DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY SUBCOMMITTEE

Wednesday, September 8, 2004

8:00 a.m.

Holiday Inn
Versailles Ballrooms
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Glenn Braunstein, M.D., Acting Chair
LCDR Dornette Spell-LeSane, M.H.A.,
Executive Secretary

MEMBERS:

Lynne L. Levitsky, M.D.
Louis J. Aronne, M.D.
Katherine Flegal, Ph.D., M.P.H.
Melanie G. Coffin (Patient Representative)
Frank L. Greenway, M.D.
Jules Hirsch, M.D.
Jack A. Yanovski, M.D., Ph.D.
Susan Z. Yanovski, M.D.
Paul D. Woolf, M.D.
Thomas O. Carpenter, M.D.
Dean A. Follmann, Ph.D.
Steven W. Ryder, M.D.
David S. Schade, M.D.
Morris Schambelan, M.D.
Nelson B. Watts, M.D.
Margaret E. Wierman, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. BRAUNSTEIN: We will call the meeting to order. This is the Food and Drug Administration, Center for Drug Evaluation and Research, Endocrinologic and Metabolic Drugs Advisory Committee meeting, on September 8, 2004. The agenda today is to discuss the FDA draft guidance document entitled, "Guidance for the Clinical Evaluation of Weight Control Drugs." The original guidance was dated September 24, 1996.

I am Glenn Braunstein, Professor and Chair, Department of Medicine, Cedars-Sinai Medical Center. I am an endocrinologist. I would like to go around the table and ask people to introduce themselves and tell us where they are from. We will start with Dr. Orloff.

DR. ORLOFF: I am David Orloff. I am Director, Division of Metabolic and Endocrine Drugs at FDA.

DR. COLMAN: I am Eric Colman, a medical officer from Metabolic and Endocrine Drugs at FDA.

DR. HIRSCH: Jules Hirsch, Rockefeller University, New York.

DR. SCHAMBELAN: Morris Schambelan, from the University of California, San Francisco.

DR. FOLLMANN: Dean Follmann, from NIH.

DR. YANOVSKI: Jack Yanovski, from NIH.

DR. LEVITSKY: Lynne Levitsky, Pediatric Endocrinology Unit, Massachusetts General.

MS. COFFIN: I am Melanie Coffin, patient representative.

LCDR SPELL-LESANE: Dornette Spell-LeSane, executive secretary for the committee.

DR. GREENWAY: I am Frank Greenway, from the Pennington Center.

DR. FLEGAL: I am Katherine Flegal, from CDC's National Center for Health Statistics.

DR. YANOVSKI: Susan Yanovski, NIH.

DR. CARPENTER: Tom Carpenter, pediatric endocrinology at Yale University.

DR. WIERMAN: I am Maggie Wierman, endocrinologist at the University of Colorado.

DR. WOOLF: Paul Woolf, endocrinologist,

Crozer Chester Medical Center.

DR. WATTS: Nelson Watts, endocrinology, University of Cincinnati.

DR. SCHADE: Dave Schade, endocrinology, University of New Mexico.

DR. ARONNE: Louis Aronne, New York City, Weill Cornell Medical Center.

DR. RYDER: Steve Ryder, Pfizer Research and Development. I am the industry representative.

DR. BRAUNSTEIN: Thank you. I will now turn the meeting over to LCDR Dornette Spell-LeSane.

Conflict of Interest Statement

LCDR SPELL-LESANE: Good morning. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the agenda, it has been determined that the topic of today's meeting is an issue of broad applicability, and there are no products being approved at this meeting. Unlike

issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees have been screened for their financial interests as they may apply to the general topic at hand. To determine if any conflict of interest existed, the agency has reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration has granted general matters waivers to the special government employees participating in this meeting who require a waiver under Title 18, United States Code, Section 208.

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.

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they apply to

each member, consultant and guest speaker.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Steven Ryder is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Ryder is employed by Pfizer Global Research and Development as senior vice president and global cardiovascular/metabolism/GI/GU development head. And, although Pfizer conducts research in therapeutic areas possibly covered by today's discussion, Dr. Ryder's role on this committee is to represent industry interests in general and not any one particular company.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant's 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 firm whose product they may wish to comment upon. Thank you.

