normal volunteers. When people took cyclosporine with orlistat there was a 30 percent reduction in the mean AUC. The information we have in terms of the outcome of that really come from the worldwide safety database and Dr. Marsh can review that for you.

DR. MARSH: This is the safety database of orlistat?

DR. DENT: Yes, the worldwide safety database from Roche.

DR. MARSH: I will share with you the data from the Roche worldwide safety database but, to put this into a little context, patients who have had an organ transplanted are usually very well briefed and educated that they shouldn't take any

new medication without first discussing it with their physician or, specifically, their transplant center.

Slide on, please. In sharing this data it is important to realize that up until November, 2005 there have been 22 million patients exposed to orlistat and there have been more than 29,000 cases of adverse events reported to the Roche worldwide safety database, of which only 44 refer to cyclosporine either as a co-suspect medication or concomitant medication. Of those, there were 38 reports of low cyclosporine levels. Of these 38, only two documented any changes in the graft status. Both of these were treated successfully. Neither of these patients actually lost their graft. In summary, although the warning on the label is that patients who are using cyclosporine should not use orlistat in an OTC setting, the data that we have had, based on the worldwide exposure to orlistat, is reassuring based on this data.

DR. WOOD: Although it doesn't reassure you very much that it works in the Rx setting.

Right? The warning.

DR. DENT: It is a slightly different warning in the Rx setting.

DR. WOOD: Right, but, you know, before we set up too high a standard for over-the-counter, I wonder how effectively the warning works there. After all, you obviously got a fair number of people who got the concomitant medicine in an Rx setting in your database so it is not necessarily clear that physicians are doing a better job.

DR. DENT: I wouldn't dare to say that!

DR. WOOD: Eric, you had something to say?

DR. COLMAN: I just wanted to follow-up on that point. The cases we saw soon after orlistat was approved came into the AERS database. It was quite evident that in one or two cases people actually had plotted out the cyclosporine serum levels and when people started taking orlistat with cyclosporine you saw a very rapid reduction in the serum level of cyclosporine. In some cases it was clearly subtherapeutic. After all, the adverse events we get are roughly ten percent of the total

events, so to say that someone would reject an organ because of orlistat I don't think is an exaggeration.

DR. FOLLMANN: Let's not forget this is in a prescription environment that we are seeing those adverse events. Presumably, there would be a lot more or some more people on cyclosporine taking orlistat inappropriately because they didn't read it well. I too thought that, you know, hey, if you have had an organ transplant and you are on cyclosporine you would be very well aware of it and never take anything that was contraindicated. That is not supported by the data that they have.

DR. WOOD: Which suggests that the current prescription warning isn't working very well either.

DR. FOLLMANN: You could say that.

DR. WOOD: Right. Neal?

DR. DENT: I would emphasize just two points, if I may. One, we will have a very solid program in place to educate transplant centers because it is an OTC medication.

DR. BENOWITZ: I want to get a little bit of clarification on the pharmacology of orlistat in terms of how long the effect lasts. I am trying to figure out the cyclosporine situation. If it blocks cyclosporine absorption, does that mean that they are both taken at the same time with meals? If not, then how long after you take a dose of orlistat do you still see some effect on absorption of the drug? Besides cyclosporine, which I think would be the most important direct interaction, there are other drugs. For amnioderone there were data talking about an average 25 percent drop in bioavailability, and if it is an average 25 percent it is probably somewhere around 50 percent in that group. There are other lipid-soluble drugs, a number of drugs that could be affected.

So, one, I wonder if you could explain the pharmacology in terms of how long it is working and what is really the critical time at which you should not take a fat-soluble drug, and also just comment about other fat-soluble drugs in general.

DR. DENT: I think there are three parts

to your question, the duration of the effect of orlistat; what other drugs have been studied; and why orlistat has this biological effect.

If I could start with the first one, it is very clear from studies that Roche has done that if the lipophilicity of the drug, as indicated by its LogP, is above 6.4--in other words, it is a very lipid-soluble drug, its absorption can be decreased. So, that gives us a way of looking at the entire universe of drugs and saying, okay, if anything has a LogP above 6.4 we should be concerned about it. For anything below 6.4 there is a very large number of drug interaction studies which have demonstrated that there is no pharmacokinetic interaction; no difference between AUCs with and without.

The second part of your question, if I remember correctly, is what is the duration of the effect or orlistat in the GI tract? I think there are two ways to look at that. One, if you stop using orlistat, how long does it take before the actual biological effect, i.e., you are not anymore

inhibiting the lipase, that is somewhere in the region of 24-48 hours based on the studies that have been done.

I can't actually say that it is that length of duration that it would take for a potential drug interaction with a lipophilic drug to go away because I don't think anybody has ever done that study. What Roche consistently recommended on highly lipophilic drugs, like cyclosporine for example, was that the drug should be taken, again, two hours before or two hours after.

The third question you asked me was what are the drugs that are affected? If I could have the slide with the highly lipophilic drugs with the LogPs? Slide on, please.

Many of these drugs are no longer on the market but these are the drugs that we are aware of that have a LogP above 6.4. I can't remember chloroquine's LogP but we looked it up yesterday and it was below 6.4.

DR. WOOD: Ruth?

DR. PARKER: I wanted to try to see what evidence we could talk about that might help us understand safety and potential for use and abuse among potentially adolescent self-selectors. From the study presented, it looks like 41 percent of the teens were not able to adequately self-select where you looked specifically for teenagers. It would have been nice in the actual use study if teenagers were actually chosen in the cohort from the beginning, how many of those that are over the age of 12 or 13 particularly, in order to pick up the potential for those that might then use the drug to lose weight intentionally.

If, indeed, it did become a drug that was sought out for use because of increased availability, and not only used but abused by teens who were not overweight to start with, what happens in terms of weight cycling when you cycle to a much below weight back to potentially a normal weight? The safety of that, with increased availability? What evidence exists to help us to think about the potential for that?

DR. DENT: To answer your question, I think it was can it be used in teens or, if it is used in teens, what is the impact in terms of weight cycling?

DR. PARKER: Just given the high number of particularly young females that seek weight loss, if this is available over-the-counter, if it is known to be a drug that is used to help people lose weight and is sought after for that purpose, when you start with what many of us--we have already discussed that people can't understand a BMI, and it is marketed for those who are, quote, overweight, and if it is a self-definition of overweight to start with and you self-perceive that you are overweight, whether or not you actually are by BMI criteria because you are not considered to be someone to understand that concept, and you use the drug or, quote, abuse the drug, what is the potential there? Is this a safety concern? And, how do we think about this?

DR. WOOD: Ruth, are you asking what the outcome would be if it was taken by people of

normal weight?

DR. PARKER: Especially teenagers.

DR. WOOD: Right.

DR. DENT: So, what would be the consequences if orlistat is used by teenagers of normal weight? First of all, I think we need to be clear that orlistat is demonstrated to be safe and effective in teenagers. In terms of the side effects that teenagers if they are normal weight might experience, given that teenagers perhaps might not be as good at following a diet as an adult, they might experience more GI-related treatment effects.

But from a safety perspective I don't think that there is a negative consequence. I think perhaps Dr. Apovian, who is a pediatrician who treats overweight people, could give you a better perspective on that.

DR. APOVIAN: Thank you. In my experience treating teenagers and also treating teenagers of normal weight with bulimia, when they are looking for drugs to help them get their desired weight

loss they are looking for something that will overnight cause a weight loss of four or five pounds to make themselves feel better after their binge episodes. So, they are looking for laxatives and diuretics that cause dehydration so on the scale it looks like they have lost weight when, in fact, they have lost water weight.

As we know from what orlistat does, it provides a slow, gradual weight loss. Approximately 150-200 calories per day are malabsorbed. This is not something that a teenage bulimic is going to continue using because the day after he or she is not going to get their desired five pound weight loss. That is my experience.

DR. WOOD: Morris?

DR. SCHAMBELAN: I have two questions. One is for the sponsor. The data we have seen this morning related primarily to 60 mg tid dosing and, yet, it is going to be packaged with the opportunity to take one to two tablets tid. I didn't hear any description of what sort of direction was going to be given to the person to

use the agent in terms of the titration. Are they supposed to titrate to toxicity, side effects, etc.? Are you advising people to end up on 120 tid? I didn't see any mention of how that was proposed to the user.

DR. DENT: Mr. Shifkovic, will you describe how that is handled, please?

MR. SHIFKOVIC: The proposed label includes instructions for individuals to start with a 60 mg dose, and that is a better way to minimize side effects as individuals start with therapy. What we saw from the AUT studies was that individuals were very successful and understood the concept of moving up to the higher dose. So, start with 60 to minimize the side effects and then transition to 120.

DR. SCHAMBELAN: So, the expectation is that a successful user will be getting 120 tid? Is that correct?

DR. DENT: I think in common with many OTC products, a one to two capsule regimen is quite common and consumers can modulate how they take the

drug.

DR. SCHAMBELAN: So, it would be two 90 capsule vials per month.

DR. DENT: If you were taking it three times a day with meals containing fat, of 120, yes.

DR. SCHAMBELAN: The second question relates to the guidance document that we worked on with the agency in 2004. As I recall, industry was advised that we were looking for individuals with a BMI of 27 or over with co-morbidities and 30 or over without co-morbidities. Yet, we are looking now at a recommendation or the possibility of a target population who are low overweight, which might be as low as 25. So, is there a difference between what we should use to guide industry versus what we should use to guide the OTC portion of the pharmaceutical companies? Why the distinction here?

DR. COLMAN: Well, the distinction came up because of Glaxo's proposal. As you know, we were deliberating whether or not the prescription drug guidance should lower the criteria down to 25.

DR. SCHAMBELAN: We recommended not to do that.

DR. COLMAN: Exactly, and you were there and I believe you recommended no.

DR. SCHAMBELAN: Right.

DR. COLMAN: And that was a recommendation. We are currently closing in on the end stages of revising the guidance. All I will say is that we value your judgment in terms of what might come out in that guidance. Clearly, this was an issue that we thought of from the prescription side of things. Internally, I think there was more of a push away from not lowering the criteria but with Glaxo's proposal we had to deal with it.

DR. SCHAMBELAN: And Dr. Flegal was at that meeting and I think we were waiting for the data which I guess was published several months ago, which I think makes me feel that the inflection point is not there to recommend that. But I suppose we can discuss that later in the proceedings.

DR. COLMAN: Yes, if I could quickly

mention, one of the things that Flegal showed is that there still is some debate about intentional weight loss in this range of people overweight, 25 to 29.9. There is some conflicting data where some show a positive effect of intentional weight loss and there are some data that show perhaps the ideal body weight, and it differs depending on age and race so it is not homogeneous. That adds a certain complexity to it.

DR. LEONARD-SEGAL: I would like to just add a word, if I might, to that answer. On the over-the-counter side, which is what we are talking about today, whether we want an over-the-counter weight-loss product as per orlistat, we have not used the BMI standard. We have the monograph which is a regulatory document, although not completed so in the deliberations it focuses on overweight as a spectrum of weightiness.

The issue I guess that it would be useful to hear something about, considering that the guidelines, in my interpretation of them, seem to focus solely on cardiovascular risk and mortality.

One way to be deliberating here today and one thing I guess we would like to hear more about is whether that is the only series of risks that we need to be considering or whether there is a broader range for some of these other conditions like osteoarthritis that I talked about, end stage renal disease which was just in the Annals of Internal Medicine--where we are going to clip our risk/benefit ratio in terms of the over-the-counter arena.

DR. WOOD: Just to go back to my point from this morning, Andrea, I thought the position was that weight loss was an approvable indication, not reduction in cardiovascular risk; not reduction in heart attacks; not reduction in some hard endpoint. Weight loss was an approvable indication. The point I was making this morning was that I see that as equivalent to, you know, use of laxatives, use of Viagra. You know, we don't demand in that setting some relationship to a hard--no pun intended--endpoint.

[Laughter]

I mean, I want to keep the conversation

focused here. If weight loss is an approvable indication, then it would be great to know that there is a reduction in risk factors. It would be even better to know that there is a reduction in mortality. However, that is not de rigueur. Have I got that right? Because it is important that the committee understands that if that is the case.

DR. LEONARD-SEGAL: You have that right. Weight loss is currently an OTC indication. I have not been part of the Rx side of discussions. It appears to me that they have been more complex. Weight loss is an OTC indication.

DR. SCHAMBELAN: But we would want to have a starting point, don't you think? I mean, we are not going to give somebody with a BMI--I hate to go back to BMIs but it is something I can get around--somebody with a BMI of 20, we are not going to use weight loss in that kind of person. So, I think that is what I am struggling with here. We sort of set a guideline that everybody felt comfortable with--maybe there was some debate--and we are sort of putting that aside and saying, well,

you know, the only indication is weight loss.

DR. WOOD: You have to start somewhere. The way I see the issue in front of us is this, they have come in with an application that says they want approval for over-the-counter use for two groups, obese and overweight. These are approvable indications, independently of what we think of this application right now. That is a separate discussion from whatever the guidelines are for the people who would benefit from weight loss in the Rx setting, it seems to me.

So, the issue that we will grapple with is whether we think this drug is approvable for weight loss, and it is certainly legitimate I guess to argue about whether the intended target is appropriate. I guess these are two separate questions and maybe that is where that comes in.

DR. COLMAN: If I could just point out, the monograph originally came about in 1982. As I mentioned, the thinking back in that era was that you could treat people short term, alter their appetite and eating habits and then stop the drug

and get a long-lasting effect. We now know that is not the case. So, in some ways the monograph does exist but it is quite old and, you know, we have put a lot of work in the Rx guidance in the last ten years so I think all that needs to be taken into account.

DR. LEONARD-SEGAL: I am sorry, I will just add one more piece. The questions that I outlined for you this morning in my presentation relate to the Durham Humphrey Amendment and what qualifies a product to be nonprescription versus prescription. I will reiterate them in one second: Does the product have an acceptable safety profile? Is there a low potential for misuse and abuse? Is there a reasonable therapeutic index of safety? Can the condition to be treated be self-recognized? When used under nonprescription conditions, is the product safe and effective? Do the benefits outweigh the risks in the over-the-counter setting? And, the big question for the day is does orlistat meet the regulatory requirements for nonprescription marketing as per

Durham Humphrey??

DR. WOOD: Okay. Paul?

DR. WOOLF: Dr. Dent, in your first talk this morning you said this is more than a pill; it is a program. You showed a slide of six pamphlets that were going to be given or that actually the public would purchase. Are those pamphlets actually present? Have you developed them? Are they available? If they are, it would have been helpful for the committee I think to have seen them since this is a program and not a pill.