DR. BRAUNSTEIN: Thank you. Dr. David Orloff with give the welcome and introductory comments.

Welcome and Introductory Comments

DR. ORLOFF: Good morning. The first thing I want to say actually before I get to the introductory comments is that I believe, Dornette, if I am not mistaken, we do not have any speakers for the open public hearing. Is that correct?

LCDR SPELL-LESANE: That is correct.

DR. ORLOFF: As a result of that, time permitting, we may try to push Dr. Atkinson's talk up to the morning before we break for lunch. I leave that up to Dr. Braunstein and to the clock.

I want to wish everyone a good morning and welcome our advisors, our guest consultants, FDA

staff and interested public.

The purpose of today's meeting of the Metabolic and Endocrine Advisory Committee is to revisit the division's 1996 draft guidance on the development of drugs for the treatment of obesity. As everyone present knows, the FDA's public health mission includes the charge to assure that safe and effective drugs are efficiently, but without cutting crucial corners, brought forward through development to the marketplace in order to diagnose, cure, treat, prevent or mitigate disease. That, broadly speaking, explains our purpose here today.

More specifically, in August of 2003 the then Commissioner McClellan established the FDA obesity working group and asked that group to develop a plan of action to address critical aspects of the burgeoning obesity problem in the U.S. within the authorities of the Food and Drug Administration.

Germane to our work here today, he charged the so-called therapeutic subgroup, which was led

by our division, to assess real or perceived barriers to obesity drug development and to make recommendations on ways to encourage the development of new or enhanced therapeutics for obesity.

In the face of this growing public health problem, advances in the understanding of the physiology and pathophysiology of obesity and the activity within the pharmaceutical industry in this therapeutic area, we took the opportunity to plan a discussion of the current guidance and its potential modification. Today's meeting is further timely in light of the recent release by NIH, announced on August 24th, of the final version of its own strategic plan for obesity research which includes intensification of efforts on pharmacologic approaches to the prevention and treatment of obesity in both children and adults.

In early 2004 we published a formal call for comments on the guidance in the Federal Register, with an open comment period until late April. Today, with the help of our advisors and

consultants, we will review what we consider to be the salient issues raised in the comments we received, as well as others that we believe are critical to ensuring that FDA's evidentiary standards for safety and efficacy of obesity drugs are, to the extent possible, in line with the science of the day.

We look forward to the formal presentations and what we trust will be a fruitful discussion to follow. I should make clear, as I believe is apparent from the agenda, that this meeting is not intended to discuss any specific drug products, approved or in development. Furthermore, in a manner distinct from a meeting of that type, we will not ask the committee and guests to vote per se on the questions we will pose. These are intended to raise the issues that we wish to hear discussed. We, the FDA staff, will listen and contribute as we see fit and, of course, respond to questions directed at us as we are able. We intend to take the information we have gleaned today back for consideration in drafting possible

revisions to our guidance for industry.

It is important for those participating and listening today to understand that by this meeting we make no formal commitment to changes in the guidance. We view this as an information gathering step in a process that may lead to changes. I know you all have the agenda and I will not review it. I have already announced the potential changes.

Finally, before we start, I would like to thank Dr. Lynne Levitsky, valued advisor particularly on pediatric matters whose term has recently expired, for service to us over the last term. She is here today formally speaking as a consultant. By her agreement to stay on in that capacity, we hope to continue to engage her in the future and look forward to her additional input into the work of the division and the agency.

Finally, special recognition goes to Dr. Glenn Braunstein who has kindly agreed to serve as the chair of today's meeting. Dr. Braunstein's second term as a member expired in June, and having

him here today is particularly fitting given that he chaired the 1995 meeting that led to the drafting of the '96 guidance under discussion. Glenn's association with the committee and the division dates to late 1991, including two stints as an extremely effective chair. We thank him once again for his invaluable service. Indeed, we are not releasing him. He too has agreed to remain a consultant. Glenn, thank you for your generosity with your precious time and for your contributions over many years to this committee, to the division and to the work of the agency. With that, I will turn it over to you.

DR. BRAUNSTEIN: Thank you, David. I appreciate that. The first speaker this morning as far as presentations are concerned is Dr. Eric Colman, who is medical team leader, and he is going to speak about the regulatory history of weight loss drugs.

The Regulatory History of Weight-Loss Drugs

DR. COLMAN: What I plan to do for the next 20 minutes or so is to give you an overview of

the FDA regulation of obesity drugs from roughly the years 1938 through 1999. Before I get to that, I did want to mention two milestones in the history of drug regulatory.

These were, first, the signature in 1906 of the original Food and Drugs Act and that was signed by President Teddy Roosevelt. Roughly 30-plus years later another Roosevelt, Franklin, signed the Food, Drug and Cosmetic Act of 1938. This Act has quite an influence on drug regulation. It affected the labeling provisions, the advertising provisions for drugs, and it was also the first time that drug companies had to submit evidence of a drug's safety before it was allowed to go onto the market. It also marked the beginning of the new drug application, or NDA, process that we have all come to appreciate over the years.

Getting started with the obesity drugs, in 1938 Myerson and colleagues reported the paper in The New England Journal of Medicine, "Benzedrine sulfate as an aid in the treatment of obesity."

These two colleagues treated roughly 17 obese patients with 30 mg of amphetamine sulfate, which is what Benzedrine is. They reported that the patients lost anywhere from 9-54 lbs. This was just one of a number of studies that started to appear in the medical literature that suggested that amphetamines may be an effective way to treat obesity.

The following year, in 1939, the agency approved Benzedrine for a host of different indications, however, obesity was not one of them. Several years later the agency approved another amphetamine. This one was desoxyephedrine. Again, there was a list of indications--narcolepsy, mild depression, alcoholism, even hay fever at one point, but again obesity was not in the list.

Now, it took four more years before the agency finally felt comfortable and granted an obesity indication for desoxyephedrine. To the best of my knowledge, this was the first drug that the agency approved for the treatment of obesity.

I have shown you here some of the language

from the labeling at that time to give you a flavor of what people were thinking. For this drug the labeling stated that the sympathomimetic amines have been found of value, when administered under the supervision of a physician, as an adjunct to the dietary management of obesity. That was the indication section.

The labeling also warned, however, against its use in persons with cardiovascular disease, hypertension or insomnia, and in those who were neurotic or hyperexcitable. So, clearly, there was an awareness that these drugs were stimulatory to the central nervous system, to the cardiovascular system.

On this last point regarding the amphetamines I want to just highlight--this is just to remind you that I will be talking a lot about amphetamines and I will be talking about amphetamine-like drugs in a moment. But when I refer to the amphetamines I am including a large number of compounds which include amphetamine sulfate, desoxyephedrine, also referred to as

methamphetamine, dextroamphetamine and a number of amphetamine-barbiturate combinations.

Soon after the amphetamines were approved in the '40s and early '50s companies began to work to try to develop compounds that, on the one hand, maintained the anorectic properties of the amphetamines but had less of the stimulatory properties. They were successful to varying degrees.

By 1960 the agency had approved five new what I refer to as amphetamine-like drugs. These are also referred to as the amphetamine cogeners. These drugs were phenmetrazine, phendimetrazine, phentermine, benzphetamine and diethylpropion.

Again to give you a sense of what people were thinking during this time, I have shown you some of the language from the labeling for diethylpropion. This drug was indicated for any obese patient, including the adolescent, the geriatric and the gravid, as well as the special high-risk situations of the cardiac, hypertensive and diabetic patient. That is probably an

indication section that most drug companies would die for at this point.

The labeling also stated that because tolerance, habituation or addiction did not develop, this drug was ideal for long-term use. Again, it is interesting to look at the labeling language from back in the late '50s.

Against the backdrop of the approval of the amphetamines and amphetamine-like drugs, there was a problem growing in this country and some people were referring to it as an epidemic. That was an epidemic of the abuse of amphetamines.