DR. DENT: Yes, they have been developed. They have been developed with the help of experts, and they were included in the NDA document that was submitted.

DR. WOOLF: I would make sort of a general comment. Whenever there are these kinds of ancillary materials, I think it would be very helpful if the FDA mandated that the committee members--or make sure that we got them, not just pamphlets but at the September meeting we were asked to approve a delivery system but never got to

see the device first-hand. So, I think that any of those kinds of things should be available to the committee. Obviously, the device probably shouldn't have been shipped out to us in advance but it could have been here. The pamphlets clearly should have been made available for us to look at.

DR. DENT: I should emphasize that the material in the pamphlets, although not exactly the same as the material that we have now, is very, very similar and were used in the actual use trial. So, they were a part of the actual use trial.

DR. WOOD: Marie?

DR. GRIFFIN: It worries me a little bit when the label says "talk to your physician or pharmacist" about warfarin, say, when the physician I don't think has the knowledge base. I mean, what is the knowledge base for what we tell those patients?

DR. DENT: Could I ask Dr. Bennett if he would give that perspective as somebody who is in the Division of Hematology?

DR. BENNETT: So, I am a hematologist and

I see patients who get warfarin. So, the end result is the prothrombin time or the INR. So, what you need to know is whether there is a change in the patient's INR. In fact, what you tell a patient who is on warfarin is that if you take a new medicine you need to have your INR checked more frequently. In my own case, for example, I can't remember whether things go up or down or where they go, but I do know that if a patient goes on a medicine I need to check the INR and change the dose of warfarin appropriately.

DR. GRIFFIN: I guess the question is do physicians really know what this drug does? You know, I don't think there is much of a knowledge base out there. So, if a patient takes a new drug they are told to contact their physician.

DR. WOOD: So, what you are saying is that there needs to be some educational plan for physicians when the phone rings at 2:00 in the morning.

DR. GRIFFIN: Right, and I think we need to know if this is a problem. I mean, there are a

lot of patients on warfarin and there are a lot of drugs, and some drugs cause more problems than others.

DR. BENNETT: What I tell patients is if you go on a new drug and you are taking warfarin you need to see me because you need to have your INR checked. Like I tried to say, it doesn't matter to me--because what do I know--it doesn't matter to me whether it goes up or down. I just need to know if it changes so I can change the dose of warfarin appropriately.

DR. WOOD: There is a difference between the potential mechanism of an interaction here from most of the ones you are familiar with. Most of these involve inhibition or induction of drug metabolism and certainly for inhibition that occurred pretty quickly. Here, presumably, it is going to produce an interaction through depletion of vitamin K if it produces an interaction. At least from the data you have shown us, the time course of that is unclear, to say the best at the moment. So, there is some need to educate

physicians about what that difference is. I mean, I suspect that your reaction as a hematologist who sees patients is based on a different kind of mechanistic interaction than actually will be seen here, a different time course.

DR. BENNETT: Well, your basic premise I don't agree with--

DR. WOOD: So, here is the question Marie has on the table, when the patient calls her and says I am starting on this drug, how long are you going to monitor the INR intensively?

DR. BENNETT: That is an excellent question. That is based on how long it takes to achieve steady state and, in fact, if you do achieve a steady state.

DR. WOOD: Of?

DR. BENNETT: Of your vitamin K level.

DR. WOOD: Right. So, how long is that?

DR. BENNETT: Unfortunately, on that slide the data was at six months, and I haven't seen the data but apparently somebody can tell you. The changes in fat-soluble vitamin levels happen

relatively quickly and are stable after that. We saw the level after six months. So, as far as I can tell, it looks like you need to monitor the INR at approximately weekly intervals and, from what I have been told, after four to six weeks I think you are back in a steady state and you can begin to monitor them less frequently.

DR. WOOD: That is an important point to get across. If we are telling people to call their physician we had better have some answers that are a bit more precise than that. Marie?

DR. GRIFFIN: I have one other thing. Is there any guidance? This is a six-month program, but what about people in whom it was successful and now they want to use it again? Is there going to be any information?

DR. DENT: The information in the label recommends that people, when they stop at six months, if they begin to regain weight after three months they can go on another course of orlistat. If they haven't lost enough weight at the end of six months we recommend that they go and see a

physician.

DR. WOOD: Okay. Miss Coffin?

MS. COFFIN: I wanted to say that I was actually one of the folks that thought that the overweight and obese definition should stay consistent so 25-30 is overweight and a BMI above 30 is considered obese. What I will tell you is that people out there are familiar with the BMI. They may not be able to tell you exactly what their BMI is, and even individuals with BMIs close to 40 are very reticent to call themselves obese. Obese is a very bad buzz word. So, keeping the labeling to say overweight is going to be more likely to reach the folks that need to be reached. I want to be very clear though as far as risk and safety goes. If a normal weight individual, say someone between a BMI of 20 and 25, were to take this medication what would happen?

DR. DENT: Dr. Apovian, would you like to address that question?

DR. APOVIAN: That is a very good question. We know that people with BMIs of 20-25

sometimes do consider themselves overweight even though they have normal weight. Orlistat, as you have seen here today, is a very safe drug. It will allow malabsorption of fat and typically about 150 calories to 200 calories of fat will be malabsorbed per day. So, I really don't see any untoward effect of a patient who has a BMI of 20 or 25 in taking orlistat.

We can also look at my core slide that showed the increased risk of co-morbidities even in patients of normal body weight. So, even patients who have a BMI of between 20 and 25, as they gain weight their risk of serious co-morbidities, such as type 2 diabetes, goes up. So, I think that anyone gaining weight in that category should think about a weight-loss program.

MS. COFFIN: FDA explained that folks between a BMI of 25-28 had a lesser weight-loss result. So, it would be even less than in someone with a BMI of 20-25?

DR. DENT: The effects of orlistat in the lower BMI of 25 have not been studied so we can't

answer you directly.

DR. WOOD: But I think part of the answer, John, was that there is a change in the absolute reduction in weight with a relatively similar percentage reduction in weight, which is sort of what you would expect, isn't it?

DR. DENT: Yes. Perhaps to help you understand the warfarin situation a little bitter, Dr. Shiffman has some data about how patients on warfarin interact with their doctor.

DR. WOOD: Well, let's not get bogged down on that because we have a lot more questions. We will come back to that if it comes back up. Dr. Carpenter?

DR. CARPENTER: I wanted to expand on Marie's comment about what happens after the six months. As presented this morning, there is six months of drug with guidance and then an extra six months of guidance. Now, I hate to speculate but my suspicion is that there is going to be weight loss and it is going to be regained, and despite the indication of six-month use of the medication,

there is probably going to be a substantial number of people that take this drug on the over-the-counter basis, if it is out there, for extended periods of time. In that setting one has to beg the question of where some level of oversight, if it is not the physician, can come into play to perhaps look for red flags in terms of toxicities that we are not aware of because the over-the-counter safety data is only at the six-month point.

An earlier suggestion in the public commentary came from the pharmacy folks in terms of a system of oversight that could be implemented at the pharmacist level. I wondered if the sponsor had considered that potential option or if a mechanism exists to include an intermediate level of oversight in such a manner.

DR. DENT: I think the first thing to reemphasize is the safety profile of orlistat. I think one of the things that really distinguishes orlistat from other weight-loss drugs is this complete lack of negative effects on

cardiovascular, CNS and so on. So, we are dealing here with a very, very safe drug.

In terms of how it is marketed, there are only two options in the United States and that is prescription and over-the-counter. We feel that this is an appropriate drug. It is safe; it is effective; and it should be over-the-counter.

DR. CARPENTER: Even though your application is for six months, there is likely to be much more chronic use of the drug.

DR. DENT: Again, I think that is a question really of how people are likely to behave when they plateau at their weight and whether they will continue to buy the product beyond plateau-ing in their weight. Dr. Shiffman can perhaps talk to what people actually did in the actual use trial and how the real challenge is probably to get people to keep using it for six months, rather than being concerned about having them use it longer than six months.

DR. WOOD: We are getting close to our break. We have managed to go through the entire

day almost without discussing the major side effects of this drug and at some point we are going to have to do that. Have you considered putting some warning on the box that is something like this, this drug should not be taken when wearing your new underwear, or something like that?

[Laughter]

I mean, you know, we have kind of avoided this issue but we can't ignore it and when we come back from the break we need to sort of grapple with that in some way. So, let's be back at 3:45.

[Brief recess]

DR. WOOD: Let's get started. I want us to discuss what we will for the moment call euphemistically the underwear problem because it sort of worries me a bit that we have spent an entire day discussing the nuances of vitamin K metabolism. I am not being facetious about it, I think we really need to have an understanding of just what all these euphemisms mean. I mean, you know, is this the sort of thing you can't take on a first date? What does oily leakage mean? I am not

trying to be gross here but I think the public, when they start using something like this, needs to understand, you know, what the operational issues are here, to put it mildly, and what the lifestyle effects would be. So, can you walk us through that a bit?

DR. DENT: Prof. Wood, to be very clear, these are very manageable treatment-related effects that are related specifically to how much fat you have in your diet. If you follow the diet and you take the drug appropriately they are manageable. Let us show you the data--

DR. WOOD: No, no, nobody is arguing with whether they are manageable. What I want to know is, really clearly articulated, what we mean by all these things. When you say "flatus with leakage" what does that mean? Does that mean, you know, I would be embarrassed sitting here right now? Does it mean that somebody couldn't drive to work? You know, I am not being facetious about this. This is something that people really need to have an understanding of before they start taking

something, it seems to me. So, I buy into the manageable and so on, but tell us in words of one syllable what this means, what happens, what one would expect to see.

DR. DENT: Dr. Hauptman, you are probably most experienced with orlistat of anybody.

DR. HAUPTMAN: When we first started this program it was quite clear that based on the mechanism of malabsorption of fat that we would get something similar. Of course, there are other compounds out on the market, food additives, that cause similar types of adverse events. But I think the ones that are of concern are really what is unintended as opposed to those things that you can control. So, there are two that are the ones that people are the most concerned about, and that is because it is an uncontrolled--at least spotting is like an uncontrolled seepage of oil without stool, whereas fecal incontinence is uncontrolled, spontaneous defecation basically because the fat is mixed in with the stool.

For the majority of people, obviously,

that doesn't happen but the person to whom it happens it is a concern. Generally it is related to their diet and generally, once they understand what caused it, they are able to control it. But in our clinical studies we explained to them what might occur in the consent form obviously, and when it happened they weren't upset. They understood that this is how the drug works, and the majority of them could control it but, obviously, there would be some accidents for patients.

But I think the most important thing is that patients didn't drop out of the studies; didn't stop the drug. They had to modify their diet or discontinue losing weight. But those are the two that are truly the ones that I think people would be concerned about. If there are specific ones that you want me to discuss in detail--

DR. WOOD: These all sound to me like things that if you wouldn't be concerned about I would be concerned about. So, walk us through each of them and tell us what you are talking about. Let's be clear here, we are amongst friends. When

you talk about soiling, are you just talking about a mark on my underwear or are you talking about something more serious? If you are talking about fecal incontinence, you know, that doesn't go down well for advisory committee members in my experience. So, give it to us straight.

Nobody is arguing with you about whether it should be expected or not or whether it is mechanistically based. We all understand that. What we need to know is when you start taking this drug over-the-counter and somebody buys it in a pharmacy and walks out the door what are the chances that they are incontinent that night? Seven percent, right? DR. HAUPTMAN: First of all, it would be several days after you start the drug. It is encouraged that you actually start to diet first in order to get a low fat diet. Some percentage of patients who at any time during the two to four years--it is seven percent but it is not every day. It is not chronic.

DR. WOOD: Well, that is reassuring but, I mean, seven percent--you know, most of us would

think seven percent once would be enough incontinence. Right?

DR. HAUPTMAN: If it is a specific concern to you you would stop the drug and you would never take it again. If you believe that the drug has benefit and you want to test it to see if the drug worked, then you would take it and you would work through the adverse events. We are not hiding them. We have always had them. We have them in our package insert for the prescription medication. If anyone remembers our drug consumer ads, we were very, very clear about what these adverse events were so people knew about them beforehand. But, clearly--

DR. WOOD: I am not trying to argue with you about it. I want you just to be really clear and explain to us and to the public what these issues mean. Incontinence occurs in seven percent of the patients. Now let's take the others. You have a list somewhere. Walk us through that list and explain to us what each of these really means to people. Oily leakage, tell me about that.

DR. HAUPTMAN: Would you please put on the slide with the list?

DR. WOOD: No, we don't need slides up. We know what it is. Give us a sense--we don't need a picture. What we need is to understand what you mean by oily leakage. Is that oily leakage with feces?

DR. HAUPTMAN: I will go through it. We broke it up into seven adverse events that were specifically related to orlistat use. The first one that we thought was the most important to patients was fecal incontinence, which was uncontrolled, spontaneous defecation.

The second one that we thought was the most important to patients was oily spotting, which is uncontrolled seepage of oil in the absence of stool. The reason that happens is that when you start taking the drug you already have preformed stool in the colon. The unabsorbed fat goes around it. It doesn't get part of the stool and you can get some of the seepage.

DR. WOOD: What do you mean by that? Is

that a teacupful, a teaspoonful?

DR. HAUPTMAN: When we did studies we actually weighed it in our clin. pharm. studies. We had pads and we actually weighed it and it was maybe 3 g or 5 g.

DR. WOOD: So, that is like a teaspoonful.

DR. HAUPTMAN: No, less than that; 5 cc I guess is a teaspoon so it is a little bit less than that. That is about the maximum that it would occur.

DR. WOOD: And what about the other issues?

DR. HAUPTMAN: Fecal urgency is what we call urgent but controlled need to produce stool. We have all had fecal urgency at some point in our life. We understand it and you get to the nearest bathroom if you need to have it. In the stool would be oil, unabsorbed fat increasing the pressure in the colon or the rectal pouch and you feel the need to defecate.

DR. WOOD: I think it is your company that has another product in which fecal urgency was such

a serious problem that people couldn't work the advisory committee was told. Right? Irritable bowel syndrome.

DR. LEONARD-SEGAL: Alastair, excuse me, do you think it would be helpful for you to hear from Karen Feibus on the number of people that dropped out of the actual use study because of GI adverse events? Would that be sort of a bottom line issue for you?