I have shown three figures here to give you a sense of the amount of use of these compounds. In 1958 there were approximately 3.5 billion tablets of amphetamines manufactured legally in this country. Approximately a decade later that had more than doubled to 8 billion tablets. Expressed another way, in 1967 there were approximately 23 million prescriptions for amphetamines, 80 percent were for women and of all the indications, these drugs were most commonly

prescribed for obesity.

The government tried to intervene to slow or stop the spread of this abuse by passing two laws, one was the Drug Abuse Control Amendments, in 1965. The second was the Controlled Substances Act of 1970. This is when the scheduling of drugs was introduced.

Moving from 1970 back to the early '60s, in 1962 there was a very important addition made to the '38 Food, Drug and Cosmetic Act. These were the Kefauver-Harris Amendments, also known as the Drug Efficacy Amendments. This legislation for the first time mandated that new drug applications contain substantial evidence of a dug's effectiveness.

You recall, I mentioned that in '38 the law said you had to have evidence of safety. This law now said you had to have evidence of efficacy. So the loop had now been closed. And, this effectiveness was to come from adequate and well-controlled investigations.

This raised a problem however. This

legislation took care of drugs approved in '62 forward but there were literally thousands of drugs that were approved between '38 and '62. The question came up what do we do about the efficacy assessment of these drugs approved before 1962? The answer came when the Commissioner called upon the National Research Council of the National Academy of Sciences to take this task on. This endeavor became known as the Drug Efficacy Study Implementation, or the DESI review process.

The formal portion of the Drug Efficacy Study was conducted between 1966 and 1969. There were a host of different drug panels, depending on expertise, and it was the psychiatric drug panel that was charged with reviewing the available data on the efficacy of the amphetamines and amphetamine-like drugs. They were told after they completed their analyses of the available data that they should classify the efficacy using one of these five descriptors, starting at the top with effective; effective but; probably effective; possibly effective; or ineffective.

They completed their analyses in 1969 and sent the results outcome the FDA Commissioner, and this is what they concluded. They felt the efficacy data supported a statement saying that the amphetamines were possibly effective for the treatment of obesity.

Regarding the amphetamine-like drugs, a little bit better--they thought that this was effective but... so, again, one step below effective. The reasons they cited for not classifying these compounds as effective were the following: Many of the studies that they looked at were of short duration. There was no evidence available that the drugs altered the natural history of obesity. There was some evidence that the anorectic effects may have been strongly influenced by the suggestibility of the patient. And, there were concerns about the adequacy of the controls in some of the clinical studies.

What were the regulatory consequences of DESI review of the obesity drugs? In 1970 the FDA concluded that the amphetamines were, indeed,

possibly effective in the treatment of obesity, and basically mimicked what the DESI review panel recommended. However, because this was short of the category of effective, the FDA directed industry to submit evidence of weight-loss efficacy from adequate and well-controlled trials and, ideally, of more than a few weeks duration. I would point out here that at this time the FDA made no comment about the efficacy of the amphetamine-like drugs. That wouldn't come for a few more years.

After the DESI review process was finished in '69, in the early 1970s the Division of Neuropharmacology Drug Products at the agency--that was a division that had the regulatory purview of these agents--clearly felt the need to develop a policy whereby they could develop and regulate obesity drugs. So, flowing from the DESI review process, three important actions occurred in the early '70s. These were the Prout Consultant Group, the Neuropharmacology Drugs Advisory Committee, and the conduct of the Amphetamine-Anorectic Drug

Project. Let me go through each one of those briefly.

The Prout Consultant Group was put together by folks in the Neuropharmacology Drug Division at the FDA. It consisted of eight external consultants and was headed by a physician named Thaddeus Prout who was an endocrinologist from Johns Hopkins. This group of eight individuals met in April of 1071 to discuss specific issues related to obesity drugs and regulation and development of these compounds.