DR. WOOD: Yes. It is more than that though. I am not trying to be funny here. I think it really is key that we have an understanding of what we are talking about here, not just some euphemistic expression of, you know, oily leakage. Well, it turns out it is 5 cc, or whatever. You know, we can sort of quantify that. Let's get a sense of all of this because if I was starting this drug I would sure want to know should I not start it if I am about to chair an advisory committee for example. You know, these are real-world issues for people.

DR. LEONARD-SEGAL: I wonder, as we are

discussing it, what happens in the prescription environment--

DR. WOOD: Well, at least you have somebody there who can explain the risks of this to you, which you don't in nonprescription. I think it is even more important in a nonprescription setting. Go ahead.

DR. FEIBUS: Hi! this is Karen Feibus. I wanted to point out to the advisory committee members that GSK did provide us with the definitions that they used with their defecation pattern work-sheet. It is actually in your briefing packet, behind the tab that says "clinical review safety and efficacy" right before the appendix section, page 98. Section 10.3 of my review has the defecation pattern terms, definitions and rules. So, that will at least give you the definitions of how GSK defined each of these adverse events.

The other thing I wanted to mention is that my background is gynecology so I have spoken to a lot of women over time who have experienced

certainly some of these side effects, not related to orlistat use but related to aging or related to side effects that they are having following just delivering children and things like that. I think it is really hard to try to quantify what these side effects might be for each individual because there is probably a very large individual variation depending on a woman's pelvic function and how her body is personally dealing with the dose of this drug. So, there is probably a tremendous range as to how much flatulence someone is going to have and how much watery leakage with mucus from the bowel is going to accompany that.

What really struck me when I was doing this review was how few people dropped out because of these adverse events. Originally, before I had to get my talk down to 20 minutes, I had a slide that went through each of these defecation-related adverse events and looked at the percentage of the individuals in the study who experienced them and how many actually dropped out. I don't remember all of them, but the percentage of users with the

highest percentage dropout was 25 percent, and that was among individuals with oily stools, believe it or not.

Among those who had fecal incontinence and for me, when I looked down this list, it sounded like the most God-awful thing ever, only 22 percent of people dropped out. So, I think people have to be made aware of what this range of side effects is. It is extremely important because, like you said, it can be extremely embarrassing. But people who experienced these side effects often chose to continue and some discontinued.

The other thing is there was information in the study about why people stopped using drug or changed their dosage, and people mentioned being in a situation where they were worried about using drug and people adjusted their usage. So, I thought those things might be helpful to you. Thank you.

DR. DENT: Perhaps it would be helpful if we give you a perspective on how we are communicating this to people. Mr. Burton?

MR. BURTON: I am one of those individuals that Dr. Feibus has just talked about. I have been a Xenical user for three years so I have taken this issue very seriously because I think, both as a person who has experienced them as well as someone who is trying to understand how to communicate to people that Alli really is not for everyone, we do not want people surprised.

Slide on. If you look through all of our in-pack materials, you can see both in the drug facts format as well as the right side of the back panel--and right now I am showing you an example of what is in the welcome guide--this is the very first thing people see when they open up the six reference guides.

If you take a look just at the boxed area--I am sure you can't read that back there, but we tell people considering the product and buying the product that these side effects, referred to as treatment effects, may disappear altogether if you follow a balanced diet with an average of 15 g of fat in each meal. Treatment effects may include

fat in your stools; loose or more frequent stools; an urgent need to go to the bathroom; and gas with an oily discharge. We are going to remind people that they are generally mild, that they do occur more frequently at the beginning of the program and may go away after a short period of time.

I have counted the number of times that we have a statement like this--if we can go on to the next slide--we devote about three full pages of the welcome guide to talking in a lot of detail, even more detail then I have just shown you here and have just read out to you, about exactly what this means to people.

We give them advice that comes from my own experience and from other patients' experience, things like waiting three days to adapt to the new diet before you begin using the product; things like starting the program on a Friday and giving yourself the weekend to adjust. If you look through the materials, we give some very explicit advice even about the types of clothing that you might consider during early parts of the program.

So, again, it is part of our proposition here that Alli is not for everyone. I can assure you that in our communication consumers will not miss this advice so they will not be surprised.

DR. WOOD: Okay. Other comments? Yes, Mary?

DR. TINETTI: Related to that, it probably won't take people very long to realize that if they are going to have a fatty meal they are more likely to get some of these effects. So, my guess is that certainly with prescription, and even more so with over-the-counter, people are going to say, okay, I am going to go out for a Big Mac today so I am not going to take my orlistat.

First of all, do you have any data about how often that happens and, number two, assuming that is probably going to happen fairly frequently in over-the-counter how is that going to affect the likelihood of benefit in terms of weight loss?

DR. DENT: Yes, we do have data on how much that happens from the actual use trial. Dr. Shiffman, if you could re-show that?

DR. SHIFFMAN: What we saw in the actual use trial was that people did typically take the product two to three times a day. People did typically settle into a pattern. We specifically asked them whether they occasionally varied from that pattern. Slide up, please.

What you see is that in the context of a generally stable pattern people did sometimes use less than their usual but, interestingly, what they reported is perhaps the opposite of the intuition, which is that people said I took less because I knew I wasn't going to eat fat, in other words, understanding that this only blocks fat and if I am eating a non-fat meal I am going to take one instead of two or skip it altogether.

Very importantly, there are several things to bring out, first of all with regard to the side effects in general. We saw that satisfaction or the converse, dissatisfaction, was not related to the incidence of these events, which goes again to the fact that people found them very tolerable and manageable. Specifically in qualitative

debriefings that were run with 49 patients in the trial, they reported very specifically that they had understood this process from the beginning. They were not surprised and they found the effects manageable.

Overall, people did vary their dose in a way that related to their understanding of the mechanism but everything we saw suggested that people understood the mechanism; they used the product appropriately and they used the discretion they had about one or two capsules in a way that was appropriate.

Questions for the Committee

DR. WOOD: I think we are probably about ready to start on the questions. Anyone have any compelling things that they want to talk about first? If not, let's start on the first question. The questions are on the board.

So, the question is has clinical effectiveness been demonstrated with orlistat 60 mg tid and 120 mg tid in the nonprescription setting? For each of these doses, please comment on the

following: A six-month duration of use; repeated use or chronic use; use in the overweight individual; and the FDA wants to add to that the distinction between 25-27 and 28-29.9. Is that right, Andrea?

DR. PARKS: Yes.

DR. WOOD: And, use in the obese individual with and without multiple co-morbid conditions.

So, do we have some discussion first of all on the question and on the sub-questions? We will take each of them separately. Any discussion on the question? Wayne?

DR. SNODGRASS: My question is about 1(c). Overweight is being defined as 25-30? Is that right? Or, is it 27-30?

DR. PARKS: Let me just clarify. Because of this morning's discussion on efficacy both from the applicant and also the FDA side, we would like to break that question out to efficacy and the low overweight patient population. If you look at Dr. Golden's slide number four, that would be BMI of 25

to less than 28, and then high overweight patients which would be BMI of 28 to 29.9.

DR. PARKER: Just for a point of clarification, I wonder why that definition is so precise when it would be going over-the-counter and all it says is "overweight" on the label.

DR. PARKS: Part of it is actually from data in their clinical efficacy study, their actual use trial, the four-month study.

DR. WOOD: But we are going to approve it or not for overweight individuals, period, with no BMI requirement.

DR. LEONARD-SEGAL: That is the current OTC indication. Yes, there is no BMI requirement.

DR. WOOD: Right.

DR. PARKER: Nor is there any description of the term overweight to help a self-selector decide that they are overweight. Am I correct in that?

DR. LEONARD-SEGAL: That is correct.

DR. PARKS: I think as you deliberate over question 1(c) it may actually help you eventually

when you get to question seven.

DR. WOOD: Let's take them in order and let's wait for (c). So, the first question is has clinical effectiveness been demonstrated with orlistat 60 and 120 in the OTC setting and a six-month duration of use? Discussion? Yes, Neal?

DR. BENOWITZ: I don't understand this question about whether it has been demonstrated in a nonprescription setting because there was only one actual use nonprescription trial, as far as I can see, which didn't even last six months. So, is this what we think is likely nonprescription or what was really demonstrated nonprescription?

DR. PARKS: I think to some extent there is going to have to be some extrapolation from the two studies that were conducted in the NDA for the prescription setting where the sponsor has actually looked at efficacy data at the six-month time point as well. So, yes, you would have to rely--

DR. WOOD: Would you be comfortable in rephrasing the question to do you think orlistat...blah, blah, blah ...and will be

effective in the nonprescription setting? That is sort of the question. Right?

DR. PARKS: That is fine.

DR. WOOD: Does that help, Neal?

DR. BENOWITZ: Yes.

DR. WOOD: Any other discussion on that? Ready to take a vote on that? Let's start with Dr. Caprio.

DR. CAPRIO: Yes.

DR. BENOWITZ: Are we just talking about six months?

DR. WOOD: Yes.

DR. BENOWITZ: I will just phrase this first by saying that I don't think that there has been any long-term effectiveness shown. As far as I can see, when you stop using this medication you regain your weight. But if the question is can someone lose weight at six months then, yes, it has been demonstrated.

DR. WOOD: Dr. Carpenter?

DR. CARPENTER: I agree, and some of that is extrapolating from four-month data to the

six-month point, looking at the previous studies to get a magnitude of weight loss that we would consider clinically effective.

DR. WOOD: Terry?

DR. BLASCHKE: When extrapolated, yes.

DR. WOOD: Dean?

DR. FOLLMANN: Yes.

DR. WOOD: Melanie?

MS. COFFIN: Yes.

DR. PARKER: Yes.

DR. SCHAMBELAN: Yes, with the same caveat.

DR. WOOD: Yes.

DR. GRIFFIN: Yes.

DR. WOOLF: Yes.

DR. CLYBURN: Yes.

DR. TINETTI: Yes.

DR. SNODGRASS: Yes.

DR. PATTEN: Yes.

DR. WOOD: Then the same question with repeated use or chronic use. Do you want to take the opportunity, before we get confused, to explain

what you mean by that? We are easily confused. Mary?

DR. PARKS: I think for this one we are talking about both a nonprescription setting and a prescription setting. So, will there be clinical effectiveness in the nonprescription setting for repeated use and also from the prescription setting data? Does that help?

DR. WOOD: Well, remind me, did we see any data on repeated use? Did I just miss that?

DR. PARKS: No, but that is why it is repeated use or chronic use.

DR. WOOD: So, you are talking about the two-year studies, for instance.

DR. PARKS: The four-year--

DR. WOOD: Right, right. Help me understand. The question we are asking here is do we think it will be effective in repeated use and chronic use? Is the question you are really asking is there concern about using it repeatedly? Curt?

DR. ROSEBRAUGH: Let me just see if this is more what the divisions want to get at.

Typically, when we have an actual use study we have it run in multiples of what the indication is. So, if it is a six-month indication we would want a 12-month actual use study.

I personally would be interested to hear the committee discuss do you think we need any idea of what consumers would do in repeat use or chronic use? As far as I know, we don't have any data in a nonprescription setting and I kind of wonder if people think we do need data like that; if it makes any difference if people do a repeat use or if they go past the six months. Does that help?

DR. WOOD: There is always a danger in saying do we want more data. I know what the answer will be.

DR. ROSEBRAUGH: Well, if the committee members think it is not something we need, that is fine. But it would help me personally to know.

DR. WOOD: Alright. So, do we understand the question? Any discussion on that?

DR. PATTEN: Alastair, shall we split this up because there are chronic use data but there

aren't repeated use.

DR. WOOD: That sounds like a good idea.

DR. SNODGRASS: You are asking about clinical effectiveness. So, we are talking about in the OTC setting effectiveness as used by the general population, not efficacy as in a controlled clinical trial.

DR. WOOD: Say that again.

DR. SNODGRASS: In other words, under trial conditions efficacy is what you would get. Actual usage in the general population would be effectiveness. So, the way this question is worded is that we are being asked to look at OTC effectiveness so you might have to take some efficacy kind of data and extrapolate what you think is going to happen in the OTC setting.

DR. WOOD: Alright. Any other discussion? Curt wanted us to rephrase the question. Do we want more data in repeated use or chronic use?

DR. ROSEBRAUGH: I don't know about do we want more data. The question is do you think we need more data for that.

DR. WOOD: More data before approval or just more data?

DR. ROSEBRAUGH: Does the committee want more data? You know, the way it is used now on the prescription side we are using it chronically but it is under the control of a physician. When it gets out OTC there is not going to be a physician there and the actual use study was cut off so that we really don't know what people do at that six-month time point. Is that a concern to the committee at all?

DR. WOOD: Maybe that will be a good way to put it. Is the cut-off at the six-month time point a concern to the committee? Then maybe we can come back to the other question. That is a good question. Andrea?

DR. LEONARD-SEGAL: Alastair, I think we are thinking about it differently. The question really is an efficacy question here and we don't have repeated use efficacy data.

DR. WOOD: Right.

DR. LEONARD-SEGAL: No one has provided

that. Generally in the actual use studies when we consider what people will do, the studies will go on longer so we can see if they stop using the medicine in accordance with the directions or if they go back on it. So, I think this repeated use question really doesn't make sense in the efficacy question, now that we think about it.

DR. WOOD: Shall we just can it?

DR. LEONARD-SEGAL: Unless Mary raises her hand and says no, I disagree--

DR. WOOD: Well, let's can that question.

DR. LEONARD-SEGAL: --I think we will drop it.

DR. WOOD: Alright. The next question relates to the use in the overweight individual in contrast to the obese individual. Right? By BMI definition?

DR. PARKS: Not obese. You are talking about question 1(c)?

DR. WOOD: I am saying it is the use in the overweight individual, parentheses, in contrast to the obese individual. Is that it?

DR. PARKS: No, it is actually just use in the overweight individual--has clinical effectiveness or significant weight loss been demonstrated in the overweight population? And, here it is to be divided into the low overweight and the high overweight population. Because in the next question we are actually asking about obese.

DR. WOOD: Any discussion? Morris?

DR. SCHAMBELAN: Can we get clarification? You are talking about between 25 and 28 for the low overweight?

DR. WOOD: Yes.

DR. SCHAMBELAN: So, to be precise, it is 25 to 28 for low overweight and 28 to 29.9 for the remainder? Is that what you are asking for?

DR. PARKS: That is correct.

DR. WOOD: What you are trying to get at here is, is there a disparity in the effectiveness between these two groups or is there a difference in the effectiveness between these two groups? Just nuance? Is that it?

DR. PARKS: Yes, to see if there is

actually a difference because, as you have heard, the definition of overweight in this OTC setting is really based on consumers' perception of what overweight is and is in contrast to what Dr. Colman presented this morning, the regulatory or scientific definition of overweight. So, are we actually parsing out an overweight population in the OTC setting here?

DR. WOOD: Well, my sense, to help get the discussion started, was that we saw a relationship between effectiveness that seemed to be proportional to the individual's starting weight so there was a percentage reduction in weight that seemed pretty constant amongst different groups but an absolute reduction in weight was different. I suppose that is sort of what we see with most body measurements. You know, you see a bigger reduction in blood pressure in people whose blood pressure is highest to start with; you see a bigger reduction on cholesterol whose cholesterol is highest to start with, and so on and so on. So, that would seem to me to fit with that inborn prejudice.

Maybe others saw something different.

DR. FOLLMANN: I would just like to comment. In the FDA statistical review they talk about tests of whether there was a constant treatment effect in terms of weight loss as a function of BMI, and they did these tests over the three different studies and found no evidence of that. So, this is consistent with the idea that there is not a differential treatment effect in terms of weight loss as a function of BMI.

DR. WOOD: Right. Any other comments?

DR. CLYBURN: I was just going to say I don't think we have enough data to say in the 25-28 range. There was only the one four-month study that had any substantial patients in that range and without extrapolating it out to six months it wasn't terribly different.

DR. FOLLMANN: Right, I think it is cutting it kind of fine to say 25-28, 28-30. You know, this test just says is there something going on; it is a continuous value of BMI.

DR. WOOD: Particularly when we are not

asking patients to use that test in the first place so the precision is not going to be there for them to make that distinction. So, they are going to just sort of grab some fat and see how it feels, and if there is a lot there they are overweight. Any other comments?

MS. COFFIN: Again, I just want to reiterate that what NIH is putting out is that overweight is a BMI of 25-30 and anything over 30 is considered clinically obese. So, I think that is what the sponsor used and that is what the consistent message is so I would like to consider 1(c) between 25-30, not 25-28.

DR. WOOD: Mary, are you trying to get here at what the eligible population is?

DR. COLMAN: Yes, I think one of things we need to keep in mind is that the NIH guidance certainly does describe overweight as a BMI of 25 to 29.9. However, they consider the appropriate use of a drug in patients who have a BMI of 27 to 29.9 if they have a co-morbidity or are above 30. So, these are distinctions with differences because

we are talking about not simply losing weight. Everyone will agree that you should maintain your weight or lose your weight if you are overweight, but whether or not you should use a drug to do that is another question.

DR. PARKS: That is also the guidance for prescription drugs.

DR. COLMAN: That is true but I don't see how it would be any different in this setting.

DR. WOOD: Well, it is different in this setting in that weight loss in itself is an approvable indication independently of risk factors.

DR. COLMAN: But the risk/benefit equation is still the same. I mean, you have to look at the individual drug but this is a general principle, you don't go to drugs right off the bat and you try to target higher risk patients with a drug. That is the point I am trying to make.

DR. WOOD: Okay.

DR. PARKS: Alastair, if I can just add, if we say that weight loss is an indication for

approval of drugs, then it is even more relevant to consider these two separate overweight subgroups because then the question is for the low overweight, the 25-28. Does that group actually meet the FDA's definition of efficacy based on either a five percent weight reduction that is relative to placebo or the categorical weight loss of five percent?

DR. WOOD: I guess the answer is it doesn't. Right? I mean, if I remember the data.

DR. PARKS: Well, that would be for the committee to vote for.

DR. WOOD: Right, but the data said it didn't. So, you are wanting us--let me make sure I got it right--whether we saw data that showed the drug was effective in an over-the-counter setting in these two subsets of BMI. Is that the question?

DR. PARKS: That is correct.

DR. WOOD: Okay. So, the question that we have to answer then is has clinical effectiveness been demonstrated ... blah, blah, blah...for use in a population with a BMI of 25 to 28 and 28 to 29.9?

These are two separate questions, although you could probably answer them together. Any other discussion on that? Ruth?

DR. PARKER: I just would like to understand does it matter if a consumer understands, number one, whether or not they are overweight and, number two, whether or not they are just overweight or obese? Does that matter?

DR. WOOD: I am not sure it does, frankly. I mean, we are all so puritanical here that we are dead set against people taking this six months before they go to their high school reunion but, you know, I am not so sure that is so bad. I think that is where a lot of people will do it.

DR. COLMAN: Can I add that the one place where it might be a concern is that the higher your BMI, the greater the likelihood that you are going to have co-morbidities which, some would argue, would be under the care of a physician.

DR. WOOD: Right. Yes, George?

DR. GOLDSTEIN: How practical is it to translate, from the point of view of the consumer,

a 25 to 28 and 28 29.9 and so on? Will you be able to make effectively the distinction between breaking that down as opposed to, say, the distinction between 25 and greater than 30, the original distinctions that were made? Will they understand? Will there be a way of translating that to the field, as it were?

DR. WOOD: I would have thought not.

DR. GOLDSTEIN: I would have thought not as well. That is why I raised the question.

DR. WOOD: I am interested in what other people have to say about that. I am just calculating mine out right now. So, to put my BMI up by that amount--you know, we are talking two or three pounds. I mean, we are talking about precision that is almost outside the range of the average person's bathroom scales, plus their eating habits.

DR. COLMAN: But to some extent it is relevant. If you look at the range of BMI of 25-30, that is spanning 30 pounds. So, if you are 5'5" and you go from a BMI of 25 to 26, that is

about six pounds. So, I don't think an individual who has six pounds of weight gain has the same baseline risk as someone who is 29.9 and has gained 30 pounds. So, in some ways it is unfortunate that the classification lumped this large group of individuals together because they are not all in the same risk category. Even though they are all called overweight, there is quite a difference in the body weight range.

DR. WOOD: Well, 10 pounds would change my BMI by 1.4. I just calculated it. So, 25-27 would be about a 10 pound change. I suppose that is a pretty substantial change. You would certainly notice that. Any further discussion? I am not sure people understand it.

DR. LEONARD-SEGAL: Alastair, would it be of value for you to hear the BMIs of the people who self-selected into the actual use study?

DR. WOOD: I think we saw that but go ahead and tell us again. The thing that struck me was not the average; the range was astronomic.

DR. FEIBUS: I think Dr. Segal just wanted

me to refresh everybody's memory that 92 percent of the individuals who selected into the actual use were either overweight or obese. Among the individuals who were of normal weight, 80 percent of them were in that sort of upper part of the range of normal weight so that weight difference was important for them even though we don't consider it to be overweight. But 92 percent were overweight or obese in the actual use study.

DR. WOOD: So, if overweight is an approvable indication, it seems to me that these people were overweight by most people's definition of it. Maybe some of them were only overweight by their own definition but they sure weren't skinny. That is for sure. I don't feel very exercised about that, I must say.

DR. PARKS: Would it be easier for the committee if you just vote on the clinical effectiveness in the overweight population, which would be 25-30, but discuss the range or the degree of effectiveness within that range? Within that range is there a spectrum where you think it would

be more effective? Does that help?

DR. WOOD: Let's try that. Dean had something to say I think.

DR. FOLLMANN: The four-month study that was done in the U.S. had inclusion criteria I believe of BMI of 25-28, which is exactly the range you are looking for there, and in that study they showed a significant effect of about a kilogram. For the higher weights, 28-30, we would have to rely on the longer-term studies which showed even more of a benefit of orlistat.

DR. WOOD: Right. Of course, there were data that showed a cut at four months so you could look at that data at four months as well, and it looked similarly proportional to me.

DR. FOLLMANN: Right.

DR. WOOD: Sonia, why don't you go first? We are on (c). I think a "yes" would mean that we thought it was effective in the 25-29 range. Sonia, you got it?

DR. PATTEN: Yes. Let me take the higher range of overweight first and say that my answer to

that is yes. For use in the lower range of overweight, I am struggling with that because NM17247 does not reassure me on that count. If I am forced to make a vote, I would go with yes.

DR. WOOD: Okay. Wayne?

DR. SNODGRASS: I will say yes for both groups, but with the lower range, 25-28, you know, it is statistically there. Is it clinically significant? Probably not clinically but statistically yes.

DR. WOOD: Mary?

DR. TINETTI: I will say yes for overweight and I will not comment on the other because I find it a moot point because we are not going to have those BMIs and anybody is going to take it if they want anyway so I am not sure why we are having the discussion.

DR. CLYBURN: Yes, and I don't see any data at the lower end of the range but, just like Mary said, I don't see that we are going to have that data anyway.

DR. WOOLF: Yes, and the little data we

have is not reassuring so I will say no.

DR. WOOD: No for what?

DR. WOOLF: No for the lower end of overweight.

DR. WOOD: Alright.

DR. GRIFFIN: I would say yes for overweight, with the caveat that there is not much data in the lower end.

DR. WOOD: And I would say yes, with Mary's comments.

DR. SCHAMBELAN: Yes.

DR. PARKER: Yes and no.

MS. COFFIN: Yes, with the caveat that the lower weight are going to get a lower absolute weight loss.

DR. FOLLMANN: Yes and yes.

DR. BLASCHKE: Yes and yes.

DR. CARPENTER: I would say yes and no. Certainly by the criteria that we were given for effectiveness there is no evidence that the lower range met the criteria of five percent weight loss or more people losing five percent in active versus

placebo so I would have to say yes and no.

DR. WOOD: Sonia?

DR. CAPRIO: Yes and yes.

DR. WOOD: Then 1(d) is use in the obese individual with and without multiple co-morbid conditions. Is there any new discussion on that? Mary?

DR. TINETTI: With my reading of the randomized trials, a lot of the people we are most concerned about were excluded--diabetes, etc., and I am not sure that in the actual use we heard very much about co-morbid conditions so I would have to say we really don't know very much about people with multiple co-morbid conditions, at least from the data we have seen.

DR. WOOD: Do you think there is a fundamental difference between the two groups or do you think they are just an extension of one another?

DR. TINETTI: Well, that is always the question, isn't it? As somebody who sees people with a lot of co-morbidities, I think very often

people with multiple co-morbidities respond differently to an additional medication. These are people who are going to be taking a lot of other medications. They may decide to stop taking their diabetic medications because this is going to cure their diabetes. So, I am not at all confident to extrapolate.

DR. WOOD: But just to be clear, they are only asking for approval in people without co-morbid conditions. Right?

DR. TINETTI: I am just answering your question.

DR. WOOD: I know, I know and I am just thinking out loud. Any other discussion? Yes, Neal?

DR. BENOWITZ: I support that and say that in the smoking field, for example, if someone is a smoker and they have known coronary disease they are usually more addicted because they keep on smoking in spite of the fact that they have good reason not to. So, the same thing could be true with obese patients who have a complication of

obesity.

DR. WOOD: Okay.

DR. CAPRIO: Let me say something. There is data from David Kelly, in Pittsburgh, in adults with type 2 diabetes and obesity, and there were very positive data for orlistat so it does help people. It is not that they are not going to take their medication for diabetes at all. They did much better, those that were taking orlistat plus diabetic medication.

DR. TINETTI: I am just talking about the data that we have been presented here.

DR. WOOD: To make sure that we are answering the question right, this question relates to clinical effectiveness and its use in the obese individual. Let's take first without multiple co-morbid conditions. That is really the only group that has been presented here today. Right? So, why don't we answer that question and make comments on the other one if you feel so inclined. How about that as a way to move us forward? Is that fair? Sonia?

DR. CAPRIO: Yes, without.

DR. WOOD: So, you are saying yes without multiple co-morbid conditions, and do you want to comment on the with?

DR. CAPRIO: Yes, it is a positive comment.

DR. WOOD: The one you just made I guess.

DR. CAPRIO: Right.

DR. WOOD: Alright. Neal?

DR. BENOWITZ: I would say yes to without and most likely it would be effective with but we have no data.

DR. CARPENTER: I agree with those exact comments.

DR. BLASCHKE: As do I.

DR. FOLLMANN: I would also say yes for without and I don't know about with.

MS. COFFIN: The same answer, yes.

DR. PARKER: I agree.

DR. SCHAMBELAN: I agree as well.

DR. WOOD: Me too.

DR. GRIFFIN: I do too.

DR. WOOLF: I don't want to change the trend; I agree.

DR. CLYBURN: Yes.

DR. TINETTI: I would say yes for without and I am not convinced with. I think Sonia's data in a highly regulated clinic doesn't tell us what is going to happen in the real world so I would say no, I am not confident with multiple co-morbidities.

DR. SNODGRASS: Yes without and probably yes with.

DR. PATTEN: Yes, and I don't know enough.

DR. WOOD: Let's go on to question two. Anything else you want on that one from the FDA side? They decided to withdraw (e) because we haven't seen any education material. Is that still the case, Mary?

DR. PARKS: That is correct.

DR. WOOD: So, we are not going to debate (e) as we never saw that stuff so I don't see how we can. Question two, are the safety and tolerability characteristics of orlistat 60 mg and

120 mg tid acceptable for a nonprescription drug? Specifically comment on the following safety concerns and the ability of labeling to convey these concerns to the consumer.

Interestingly, the one that is not here is the one that I suspect a lot of consumers are going to think of first, which is the underwear issue that we talked about. You know, I think that should be front and center and the company says that they have got it there so that is fine.

Why don't we take the stem question first and then address each of these in turn? Are the safety and tolerability characteristics of the two doses acceptable for a nonprescription drug? Discussion? Silence! Dean?

DR. FOLLMANN: I just wanted to reiterate the comment I had about cyclosporine. When they looked at 50 patients with cyclosporine, one in ten thought they could take it. And, what Eric told us earlier was not reassuring in that use of both cyclosporine and orlistat resulted in very low levels of cyclosporine and graft rejection.

DR. WOOD: Well, that is further down. Let's just take the general stem first and then get to that. Anything on the general stem? Sonia? The question that is on the table, to which there is a yes or no answer, is are the safety and tolerability characteristics of the doses acceptable for a nonprescription drug?

DR. PATTEN: But are you dealing specifically with the fat-soluble vitamins?

DR. WOOD: No, we are going to get to that. We have been specifically asked to comment on the following safety concerns so I am separating these two out.