They issued these four statements back to the Neuropharmacology Division: They felt that, in fact, weight-loss drugs did have some potential value. They felt that the efficacy trials for these drugs should be at least 12 weeks in duration; that the long-term follow-up of patients was not the responsibility of drug companies; and that the efficacy of the weight-loss drugs should be defined as statistical superiority of drug to placebo. This is an interesting point. This group was specifically asked to define clinically

significant weight loss. Either they could not do it or they did not want to do it but, in any event, they said you should consider this as efficacy. In other words, if the weight loss on a drug is more than the weight on the placebo and the difference is statistically significant, then you have a drug that works .

About five months after the Prout Group met and made their recommendations, the Neuropharmacology Drug Division convened its own advisory committee, in September of '71, and again they wanted to get input about how to develop and regulate the obesity drugs. They were also asked to provide a definition of clinically significant weight loss. They did not venture an answer. Instead, they referred back to Prout's recommendation that efficacy be defined as statistical superiority of drug to placebo. This was another group that could not define clinically significant weight loss.

So, after two groups deliberated on this the agency still had no working definition of

clinically significant weight loss. The Amphetamine-Anorectic Drug Project somewhat approached this problem in a backward direction. This was a meta-analysis conducted by members of the Neuropharmacology Drug Division, along with agency statisticians. The overall goal was to try to, once and for all, quantitate the efficacy of the amphetamine and the amphetamine-like drugs. At this point there were data available for fenfluramine and sanorex.

This meta-analysis was quite large. It included 200 clinical studies. These studies ranged in duration from one month to six months. I would say that the average study was six to 8 weeks in duration. There were about 10,000 patients involved in the whole analysis. At the end of the day, when they got done analyzing these data, they issued two conclusions. The first one doesn't sound very impressive but this is what they said: Patients treated with active medication did, in fact, lose some fraction of a pound a week more than those on placebo. The second conclusion was

that the data did not suggest that one drug was superior to another, nor that the amphetamines as a class were more effective than the amphetamine-like drugs. This would have major implications, as we will see in a few minutes.

What were the consequences of this meta-analysis? In 1973 the agency officially declared that the amphetamines and the amphetamine-like drugs were effective for the treatment of obesity. You will recall that in 1970 they said amphetamines were possibly effective and they didn't say anything about the amphetamine-like drugs. So, from doing this meta-analysis, they felt comfortable in declaring that these two sets of compounds were both effective for the treatment of obesity.

The second thing that came out of this project was class labeling. I mentioned the abuse problem, the speed epidemic that had continued through the '60s and into the '70s. So, the abuse of the amphetamines was still very much on the minds of the senior leadership at the FDA. So,

people started to reason, well, if you limit the use of these drugs just for a few weeks you can't get abuse. So, if we limit their use to only a few weeks we take care of the abuse problem and that way we tidy up the risk/benefit profile for these drugs. So, they made a blanket case and not only were the amphetamines indicated for short term and a few weeks actually shows up in the label. People have often referred to this as a few months but the label actually says a few weeks.

Instead of just limiting it to the amphetamines, they threw it over to the amphetamine-like-like drugs as well so at this point all these drugs became indicated only for short-term use, a few weeks use, and I would submit that was largely driven by concerns about abuse, street abuse.

The next notable event in this history came in 1979 when the agency announced its plans to remove the obesity indication from the amphetamines. They still hadn't had enough; they wanted more. They felt that they had good reason

to propose this removal. One of the things that backed them up, they believed, is that there was continued evidence of abuse of amphetamines. They knew it was largely coming from this database referred to as DAWN, which stands for the Drug Abuse Warning Network.

The other point has to do with, as I just mentioned, the risk/benefit profile of the amphetamines relative to the amphetamine-like drugs. The FDA had clearly said that they don't think the efficacy is any different for the amphetamines than the amphetamine-like drugs but we do believe that the abuse potential was more of a problem for the amphetamines than the amphetamine-like drugs. Therefore, amphetamines have a less favorable risk/benefit profile versus the amphetamine-like drugs. If you took the obesity indication away from the amphetamines people in this country would not suffer at all; they had have the amphetamine-like drugs that worked just as well.

The industry had a chance to respond to

this proposal and they did so. I have listed four of their rebuttals here. For one thing, industry felt that the FDA analyses of the DAWN data were incorrect. They just didn't believe that there was evidence of continued abuse.