DR. PATTEN: Well, I have a question on the underwear issue and that is this, I can see people in the OTC setting having this problem as about 50 percent of the users did in the actual use study and, particularly if they are having runny stools, turning to another OTC drug, something like Imodium. I am wondering what happens in that event. Have you given any thought to that? People are going to try to deal with this for sure because

it is a very unpleasant side effect.

DR. DENT: [Not at microphone; inaudible]...those kind of compounds don't have any effect.

DR. PATTEN: So, they just postpone the inevitable?

DR. WOOD: No, you just keep leaking.

DR. HAUPTMAN: Importantly, we didn't see [not at microphone; inaudible].

DR. PARKER: I have one other question about the GI soiling and side effects, and that is whether or not it is impacted by exercise; whether or not it is more common. The gut tends to be quieter when the body is quiet, and whether or not this would discourage people from exercising.

DR. HAUPTMAN: We didn't look at it with exercise, but what is important is that when you sleep at night we almost had none of these adverse events because sphincter tone is increased and there is a double sphincter as well. I don't know what happens with exercise but I can tell you that during sleep you didn't get any of these adverse

events.

DR. SHIFFMAN: Just to answer that question in terms of patients' actual behavior, what we saw in the actual use trial was a marked increase in exercise, both duration and frequency. So, people generally increased exercise rather than decreased it.

DR. PARKER: In the actual use study did you query to find out whether among those who were exercising and using it they had more GI effects during exercise?

DR. SHIFFMAN: We haven't done that particular cross tab but, again, overall you see an increase in exercise.

DR. WOOD: Sonia, back to you. The question is are the safety and tolerability characteristics of the doses acceptable for a nonprescription drug?

DR. PATTEN: And we are talking about all of these in terms of safety--

DR. WOOD: No, we are just talking about what is on the screen right now.

DR. PATTEN: Safety concerns, okay.

DR. WOOD: And then we will go through each of these in turn.

DR. PATTEN: So, we are talking about general safety concerns and the ability of labeling to convey these. Is that right?

DR. WOOD: Right.

DR. PATTEN: I think that in my mind there are some profound safety concerns regarding cyclosporine and warfarin. I think that the labeling needs to be very explicit and very conspicuous to inform people about these possible safety hazards. What I saw on the label that is part of the NDA did not assure me that that was the case. I was not reassured by the fact that people on warfarin and people on cyclosporine incorrectly selected themselves into the group to use so I have concerns.

DR. WOOD: So that is a no?

DR. PATTEN: That is a no.

DR. SNODGRASS: Well, I have a dichotomous answer. When we get to the next part it will be

different than this answer. Looking at just this first question from sort of a pharmacologic context only and that it is minimally systemically absorbed, I would actually answer this first part--is the systemic safety and subjective tolerability acceptable in general without consideration of these other issues--that would be yes.

DR. TINETTI: No.

DR. CLYBURN: In general yes.

DR. WOOLF: Yes.

DR. GRIFFIN: In general yes but I am concerned about repeated use and that we don't have any information about long-term use in this kind of setting.

DR. WOOD: Yes.

DR. SCHAMBELAN: Yes, but I want to reserve discussion for the other specific questions because I can't see how we can separate these, frankly.

DR. PARKER: I agree and I share the issue related to the repeated use.

MS. COFFIN: Yes.

DR. FOLLMANN: No.

DR. BLASCHKE: Generally yes.

DR. CARPENTER: Generally yes, and with comments for the next round.

DR. BENOWITZ: Yes.

DR. CAPRIO: Generally yes but I share the comment of the repeated use.

DR. WOOD: Do you want to give us the vote on that, Darrell? While you are counting, we will go to the fat-soluble vitamins and then we will come back to that. Any comments on the fat-soluble vitamins?

I felt that that wasn't well dealt with. I think that there should be a way of making sure that multivitamins are actually delivered to patients, and preferably in the package. The expiration date problem just seemed to me less than an insoluble problem, if that is the reason they aren't packaged together. The reality was that of the people who were not taking multivitamins before they started on the drug, only 50 percent of them

actually started on multivitamins in the study. So, that is the increment you are working with. The others were already on it so it is hard to know what they did. The third thing was that many of them didn't seem to be taking it at the right time. So, I think the sponsor needs to come up with a better strategy, including I think packaging it together, to make sure that the people do what they are asked to do, and that doesn't seem to be a big job. Yes?

DR. CARPENTER: I have concerns about this as well, but I could accept the sponsor's comments regarding preferences for vitamins, and people have ways that I don't understand nor will many physicians even understand why a certain vitamin is chosen by one particular patient over another. I didn't think the coupon idea was that bad, but I thought that if, for instance, as with the age issue it can be bar coded at the point of sale to enforce an age issue, it can also be bar coded to enforce a vitamin or even, for that matter, ask the question of cyclosporine or warfarin use at the

point of sale in the same manner the age component is planned to be done. But I think if some mechanism like that could be put into place it would reassure a lot of our concerns about the safety issues.

DR. WOOD: Well, I am not so reassured about the coupon, I must say. It seems to me that is sort of a way to increase sales of something else. But the bottom line that we are dealing with here is making this drug safe and effective over-the-counter. If to be safe and effective, which is what the sponsor says, it needs to be taken with a vitamin two hours before, then it seems to me that that is part of the package that should be delivered to the consumer to do that and it shouldn't be something that they have to run around to find and pay more for. It is part of the package for effectiveness and safety.

DR. CARPENTER: But 50 percent of the group is already taking their preference of vitamin so--

DR. WOOD: No, their preference is not

evidence based. That is for sure. Neal?

DR. BENOWITZ: I have some concerns about the idea of mandating vitamins or some particular vitamin with it. One, we haven't seen that vitamins work; that it makes a difference. The second thing is a lot of vitamins do have vitamin K and if we are looking at the warfarin population it gets a little bit tricky when you start giving someone vitamin K when they are on warfarin and, you know, it differs in their diet. So, I think it would make the warfarin part more complicated--not that it is not manageable but it would make it more complicated for management.

DR. WOOD: I know but right now it is open-ended. They could be taking vitamin K or not. So, I mean, we haven't solved that problem; it is still there.

DR. BENOWITZ: Well, presumably a physician who is managing the warfarin would advise their patient about taking vitamins with vitamin K. They could take vitamins without vitamin K or take it every single day, one way or the other.

DR. WOOD: That is an interesting question because I am not sure--I mean, isn't the point here that you would want them to take vitamin K if they were taking warfarin with this drug? I understand the issues of vitamin K but the point here is you are going to change the vitamin K levels.

DR. BENOWITZ: Well, you want to maintain the vitamin K levels to be stable so if the person was taking vitamin K at first and was stabilized on the dose, that is fine but you wouldn't want them to start taking vitamin K fresh without having the person managing the warfarin realize that.

DR. WOOD: Okay. Other discussion? George?

DR. GOLDSTEIN: A comment on the other side of the vitamin issue, if a person is already taking vitamins and is presented with a package that seems to require them to take additional vitamins, what about the issue of excessive A or D? None of us are really concerned about B and C but the accumulation of vitamins A and D can cause some serious problems over a long period of time, as you

all know.

DR. WOOD: Presumably you would only take one. You would have to be instructed to only take one.

DR. GOLDSTEIN: I think that is something that needs to be considered.

DR. SNODGRASS: May I comment on that? The data in adults is that vitamin A at the 5,000 units a day was too much for the multivitamins. It is down to 3500 units because of osteoporosis. With vitamin D it is the opposite. There is a general trend in some portions of the adult population to be low in vitamin D.

DR. WOOD: Other comments on the vitamins? Do you want us to go around on this or have you got the discussion?

DR. PARKS: Go around on this.

DR. WOOD: Okay. Sonia?

DR. CAPRIO: My answer is no, I would like to have a better strategy in the package, better advice for when and how to take them.

DR. BENOWITZ: I would like to see some

label changes but I am not particularly in favor of mandating that there be vitamins in the package.

DR. CARPENTER: As per my earlier comments, I think addressing the issue but not co-selling the vitamins is essential. But I think a point of sale check for the drug and the vitamins would be very helpful in terms of safety issues.

DR. WOOD: Terry?

DR. BLASCHKE: And I am not concerned about the vitamins, with the exception of addressing the warfarin issue.

DR. FOLLMANN: I am also not concerned about vitamins.

MS. COFFIN: I am not concerned about the vitamins either. I think that if you surveyed the general population you would find varying levels of vitamin deficiencies and over-use so I am not sure that this is related to that.

DR. WOOD: Ruth?

DR. PARKER: I am not overly concerned with the vitamin issue.

DR. SCHAMBELAN: I agree with that

position.

DR. WOOD: I actually don't think it matters but the company came here and told us it had to be done and I don't believe they have actually come up with a strategy to get it done, and they need to decide either it doesn't need to be done, which might be a reasonable position, or it does need to be done. But I object to this sort of sitting on the fence, that it does need to be done but we don't care if it is done. You can't have it both ways. So, I have an ambiguous answer. Marie?

DR. GRIFFIN: For six months of use I am not concerned. For chronic use I think it could become a problem so I think the label needs to be clear.

DR. WOOLF: I will agree with that and I would also add the caveat that the warfarin issue has to be dealt with in much better labeling.

DR. CLYBURN: I am not concerned about the vitamins.

DR. TINETTI: I am not concerned.

DR. SNODGRASS: I am concerned for the chronic use and the warfarin issue but otherwise, no, it is not a big issue.

DR. PATTEN: I am not concerned except for warfarin, and I think it would be very important to eventually have repeated use data to see what the impact might be.

DR. WOOD: Okay. What about drug-drug interactions, specifically cyclosporine and warfarin? A lot of people wanted to talk about that. Who wants to go first?

DR. TINETTI: I think that we didn't get very good answers to the warfarin issue. I think it was a little bit cavalier to say, well, it is just like any other interactions. It is really not like any other interactions. You can see this would be particularly a problem with three-way drug interactions if they are taking another drug, such as an antibiotic that is going to further deplete their vitamin K. So, I was under-whelmed with the discussion on warfarin and we heard how many people are on warfarin. People don't tell their doctors

about over-the-counter medications, no matter how much we tell them to do that. So, I think that hasn't been adequately dealt with yet.

DR. WOOD: Other comments? Neal?

DR. BENOWITZ: To follow-up on an earlier comment, and I think it might have been Mary's, about educating physicians and giving them the appropriate data, I don't think we have this. I think we really need a long-term warfarin interaction study that might go over a couple of months in people with stable dose to see in a systematic way whether orlistat affects dosing and what the time course is so that doctors know what to do.

DR. WOOD: So, you would suggest making that requirement?

DR. BENOWITZ: I would like to see that, yes.

DR. WOOD: Other comments?

DR. SCHAMBELAN: I am concerned also about other drugs that might have the same types of interactions, particularly amnioderone. I don't

know whether a 30 percent decrease in AUC has clinical significance. Someone like Neal could probably answer that better than I, but I think we shouldn't just stop short of listing two drugs in terms of drug interactions.

DR. GRIFFIN: Yes, I was concerned about that same issue because it sounds like the cyclosporine thing came up because of AERS reports, not because of something that was known about the drug. Then, what happens to the other drugs even though they are uncommon? A decrease in the level of amnioderone could have very bad effects.

DR. WOOD: Other comments? Wayne?

DR. SNODGRASS: The labeling clearly has to address these kinds of issues.

DR. WOOD: I think what Neal is saying is we don't have enough data to address it clearly in the label. Is that fair, Neal?

DR. BENOWITZ: Well, I think the label might be okay or could be strengthened, but I think the physician--

DR. WOOD: Right. So, labeling it to say

talk to your doctor is fine, except the doctor needs to know what to do when the phone rings. That is the point, is it?

DR. BENOWITZ: Yes.

DR. WOOD: Any other comments on that? What about other drugs, just to make sure we have covered that?

DR. PARKER: I had one comment just in terms of the whole poly-pharmacy, encouraging perhaps on the label patients to take this along with their other medications with them when they see their doctor. So few people can actually tell you what they are on and it might be useful consumer-based information if they were advised to take this with them when they see their doctor so their doctor knows they are on it.

DR. WOOD: Any other comments on the drug interaction question?

DR. BLASCHKE: Just a quick comment, I very much agree with Mary that it is very difficult to get histories of OTC drug use from patients. So, depending on the patient to tell you that they

are taking this I think is a problem. I like Ruth's idea. We do this in our clinic in a sort of brown bad exam.

DR. WOOD: Alright. Would it be fair to summarize that we do have concerns about the physician information for warfarin and that there should be some studies on that? What about the issue of the cyclosporine labeling and how that played out in the labeling? Are there any issues you want to discussion with that?

DR. BENOWITZ: I just would say that one consequence of not paying attention is that you may have organ rejection. I think it should be very frank; not just say see your doctor but say what the consequence may be.

DR. WOOD: You may lose your kidney.

DR. BENOWITZ: Yes.

DR. CARPENTER: Given the seriousness of what could happen with decreased cyclosporine levels and rejection, shouldn't this just be an exclusion?

DR. WOOD: It is.

DR. CARPENTER: An enforced exclusion.

DR. WOOD: Well, how do you enforce it?

DR. CARPENTER: Point of sale check.

DR. WOOD: But that is not OTC.

DR. CARPENTER: Well, you are doing it for age.

DR. WOOD: What do you mean by point of sale?

DR. CARPENTER: Ask the purchaser at the time of sale. They have stated that they are doing it for age.

DR. WOOD: Well, I am certainly not in favor of a 16 year-old checkout clerk taking a medical history at the checkout.

DR. CARPENTER: No, no, the way--

DR. WOOD: I mean, a point of sale check on other drugs would involve somebody saying to you tell me the other drugs you are on, sir, and then a barely literate 16-year old looking down this list to decide. The liability risks there are astronomic.

DR. CARPENTER: We were told earlier that

this drug wouldn't be sold to children or to people under 18 because of the way the product would be bar coded.

DR. WOOD: Well, that is different from a drug check.

DR. CARPENTER: Well, does it have to be? Can you program the same simple yes/no information, over 18 or under 18; on cyclosporine or not on cyclosporine and not sell it to those people?

DR. PARKER: Is that true? It is true about the under 18?

DR. WOOD: We are coming to that. Hold that thought.

DR. DENT: We are very aware of the issue with cyclosporine [not at microphone; inaudible].

DR. WOOD: I think the person making the recording can't hear you. Grab one of the microphones, John.

DR. DENT: We are very aware of the issue with cyclosporine. We have plans that include making sure that we contact the entire network of transplant centers with information, educating

transplant physicians, ensuring that people who are discharging transplant patients have the information about cyclosporine. But those plans have not been reviewed in the brief by the FDA. We are aware of it. We think it is important and we will follow-up with it.