Secondly, they argued that if illicit production and use of the amphetamines was a real problem, that was the purview of the state medical boards and the Department of Justice; it wasn't something the FDA should get involved in.

Thirdly, they said, wait a minute, abuse requires use beyond a few weeks and our drugs are only approved for a few weeks. So, if this is a problem we are talking about off-label drug use and, once again, that is not something the FDA gets involved in.

Finally, the risk/benefit issue--they felt that the risk/benefit equation should be made on its own merits, in other words, relative to placebo. In this case, the agency was saying that the risk/benefit profile of the amphetamines was less favorable than the risk/benefit profile for

the amphetamine-like drugs. According to industry, they didn't think that was a legitimate or legal or regulatorily tenable reason to take away the indication.

I have to say that after all this bickering the industry won out because this planned action never took place. The agency never removed the obesity indication from the amphetamines and, to this day, I know of one amphetamine that still has in its label its use for short-term treatment of obesity.

We now enter the 1980s, and I think the 1980s in terms of obesity drug development really should focus on one particular happening, and that was the start of the phen-fen studies. In the early 1980s, a clinical pharmacologist from the University of Rochester reasoned that the stimulant effects of phentermine would counter the sedative effects of fenfluramine such that the two together would provide a very tolerable combination that could be used over long-term use. So, he and his colleagues started these studies in the '80s.

In 1992 they published a number of papers citing the main results of these trials. They concluded that yes, indeed, the combination was tolerable and that people could take these drugs over the course of years, and that it was safe and effective.

Again, these were published in 1992. They had a major impact on subsequent use of these drugs, as I have shown here, in this table. These are the estimated total number of prescriptions for phentermine in 1992, 2 million. For fenfluarmine there were about 70,000 prescriptions in 1992--again, the year the papers were published. Four years later these numbers had gone from 2 million to 11 million and from 69,000 to 7 million. I am not saying all of this was due to these papers but a large part of it was.

There was another event that happened around 1992, and that was the transfer of the regulatory responsibility of the obesity drugs from neuropharmacology to the Division of Metabolic and Endocrine Drugs, where they are now. When the new

drugs arrived in the new division there was fairly strong feeling that effective drug treatment required long-term or indefinite treatment. Therefore, why don't we have long-term pre-approval trials? There were other thoughts within the division. There was a strong sense that we need to get this formulated into a guidance policy. They convened their advisory committee in a two-day meeting in 1995 to discuss how to develop and regulate obesity drugs, with an eye to issuing an obesity guidance document.

They had a successful meeting. The obesity draft guidance was issue in 1996. I just show you two of the more important components of that guidance document, and these will be issues that we will be discussing later today.

In terms of efficacy, a 5 percent benchmark was chosen. At that time, people could point to the fact that if people lose as little as 5 percent of weight they could get improvements in lipids, blood pressure and cholesterol and, therefore, this was a clinically significant weight

loss. So, now we finally have a definition for clinically significant weight loss.

On the other side, in terms of the size and duration of phase 3 trials, I think most people felt comfortable that we had agreed that one year of a placebo-controlled trial would be an adequate exposure to assess efficacy and some degree of safety. A lot of people felt though that of these 1500 patients who made it out to a year, 200-500 should be rolled over into an open-label exposure for a following year, again, to get another sense of safety. We will be talking about these issues as well later today.

Just briefly, long-term treatment of obesity, from FDA's perspective, came about when dexfenfluramine was approved in 1996. We all know it was removed from the market the following year because of valvulopathy. A couple of months after the removal, sibutramine, or Meridia, was approved. I have shown you here the actual labeling for the indication. Meridia is indicated for weight loss and weight maintenance. Xenical, the most recently

approved drug, in 1999, has the same indications, weight loss and weight maintenance, but it also has an additional indication and that is to reduce the risk for weight regain after prior weight loss. These are issues that we hope committee members will engage in a dialogue later this afternoon in terms of what these terms mean; how they should be defined, etc.