DR. WOOD: Well, I think the bottom line here should be that the FDA should follow-up with it. I think there is not enough of that done and we should actually check that whatever is proposed produces an effect. So, we should expect that whatever plan is introduced reduces the number of cyclosporine patients who take this drug if it were to go over-the-counter within two years, and that we actually demonstrate that that is the case, not just, you know, hope for the best.

DR. FOLLMANN: I guess the thing with the company's plan is that it is geared towards the doctors and we are really concerned more about the patients who will read this and say, well, I am on cyclosporine but I want to do it anyway. I think it would be helpful to have the transplant doctors

give advice to the FDA about what levels of cyclosporine are subtherapeutic and will this be a real problem or not. There is just not that expertise here, as far as I can tell, today.

DR. WOOD: No, I don't agree; I think there is. If you reduce the AUC for cyclosporine we know what happens.

DR. FOLLMANN: Well, the company's reports I think were in normals where they reduced it by 30 percent and we don't know if that would be similar in patients who have undergone transplantation.

DR. SNODGRASS: It is a real variability if you look at other ways it gets reduced so it would be quite variable.

DR. PARKER: Whose liability is it if there is a transplant rejection for a patient who takes orlistat over-the-counter when they are on cyclosporine?

DR. WOOD: Well, I am not sure we are going to get into that. I think the issue is that the company needs to demonstrate that whatever plan they put in place actually works, and I think, you

know, that is the bottom line. The FDA needs to ensure that that actually happens. Although this won't be a high frequency adverse event, this will be a devastating adverse event to anyone who loses an organ. I think there are two steps to that. One is the plan you have in place or you are putting in place, Dr. Dent. The second one is that the OTC Division ought to demonstrate that that works a year from now and we know that people on cyclosporine are not taking this drug. Any other comments? Yes, Mary?

DR. TINETTI: I guess I am a little confused. If the company understood that this was a problem why are we reviewing this now rather than after they have dealt with that problem? If we are so concerned that this is a major issue, shouldn't we be addressing whether it is appropriate to go over-the-counter once we have evaluated that as opposed to leaving it for after our approval?

DR. WOOD: Do you want to respond to that?

DR. DENT: When the actual use study was run and there were two people with cyclosporine we

needed to find a mechanism to get a large enough number of people to understand how they would behave. If you do a self-selection study, you know, with the goal of finding 50 people who had transplants and were on cyclosporine the number of people you would have to enroll is massive. So, what we did was identify an approach going through this database, as Dr. Shiffman described to you, and then specifically targeted people who had transplants but without them knowing why they were specifically targeted. So, that was a part of the reason why this was so late in the process.

DR. WOOD: I think the point she is making though, John, is that that second study still showed there was a problem, and the question she is asking is do we have a solution to the problem and the answer to that is no. My answer to that would be that the number of people who are actually on cyclosporine is relatively small and I am not sure you should deny drug to the total population if a small proportion can't follow the instructions, but that is perhaps a philosophical question.

DR. SNODGRASS: I think there are 7,000 to 10,000 kidney transplants per year in the United States. That is an accumulating figure.

DR. WOOD: It is still a small number by comparison to the numbers we are talking about here.

DR. DENT: And we will be instituting a system where the pharmacists, when they dispense cyclosporine, have information about warfarin so they will communicate it to the patient, as well as the patients getting that information at discharge.

DR. WOOD: Any more discussion on this? Mary, are you happy? Unhappy?

DR. TINETTI: He answered the question. I don't necessarily agree with the answer but he answered the question.

DR. WOOD: Alright. Any further discussion on this? we can do a wrap-up after we finish and see. Other concerns--pancreatitis, liver toxicity and stones? I am not sure that the pancreatitis issue is entirely clear yet. It is interesting that the FDA is working on it, which

sort of left you with a sense of some discomfort, I would say. Obviously, it wasn't fair to share that data with us. Any other comments?

DR. SNODGRASS: I would just say that this raises the issue of a need for post-marketing surveillance, at the minimum.

DR. BENOWITZ: It was surprising to me, given the data on oxalate excretion, that there were not people who had stones. Has this been looked at systematically whether it increased the risk of renal stones?

DR. WOOD: It may be one of these things that just isn't picked up in a spontaneous reporting system.

DR. HAUPTMAN: Can I address you? We had no significant effect on oxalates. The mean changes were no different on orlistat and placebo. The total number of stones was less than one percent in all treatment groups, a little bit higher in the orlistat group in the two-year studies but in the four-year studies there was 1.4 percent--equal. So, there was a minimal increase

in free fatty acids to bind with calcium so we saw no increase in oxalates. We may have an occasional patient who had an elevated oxalate level in terms of a marked value but that was the same in orlistat and placebo so we didn't really see that.

DR. SNODGRASS: May I comment on this? Correct me if I am wrong, what I interpreted from the materials was that in the two-year study at 60 mg tid to placebo this was ultrasound detected stones, whereas 0.5 percent in the 60 mg tid was 1.5 percent.

DR. HAUPTMAN: I don't have the data in front of me but that is ultrasound evaluation. For actual stone measurements for people who had symptomatic stones it was actually the same in orlistat and placebo, and in the four-year study the percent, like I said, was 1.4 percent. But the numbers that you were talking about, although being different, weren't statistically different and were quite small in terms of numbers.

DR. WOOD: Any other issues about that? When we took the stem people wanted to come back to

that. Do we want to go back around again or are people comfortable and have said what they wanted to say? No? Let's move on then. Is that fair?

The next one addresses the pediatric issue. This proposed nonprescription product is targeted for overweight adults greater than or equal to 18 years of age. Do you have specific concerns regarding possible use in the following populations, pediatric, underweight or normal weight, those with eating disorders, obese individuals with and without multiple co-morbid conditions?

Now, when you say do you have specific concerns, I guess we all have specific concerns about patients who are of normal weight and under 18 taking the drug. Is the question do you think we can prevent it with the plan that is proposed, Mary?

DR. PARKS: Were you talking to us, Alastair?

DR. WOOD: Yes, I was.

DR. PARKS: We were talking to each other.

Very sorry.

DR. WOOD: The question that you are wanting us to answer here is do we have specific concerns regarding these populations. I imagine the answer to that is going to be yes. Nobody wants to be giving this to underweight and children or adolescents. But I think the real question you are asking there is do you think the plan will prevent that use. Is that what you are asking?

DR. LEONARD-SEGAL: Go ahead, Mary.

DR. PARKS: We would like to get a discussion on the adequacy of the labeling.

DR. WOOD: Alright. Discussion? Mary?

DR. TINETTI: I want a clarification on the FDA regulations. For another drug that we evaluated a bit ago we were under the impression that the FDA either is not allowed or frowns against--you knew this question was coming--having a drug that was available only by prescription for one group, i.e., the under 18, but could be over-the-counter for another group, the over 18. Granted, this is 60 mg versus 120 mg but the

expectation is that 120 mg are going to be taken. So, just clarify for us that this is okay, if this is approved, by FDA regulations.

DR. LEONARD-SEGAL: Mary can tell me if I am wrong. I think in terms of the prescription dosing orlistat 120 mg is the dose that would be prescribed for children if a physician was going to prescribe the product. So, there is no differential per se in terms of pediatrics in the Rx environment from adults. In terms of what is okay, separating those under 18 from those over 18 I think we don't know yet.

DR. WOOD: Let's get to the point here, guys. Didn't the late commissioner have something to say on that?

DR. TINETTI: The former commissioner; I don't think he is late.

DR. WOOD: Sorry.

[Laughter]

DR. GANLEY: Yes, I think that is sort of in a flux right now so I don't know what the answer is on that. You know, to me one of the issues is

that it comes down to the intrinsic safety of a drug and what are the consequences if a certain population takes it who shouldn't take it. I think you have made your point clear on cyclosporine where it could end up with catastrophic outcomes. We have drugs out there right now that are labeled to be used in predominantly adult populations. I think Prilosec is labeled predominantly for above 18 years of age.

DR. LEONARD-SEGAL: Completely above 18 years of age.

DR. GANLEY: Aspirin actually has labeling for all ages. It is the professional use labeling that is geared more towards adult cardiovascular--

DR. WOOD: There is the Reye's syndrome label.

DR. GANLEY: Yes, it does not preclude use of aspirin however in children.

DR. WOOD: Children with fever.

DR. GANLEY: Right. So, I don't want to give an absolute answer on what we can and can't do because, as you have noted, there is a notice that

was published this past fall asking the specific question about the availability of a drug both Rx and OTC, and parsing out what populations could be using it.

DR. WOOD: But if we were to take the Prilosec model for example, Prilosec is on the shelf and available for purchase; it is just not be used by under 18.

DR. GANLEY: Right.

DR. WOOD: Just to make sure we are understanding, there is no--what shall I say?--there is no system in place to prevent 18 year-olds buying it.

DR. GANLEY: And I think at the time, with Prilosec the issues with heartburn aren't as prevalent in the teenage population as, for example, being overweight. So, in that context, it wasn't at the time I think as much of a concern because we just didn't think there would be much use of that in that population to begin with. In this population it may be a little different so I think it comes down to how important is it that it

not get into the hands of children and, if children would use it, what are the consequences?

I just wanted to touch on this issue about the bar coding at the time of purchase. Now, something was done ten years ago with nicotine products that sort of encouraged some type of limitation of sales to folks over 18 years of age. I think, from a legal perspective, it is not clear even if we impose it that that is enforceable. So, if that is the basis for you making a decision on the availability in that age population, you need to take that into your thought process. It may be something they agree to voluntarily but it may not be something we can enforce.

DR. WOOD: That is helpful. Would it be fair to break this issue down into two parts? First of all, do we think the drug behaves differently in under 18 overweight individuals, and then deal with other parts after that? Because one is a therapeutic question and the other is an abuse question.

DR. GANLEY: I think the way I sort of

look at it is, you know, what mechanisms can you institute within labeling that would not encourage use in a certain population, whether it be by a parent buying it for a child or by the child buying it themselves? If they did purchase it, what is the downside to that?

DR. WOOD: Right. We will try to get at that.

DR. GANLEY: So, you are trying to put mechanisms in place that don't encourage use in that population, and it could apply to these other populations also.

DR. WOOD: Right, all bulimics are not under 18.

DR. GANLEY: Exactly.

DR. WOOD: By any stretch.

DR. GOLDSTEIN: Alastair?

DR. WOOD: Yes?

DR. GOLDSTEIN: A comment, Dr. Ganley is quite correct. There is a long history of shall I say legal entanglements on issues like this. But there is also a long history of companies like the

sponsor who have worked this out, with the public interest first in mind, with the agency in discussions. I would submit that it might be best to leave it to the sponsor and the agency because everybody recognizes the imperatives, and I speak both as a pediatrician and as an industry representative.

DR. WOOD: Okay. Any other comments? Wayne?

DR. SNODGRASS: My concern would be, you know, it is one thing about the drug and the molecule itself and there is probably not a lot of difference between the younger age group and the older age group. The real issue here is, and I am talking about the obese child, their need for a workup. This is a real issue here in the teenage and younger obesity group. If they are bypassing a workup, that is a major "side effect" from this being available to them because there is hypothyroidism--and you can start a list--and it is a big enough issue that I would certainly be very opposed to having 18 and under having general OTC

access. If it is clearly labeled that it is not for use in that age group, I don't know what else you can do in the OTC setting. But if you say it is for use in that group, I think then there is a significant proportion of those who are obese that won't get the workup they need.

DR. WOOD: Right, but I think the company is looking for approval only in over 18 so the labeling, presumably, will be confined to over 18 year-olds. The question is do you have specific concerns regarding possible use in the following populations. The assumption here I guess is that it is being labeled only for over 18 and that this is being used by people outside the label.

I guess the way I was trying to think about this was that possible use could include people taking it because they are obese with the caveats that you have, and then the other one is people who are not obese, which is sort of (b) I guess. These seem to me somewhat different.

DR. PARKER: It seems, Alastair, that the data we have are on that teen study where 41

percent were not able to correctly self-select, for whatever reason. The actual use study does not include in the cohort--it would be great if it did--kids 12 and over so that you could grab that to see how many in whatever age group could correctly self-select. So, it seems to me that the data we have are that 41 percent in this target age were not able to correctly self-select, unless I am missing something.

DR. WOOD: Well, one approach I suppose is to take the same approach I proposed for the last one and say, you know, we don't think it should be used. If it is labeled for over 18 years of age, then let's go back a year from now and see what proportion is being used in under 18 year-olds. If a significant proportion is being used in under 18 year-olds, then we need to revisit the strategy. I would like to see data rather than just this kind of labeling.

DR. GANLEY: John may be able to touch on it better than I can, but when the original nicotine went over-the-counter there were concerns

about potential for abuse--I don't want to characterize it as abuse but possibly becoming addicted to the nicotine in the teenage population, and there was a phase IV commitment that the company has to do some post-marketing study to assess that issue. John can touch on it better than I can.

DR. DENT: And we did. We monitored for all reports of misuse by teens. Whenever we heard of one we investigated it. We even sent people into stores to try and buy nicotine that were under age. And, we monitored and tracked the performance and behavior for six years. At the end of those six years we agreed with the FDA that there was no risk and that we no longer needed to monitor. So, we can do that and I think that is a very sensible and appropriate approach, Prof. Wood, that would give real-world data as to what actually happens.

DR. WOOD: Okay. Other thoughts? Anyone disagree or agree with that? Go ahead.

DR. CARPENTER: I would just like to get clarification on comments that you made earlier

about the program you had in place. Was that discontinued as well, or just the monitoring, in terms of the restriction of sale?

DR. DENT: Nicotine replacement therapy is still age restricted. It is for sale only to 18 year-olds and over.

DR. WOOD: And would we have any concerns apart from the misuse and the diagnostic issues? Would we have any concerns that the actual pharmacology would be different in the under 18 year-olds? I don't think I would.

Based on data from the label comprehension study, did subjects demonstrate adequate comprehension to support safe and effective use of orlistat by consumers? Please describe the factors or data you considered in making your decision. Discussion? Yes?

DR. BENOWITZ: I hope I am remembering right but I thought there was a discrepancy between the FDA analysis and the sponsor analysis with respect to the percentage of people who appropriately chose. I thought in one case the

sponsor said 87 percent and the FDA said 46 percent. Was that on the same data? Is that correct?

DR. WOOD: It was the answers that were marked as acceptable in one set of data and not acceptable in another. That is in the FDA's write-up as well.

DR. LEONARD-SEGAL: Dr. Benowitz, don't confuse the actual use study and the label comprehension study.

DR. DENT: Would it be useful to address the nature of the discrepancy?

DR. WOOD: No, I think the nature was pretty obvious actually, that answers were scored inappropriately. I mean, it is not clear that it was as clear as the initial cut on the data would have suggested I think. That also may need some further work. Any other comments on that? Any discussion?

Did the subjects demonstrate adequate comprehension? The question here is did they demonstrate adequate comprehension to support safe

and effective use of orlistat by consumers?

DR. CLYBURN: One thing I noticed is that they said that the data was available in Spanish but there were zero Spanish-speaking patients in their label comprehension study.

DR. WOOD: Probably just as well, eh? Was it available in Spanish at that time? We will take that under advisement. Can we answer that question yes or no? We will start with Sonia, on the right, this time. That is right up your street, Sonia.

DR. PATTEN: And my answer is no, and my factors are the data that I considered are the data on incorrectly identifying as candidates here. Thirteen percent incorrectly selected for exclusion; 12 percent incorrectly selected for inclusion; 28 percent of warfarin users incorrectly selected; teens, 41 percent inappropriately selected. There was approximately 50 percent that made the wrong decision about vitamins, and those that used vitamins made a wrong decision about the timing. So, those are the factors that lead me to say no.

DR. LEONARD-SEGAL: I am sorry, I am confused--

DR. WOOD: Wait, I think we are looking at different studies here.

DR. LEONARD-SEGAL: Yes.

DR. WOOD: We are looking at the label comprehension study. Am I misunderstanding?

DR. LEONARD-SEGAL: The label comprehension study is what we are asking about.

DR. WOOD: Yes, we are looking at question four and that relates to the label comprehension study. Right, Andrea?

DR. LEONARD-SEGAL: Yes, question four is about the label comprehension study. It is not about self-selecting to use the product. It is about understanding the iteration of the label that was designed after the actual use study was done and prior to the label that accompanied the orlistat application to this advisory committee today. There are three labels. The label comprehension study looked at the second label so we are talking about that study.

DR. WOOD: Right, and I think also the question skillfully asks you to sum everything up in your mind, I think, to reach a conclusion. So, it is not what grade did they get on the label comprehension study so much as does all of that sum to making it safe and effective for use, which could include errors that you have taken into account.

DR. PATTEN: Then I will change my answer and I will vote yes because my recollection is that there are fairly high percentages of participants who gave correct answers to the scenarios and to the questions about the label.

DR. WOOD: Okay. Wayne?

DR. SNODGRASS: Yes.

DR. WOOD: Mary?

DR. TINETTI: Yes.

DR. CLYBURN: Yes.

DR. WOOLF: Yes.

DR. GRIFFIN: Yes.

DR. SCHAMBELAN: Yes.

DR. PARKER: Absolutely no. Maybe I have

the wrong one again but if I am correct, this is one where I circled and remembered that, for example, 21, 22 percent could not understand that you don't take the drug if you are not overweight--double negative; didn't get it. That seemed pretty big to me.

DR. WOOD: I guess, Ruth--

DR. PARKER: Though it has been changed, it has not been retested--

DR. WOOD: No, I understand--

DR. PARKER: --which I think is really important. In what was tested it wasn't there, and then it has been changed and we have no data on it. So, from the evidence that was presented about the one that was presented, that is what we got.

DR. WOOD: But the question is, remember--I am not arguing with you, I just want to make sure we are all on the same page--adequate comprehension to support safe and effective use. So, you think these would not support safe and effective use?

DR. PARKER: I think if you can't

adequately self-select whether or not you are overweight, that is a significant problem and the data from the study seem to indicate that 21, 22 percent were not able to do that. It has been changed since then but there is no further data, unless I am missing something.

DR. WOOD: Okay. Melanie?

MS. COFFIN: Yes.

DR. WOOD: Dean?

DR. FOLLMANN: Yes.

DR. CARPENTER: Yes.

DR. BLASCHKE: Yes.

DR. BENOWITZ: Yes.

DR. CAPRIO: Yes.

DR. WOOD: Do the results from the actual use study suggest that consumers make correct self-selection/de-selection decisions and that consumers comply with dosing directions? Comments? Sonia?

DR. PATTEN: Where are we now?

DR. WOOD: We are on five. We are not asking you to vote.

DR. PATTEN: That is the question that I asked.

DR. WOOD: Exactly. That is why I am giving you a chance--

DR. PATTEN: So, here my answer would be no. The actual use study data do not suggest to me that consumers make correct self-selection/de-selection decisions, nor that they comply with all of the instructions that they are given. But I would like to add a comment to this. I really am confused about label versus actual use because in actual use studies people have to read the label and then make a decision about how to behave based on that. Right?

DR. WOOD: Right.

DR. PATTEN: So, in a sense, both are label comprehension studies.

DR. LEONARD-SEGAL: Can I clarify something just in terms of the order of things? This was sort of done backwards. Generally we recommend that sponsors do label comprehension evaluations before an actual use study is done. In

this situation maybe Roche did do a label comprehension study. We don't know about it; we didn't see it. But they did an actual use study and then, based upon that actual use study data, it appears that GSK said, oh well, it looks like there could be some improvement here so they devised a new label based upon the deficiencies I guess they saw in the actual use study and tested that in label comprehension. Then the label that accompanied the NDA, which is the label that is in your packet, is yet an iteration of the label that was changed as a result of the label comprehension study.

Does that help to sort of sort that through for you? Oftentimes label comprehension studies really just ask about how well consumers understand the different points on the label. The self-selection question is a separate issue and if they are asked to apply the information to themselves. If they do that, then we call it a self-selection study. The actual use study here did not test the comprehension of the different key

elements in the label but it did test self-selection and use. Does that clarify it for you?

DR. GANLEY: Can I just confuse it more for you?

[Laughter]

I think it was Dr. Feibus' slide number 16, and I think if you look at the labeling for the actual use study, it actually tried to exclude people that had co-morbidities, you know, if you had high blood pressure or high cholesterol. And, they did not fare very well in that. But the labeling that they proposed for marketing now does not have those. There are relative contraindications. Okay? So, the self-selection data in that study is hard to compare currently because they have essentially said anyone can take it that is overweight. That is sort of the caveat there.

DR. WOOD: You mean slide 17? Is that the one?

DR. GANLEY: Slide 16. It may be easier

if we can show it up there. So, the failure of self-selection there was basically because they had relative contraindications that the initial sponsor, Roche, was trying to carve out. They were trying to carve out this overweight population that did not overlap with the prescription indication, which was an obese population with a BMI greater than 30 or a population with a BMI of 27 with co-morbidities.

So, you can see there, for example, in the second "ask your doctor" where it has diabetes, high blood pressure, high cholesterol and triglycerides, they are gone. Okay? If you go back and look at the data, that is why they are failing, because people were failing on separating out that I shouldn't be using this. Well, they have gotten rid of that now. The question is, is that okay.

DR. LEONARD-SEGAL: Karen is actually going to show you the crossed out warnings that were on the actual use study label that are not on the orlistat OTC label. There is a slide where

they slash those out in red.

DR. FEIBUS: And I am going to throw out another comment because I thought about this a lot when I was reviewing the study because, clearly, it is different. You have four warnings that are taken away.

But before I go to that slide I want to show you that earlier we talked about the fact that this problem with absorbing food warning was moved up to the "do not use" section whereas before it was down here. Then you have the "do not use if you are not overweight" warning which was new, added after the label comprehension study. You have the kidney stone warning that is entirely new to the NDA label and was not there in the actual use study.

So, when looking at the self-selection decisions in the studies, you sort of had the situation where there are these self-selection rates of 35-50 percent, but the "taking diabetes medicine" is no longer a "do not use" contraindication. It is now in the "ask your

doctor before use" or "ask a doctor of pharmacist before use" section. And, you don't know how moving that warning would change somebody's self-selection decision and if they would make a different choice looking at the overall label based on the whole collection of warnings and where they are.

The same thing when you look at this slide. Four of these warnings disappear. The problems with absorbing food warning is no longer in an "ask before use" warning. It is now a "do not use" warning.

DR. WOOD: What is that supposed to mean, anyway? I never understood that.

DR. FEIBUS: Problems absorbing food?

DR. WOOD: Yes.

DR. FEIBUS: People with malabsorption problems.

DR. WOOD: A lot of them are obese.

DR. FEIBUS: I think it was just because of the issue of malabsorption and then the drug causes a different kind of malabsorption because of

its mechanism. That was my assumption when I read this.

But I grappled with this, trying to figure out what does this mean in terms of the NDA label, and you really can't figure that out because people made these self-selection decisions looking at the whole actual use study label with the distribution of warnings, where they were, applying it to themselves. Then, when you move some of these warnings around and change some of these warnings I am not sure we know how that self-selection process would change.

DR. WOOD: It is certainly a strategy for people in the audience to note for future applications though. If the first, you know, actual use study doesn't work you delete the ones that didn't work and only put that on the table! Does that help? Sonia?

DR. PATTEN: I guess it helps a little bit but I guess I come away from this with a suggestion that there needs to be a re-study with the new criteria in place for self-selection.

DR. WOOD: Well, I guess the question, without being facetious about it is, we need to sort of cut to what we think is important in the actual use study and say did the people not use the drug appropriately based on the current labeled indication, taking into account what Charlie said. I think it was Charlie that said that they originally came in with much more granularity in the patients who were going to take the drug than they are left with now. We have already agreed that we don't think that matters very much, meaning that they were dividing patients into morbid--you know, all sorts of things which have all vanished, and patients with different degrees of obesity and co-morbidities and so on, and all that is gone. Right? That is the point you were making Charlie? Right? So, for better or worse, it is a much more homogeneous, simpler decision to make and the decisions that people were unable to make I guess have vanished.

DR. PATTEN: Well, based on what Charlie just said, since the sources of error in

self-selection and de-selection have pretty much been eliminated, then I would have to say yes, the results suggest that consumers would make correct decisions.

With regard to dosing directions, does this refer, Alastair, only to dosing with the medication or does it also refer to dosing with vitamins?

DR. WOOD: Don't ask me!

[Laughter]

DR. PATTEN: Anyone?

DR. WOOD: What do I know!

DR. LEONARD-SEGAL: The question was with regard to the orlistat.

DR. WOOD: Yes, I figured it means the dosing for orlistat.

DR. PATTEN: Then my answer here would be yes.

DR. WOOD: Wayne?

DR. SNODGRASS: I am going to answer no to both questions. I just don't feel comfortable with the data.

DR. TINETTI: I have to say no. It sounds to me a little bit like a bait and switch. They didn't understand the original thing so now we have eliminated all of those and are supposed to take it on faith that they will do it correctly, and I say no, we have no comfort that they are going to select correctly. For (b), I think they would do okay for the dosing directions.

DR. CLYBURN: I would say yes just because 92 percent of the people who were consumers were overweight or obese, but I still have the concerns that we talked about earlier with cyclosporine and otherwise. Then, did they dose correctly? Yes.

DR. GRIFFIN: No and yes.

DR. WOOD: I think the answer to (a) is yes in that they did make the correct selection based on the new criteria. If (a) had asked did they get the test right the answer would be no, but I am approaching this from did they get the operational use of the drug right and it seemed like they more or less did within reasonable limits. We have seen a lot of examples where this

is not that great anyway. Did they comply with the dosing directions? Yes.

DR. SCHAMBELAN: I am going to say no and yes.

DR. PARKER: No and yes.

MS. COFFIN: I am going to say yes and yes because the majority of the people did self-select that they were overweight or obese.

DR. FOLLMANN: Yes and yes.

DR. BLASCHKE: Yes and yes.

DR. CARPENTER: No and yes.

DR. BENOWITZ: No and yes.

DR. CAPRIO: Yes and yes.

DR. WOOD: Okay, onwards we go. Number six, do you believe that the potential benefits of nonprescription orlistat outweigh the risks? Discussion? No? Alright, Sonia on the left?

DR. CAPRIO: Yes.

DR. BENOWITZ: I think this is a very complicated question. We still haven't seen data that there is persistent benefit, that there is long-term benefit. We see that there is short-term

benefit. Especially the actual use study but even the other studies don't suggest to me that there is going to be any benefit once a person stops the drug. If they keep on taking it, that may be a totally different story but that is not what we are being asked for.

On the other hand, the alternatives, which are dietary supplements, are in many cases harmful. They work mostly because they have a lot of caffeine and some of them have as much as 300 mg per dose and if you take them properly you are taking a gram of caffeine a day. So, one benefit of orlistat would be perhaps that people would not be taking dietary supplements which I think might be a useful benefit.

I also think that orlistat is pretty safe. So, I would say, with that equation, probably the benefit outweighs the risk, but for a convoluted reason.

DR. PARKS: Alastair, can I just ask for a favor. If you are going to vote yes on that, could you elaborate on what the benefit is?

DR. WOOD: Okay. Do you want to go back to Sonia?

DR. CAPRIO: I think there is a great benefit. Even a small weight loss is very important.

DR. WOOD: Okay.

DR. CARPENTER: Qualifying that it is in the short term, I would say yes. I have the concerns about what really happens in the end after extended periods of time, but if we confine this to the short term I would have to say yes.

DR. BLASCHKE: I am going to say yes, and my convolutions are pretty much what Neal described. I think there isn't any other effective over-the-counter preparation. The other preparations are less safe. I have more confidence in the long run in this as an integrated issue and I think we need more data, but in the long run I have to go with this as a yes.

DR. FOLLMANN: I would say yes. You know, the stuff lowers weight not by as much as we would like and we don't know what will happen in the long

term perhaps but on balance I think it is better to have it available in an over-the-counter setting than not.

MS. COFFIN: I would say yes. Again, it is a small amount of weight; it is a short-term usage but it is one more tool to help folks that are out there and, frankly, pardon the pun, they are hungry for help towards this end. So, anything that can be added as a tool will be helpful.

DR. WOOD: Ruth?

DR. PARKER: I would say no. As a prescriber, I would advise patients to use their limited resources to go strongly into diet and exercise. If I were to say yes it would be because I would be glad that they would be getting the kit that encourages these other activities more than the pharmacologic impact of the pill, given that I don't really have the actual use long enough out to give us information on repeated use and on what really happens with some of these other issues that we have addressed. And, I definitely have a concern about use and abuse in the under 18 age

group.

DR. WOOD: Morris?

DR. SCHAMBELAN: Well, at some point or other I still want to come back to my point earlier about what we have been asked to do in the prescription field versus what we are being asked to do in the OTC world. I don't like leaving us with a disconnect and I am not sure whether it is in this point or number seven that we should be coming back to the point that I made earlier.

DR. WOOD: And the point is in relation to?

DR. SCHAMBELAN: Well, we have a guidance that this committee discussed a while back about where drug therapy belongs, and this is drug therapy whether it is OTC or Rx therapy, and we are including people here that we are not recommending treatment for in the prescription world. So, is it this point or in number seven where we have an opportunity to comment from that perspective?

DR. WOOD: Why don't we have that discussion now? I thought we had been through it.

DR. SCHAMBELAN: Well, just because there is a Bill that, you know, talks about availability of drugs that are OTC, I still have a hard time justifying in my mind why we should sit here as a panel with recommendations about where drug therapy belongs for treatment of obesity and then suddenly say, well, we are in the OTC world and that is a different world and we can include people who aren't as obese. I don't think that got clarified for me.

DR. LEONARD-SEGAL: We live in a regulatory milieu, as I said earlier this morning, and the issue is does this product meet the regulatory requirements for a nonprescription product as I stated earlier. That is really the decision I think that you need to make. The debatability about what is going on in the prescription side versus what goes on in the OTC side in terms of standards for treating obesity is really a different question.

DR. SCHAMBELAN: Well, I have a hard time with that. If you are going to be less stringent

in the OTC world than we are in the Rx world, that seems convoluted to me.

DR. LEONARD-SEGAL: You need to be considering the risk/benefit of the drug.

DR. SCHAMBELAN: Well, we do in both settings.

DR. LEONARD-SEGAL: Yes, that is very true.

DR. SCHAMBELAN: We wouldn't even need to have this discussion if we were in the other world. Right?

DR. LEONARD-SEGAL: Well, I don't know because I don't belong to that other world.

DR. SCHAMBELAN: Half of the people on this panel do.

DR. LEONARD-SEGAL: I understand, but you need to bear in mind the regulatory guidelines that we have to work with. That is important. That is key and that is the question here.

DR. WOOD: I think the question, Andrea--if I can just chime in and see if I can help clarify--it seems to me the question that GSK

is here asking is for over-the-counter use for a drug to produce weight loss, just weight loss. And, the issue that you are debating, rightly, is what level of weight loss could we expect to be associated with a beneficial healthcare outcome. Although these are clearly related issues, they are not the same issue, and the issue they are asking approval for is just weight loss. Rightly or wrongly, that is an approvable indication based on regulatory issues and all of that flim-flam. The sort of fairness doctrine determines, it seems to me at least, that if they come to an advisory committee with an approvable indication, such as the treatment of athlete's foot for example, we don't necessarily have to demonstrate that there is some long-term morbidity or mortality benefit from that. So, that is I think where the disparity is. They are not the same. They may overlap and they might really end up with somewhat complementary issues but they are not totally overlapping, at least in my view.

DR. COLMAN: This might help, when we

discussed the guidance and lowering the criteria, that was for the guidance and that was a general question obviously for any future drugs that would come to us as a prescription agent. It might help if you just tried to limit your answer because we are talking about orlistat in this case and there are some differences between this drug and all other obesity drugs. So, perhaps that would make you a little less uncomfortable.

DR. SCHAMBELAN: I am comforted by the fact that this is probably not systemically absorbed; doesn't have CNS effects. That alters the risk/benefit ratio for me so in that context--to move this along since people want to finish up--I would say yes in terms of that specific question, although in whom I think is as important as yes and you are not permitting us to say in whom basically.

DR. WOOD: Well, I am not stopping you from saying anything.

DR. GANLEY: Can I just add something? I think one way to think about it is to say, well, if

we want to adhere to the guidance there is a population that was identified there that should be treated and that is the advice of a group of experts. One way of thinking about it is, is that a population that can be over-the-counter? Because you could say that if this drug is over-the-counter that is who it should be directed to.

Alternatively, you could say it is not that population, it is a lesser weight population, which Roche originally was proposing--to carve out a separate group there. Alternatively, it could be the entire population. So, I don't think it is wrong to say there may be an advantage to benefit/risk, but then you have to identify the population and it goes back to, well, how do you do that? How do you carve out the population if you wanted to have a separate population that is distinct from everyone that is overweight? Then you have to think about what are the consequences if someone who is not within that population takes this therapy. Does that preclude it from being marketed?

DR. WOOD: Because of safety you mean.

DR. GANLEY: Yes, obviously.

DR. WOOD: Right.

DR. GANLEY: Eric is right though, and others have noted it, this is a different sort of drug in that it is not systemically absorbed so we have less discomfort on the risk side. But, clearly, there could be a situation where there is maybe marginal benefit in someone who has a low BMI and I think that is what they were trying to get at earlier. The risk may be greater and you may say the risk outweighs the benefit in that population. So, that is a no-starter for me and I am only directing it at people who really can benefit from this because I can decrease their weight and improve these co-morbidities.

DR. SCHAMBELAN: Yes, well, that is why it is hard to get enthusiastic about somebody with a BMI of 25.5 who is going to be having fecal incontinence.

DR. GANLEY: You still have time to change your vote.

DR. SCHAMBELAN: I am going to leave it at yes with that caveat.

DR. WOOD: I am going to say yes and for some of the reasons which I have discussed. I think the risks seem relatively small although I do have concerns that what we euphemistically call the underwear risks need to be really and clearly outlined to people because I think these are real risks and they, you know, have all sorts of social consequences. So, I think my answer is yes.

DR. GRIFFIN: I say yes. I am less concerned about the underwear risk because I think if people have them and it bothers them they can stop it. I am more concerned about the rare serious adverse events but I still think I would say yes.

DR. CLYBURN: I am going to say yes but I am still very conflicted because I think the benefit, particularly in the low overweight group, is at best marginal, but I think that the side effect profile is not bad either.

DR. TINETTI: I am going to say no. I

think that from a public health perspective there are going to be a lot of people who are going to have very little benefit from six months, particularly the people with less overweight, and the potential for adverse effects, particularly with things like warfarin, are such that from a public health perspective I don't think we have heard a good benefit/harm ratio.

DR. SNODGRASS: I am going to say yes, realizing that, as has been said, the benefits are probably less than people thought. Also, if warnings and monitoring address the following issues, that is, the limits on age; some warning about not to be used under age 18 and not to be used if--and you can specify weight and height together. You can do something to give some information so that those who are under a BMI of 25 can kind of figure out that they probably might not want to consider it. So, I think if those are put on there and emphasized, then I am going to say yes.

DR. PATTEN: I am going to say no.

Although there is the potential for benefit for that portion of the population for which this is aimed, I believe that if this were to go OTC--I am thinking now in terms of the entire population--there will be significant segments of people who should not use the drug who will use the drug. We don't know enough about the consequence of that, nor do we know enough about the consequences of repeat use of this. When people who are appropriately using it have a relatively small weight loss, they stop taking the drug after six months, at what point would they make the decision to resume use of the drug and what might the consequences be? What would the cyclical pattern look like? We just don't know.

DR. WOOD: Onwards to number seven, the 64 million dollar question, or whatever. Should orlistat be approved for nonprescription use? If no, please discuss the deficiencies of the clinical program. If yes, is the adult population for which orlistat is targeted in the prescription--well, let's leave (b). In fact, let's go round and just

do a yes/no first and then we will know which answers we need to contribute to. How about that? Sonia?

DR. CAPRIO: Yes.

DR. BENOWITZ: I would say yes but I have a lot of problems with the package that was put together. I have a lot of complaints about it but on balance I would say yes. I would like at some point to articulate my concerns for future applications.

DR. CARPENTER: A qualified yes.

DR. BLASCHKE: I will just say yes.

DR. FOLLMANN: Yes.

MS. COFFIN: Yes.

DR. PARKER: No.

DR. SCHAMBELAN: Yes.

DR. WOOD: Yes.

DR. GRIFFIN: Yes.

DR. CLYBURN: Yes.

DR. TINETTI: No.

DR. SNODGRASS: Yes.

DR. PATTEN: No.

DR. WOOD: Okay. I guess everybody has deficiencies so why don't we just have a discussion of the deficiencies. If no, please discuss the deficiencies of the clinical program. Let's have the "no's" first do the discussions of the deficiencies. Ruth?

DR. PARKER: I felt like the data provided by the actual use study and the order of the label comprehension and the actual use really wasn't adequate. I think the manufacturer should do better than that. If it isn't done before it is approved, I have worries that it may not be done later, and I think the appropriate time to have it done is before approval.

I think the actual use study should be longer. I would say at least 12 months to allow for data that would give insight into the repeated use issue. I have concern about the cyclosporine and the warfarin, and I also would find a way to look at how you capture better data on self-selection, particularly for younger kids.

I think our insights into the example

being used, Nicorette gum--I don't know why there are so many wrappers all over the place among young girl users. It is very common and, yet, our ability to capture some of this data really worried me about safety and long-term implications, and I just think, you know, we need stronger data to help us make that decision.

DR. WOOD: Other concerns, deficiencies? Neal, you had some?

DR. BENOWITZ: Yes, I thought for an actual use study this was really a not very satisfying study. There wasn't the right label. There wasn't the right duration to make any sense of it. There were not proper outcome data. The educational package which they touted as being so wonderful, which I don't doubt, wasn't tested--

DR. WOOD: And wasn't there; wasn't circulated.

DR. BENOWITZ: I don't think this is the way a package should be put together for an over-the-counter switch. I think there are a lot of things that could have been done that just

weren't. And, I think that the chronic issue is really important because that is the only way it is going to be effective, that people use it either repeatedly or chronically, and that should have been tested.

DR. WOOD: Other comments? Sonia?

DR. PATTEN: I agree with everything that has been said and I would like to add that I worry about the tremendous under-representation of ethnic minorities in the label comprehension and the actual use studies. If we think of this from a public health or population point of view, some of those populations are at enhanced risk for obesity and all of the adverse sequelae for overweight and I think more work needs to be done to include them into this kind of research so we learn something.

DR. GRIFFIN: I guess I just want to second some of those opinions about the relatively small actual use study. If the market is potentially five million people I would really like to see a much bigger study of actual use with long-term follow-up data on persistence of weight

loss. I am not sure whether FDA can require that pre-marketing or post-marketing but I think--I can't remember, 453 people in the actual use study for a market that is five million. I don't think that is very good.

DR. WOOD: Mary?

DR. TINETTI: I think everything has been said.

DR. WOOD: I would just add that I think there is a significant number of phase IV studies that need to be done here, and there needs to be some expectation that they will be completed in a reasonable time. But most importantly, the results of these studies ought to inform future changes to the labeling and use. It shouldn't just be a kind of interesting to know thing because I think there are a lot of holes from where we are sitting right now and we ought to get that data and use that to inform us as we move forward.

DR. SCHAMBELAN: I would just like to add my concern about casting too broad a net in terms of the population for targeting of this therapy. I

think if we went around this table, without embarrassing our advisory committee members, the mean BMI would be over 25 and most of would be considering this therapy, maybe with the exception of Wayne who is nodding his head over there--

[Laughter]

DR. WOOD: Yes, I think everybody recognizes that this is going to be taken by lots of people who are--

DR. SCHAMBELAN: With no demonstrated health benefit. I think that curve is not taking off necessarily at that point.

DR. WOOD: I think Neal's point, made earlier, is one that I think heavily influenced my thinking as well that there are lots of other dietary supplements being taken by people right now to achieve the same goal.

DR. SCHAMBELAN: They may decide to take both.

DR. WOOD: Right. Any other no comments even from people who said yes? So, (b) is if yes, is the adult population for which orlistat is

targeted in the prescription setting different from the adult population in the nonprescription setting? If so, how would these two populations be identified? I must say, I can't see how they are possibly different but I would be interested to hear what other people think.

DR. GOLDSTEIN: Other than what the lawyers and others call the learned intermediary.

DR. WOOD: Yes, but that is not the population.

DR. GOLDSTEIN: That is right.

DR. WOOD: The question is, is the adult population for which it is targeted different? I don't think it is different.

DR. GRIFFIN: No, I don't think so either. I think one of my considerations is I am not sure that this is any safer in a prescription setting than in a nonprescription setting, despite the learned intermediary, because I think that there are knowledge gaps that physicians don't have and that is the problem, not whether it is prescription or not.

DR. WOOD: Yes, your point is well made that if the phone rings what are you going to say? Anyone want to add to that? Anyone think that it is different? Yes, Mary?

DR. TINETTI: I raised this question before but people under managed care, now that this is going to become over-the-counter what assurance do we have that, you know, what is now being covered will no longer be covered?

DR. WOOD: Well, that is a problem that comes up every time a drug goes over-the-counter and the short answer is it is none of our business. I am not being facetious but it is part of the fault of our crazy healthcare system.

DR. PARKS: I have a question because several committee members mentioned that the availability of this product is certainly welcome because we don't have any approved over-the-counter products for weight loss but we have plenty of dietary supplements, basically unregulated products out there. We heard earlier this morning from the applicant that consumers cannot make the

distinction between dietary supplements and OTC products. So, my next question here is do we have any evidence when we move something, not necessarily a weight-loss drug but when we move something from the Rx to OTC setting--the argument is that because there are dietary supplements out there the use of dietary supplements actually goes down because of the availability of an OTC product. This issue was actually raised one year ago with MegaCor.

DR. WOOD: I don't have any evidence. I think the FDA does have the ability to regulate some of these compounds if they get outrageous and some of them on late night TV seem to me totally outrageous. I don't know why letters have not been issued.

DR. PARKER: I would even broaden the question to say will there be any evidence that it increases the use of supplements when there is increased marketing and advertising that there is something you can take to help you lose weight. We really don't know which way the use of the

supplements will go. That can be captured in actual use but wasn't, what happens to supplements. That wasn't a part of it I don't think.

DR. WOOD: So, maybe our message is it is time for some letters.

DR. PARKS: You mean letters to our congressmen.

DR. WOOD: Letters to stop people advertising outrageous claims on television.

DR. GOLDSTEIN: Freedom of speech.

DR. WOOD: Any other comments? If not, we are through I think. Thank you very much.

[Whereupon, at 6:10 p.m., the proceedings were recessed, to be reconvened on Tuesday, January 24 at 8:00 a.m.]

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