So, if I could provide you with a global summary, I think it is safe to say that defining or quantitating the efficacy of weight-loss drugs has been problematic. It certainly has been a challenge from a regulatory perspective. It wasn't until the mid-1990s that we had a workable definition of clinically significant weight loss, and that is the 5 percent benchmark. We still don't have a definition of clinically significant drug-induced weight loss--that is a different issue.

On the other side of the coin, I also think it is safe to say that the regulatory history of the obesity drugs has seen its share of highly

publicized safety problems. Beginning with the abuse of the amphetamines in the '40s, '50s, '60s and beyond, primary hypertension became an issue with a drug called aminorex that was used in Europe in the '60s. It was never in this country.

But this condition was subsequently linked to fenfluramine and it was a major issue at the time that dexfenfluramine was approved. It was well-known that this drug increased the risk of BPH in people who took dexfenfluramine. That was before dexfenfluramine was approved. These concerns were only later overshadowed by the cardiac valvulopathy that showed up a year after their approval. These were all very, very highly publicized events, basically so many in the population were exposed to these drugs.

Finally, the approval of Meridia or sibutramine, back in '97, was accompanied by very strong warnings, precautions and concerns regarding the effect of that drug on blood pressure and pulse.

Let me close. Since the topic of today's

discussion is the obesity guidance document, I thought I would just provide a visual reminder of the goals of not only this guidance document but I think of all guidance documents, and that is obviously, on the one hand, to facilitate industry's development of safe and effective drugs but, just as importantly, to provide regulators with the best available evidence upon which to judge a new drug's risk/benefit profile before the drug is approved. Obviously, those two things require a certain amount of compromise and juggling but I will leave you today with that thought. Keep that in the back of your mind as we deliberate the various proposals to change the guidance document. Thank you.

DR. BRAUNSTEIN: Thank you, Dr. Colman. Are there any questions from the panel for Dr. Colman?

[No response]

Thank you. We will move on then to Dr. Katherine Flegal's discussion of the epidemiology of overweight and obesity.

The Epidemiology of Overweight and Obesity

DR. FLEGAL: This is the outline. I am going to give a very brief overview of trends in obesity and overweight in the United State,; a history of regulation of weight-loss drugs, a brief history of definitions of overweight; some population estimates; prevalence of overweight categories and comorbidities; and kind of a brief discussion of some of the aspects of possible benefits and risks of weight change in mildly overweight people with comorbid conditions.

Most of the data I am going to present today come from the series of National Health and Nutrition examination surveys in the U.S., NHANES. Many of you are familiar with this but I know some of you aren't. These are a series of cross-sectional national representative surveys, conducted by CDC's National Center for Health Statistics, in which weight and height are measured and many other actual measurements are taken. We have a series of these dating back to the 1960s up until today. So, we have a little over 40 years of

data on the U.S. population from these surveys. The most recent one began in 1999 and is continuous, representing some data from 1999 up to 2002 in that survey.

This slide shows the age-adjusted trends in obesity, defined as a body mass index of 30 or above in the United States. Starting back in 1960, the prevalence was only about 10 percent for men and today it has gone up to almost 30 percent. As you see, the prevalence was really fairly constant from 1960. In '71 to '74 and '76 to '80 there were not large changes for either men or women. In the '89 to '94 survey the prevalence went up sharply and somewhat unexpectedly, and in the most recent survey it has gone up again so we see this continuing trend.

This is the same setup. This is for overweight defined as a body mass index of 25 or above so it includes the obesity data I just showed you. Again, the prevalence was relatively stable over the first three surveys and then increased. One thing to note is that the prevalence of

overweight with these definitions has been pretty high since 1960. Almost 50 percent of men and 40 percent of women were overweight in 1960 according to this definition.

As you have just seen, the definitions of overweight and obesity that I am using are based on body mass index which is calculated as weight in kilograms divided by height in meters squared. There are two definitions of overweight in this system. One is a body mass index of 25 up to 29.9 or a body mass index of 25 or above. Obesity is then defined as a body mass index of 30 or above and a healthy weight as a BMI of 18.5 but less than 25.

These definitions have been a long time getting systematized and standardized. This is a very brief overview, but basically definitions of overweight up to the early '80s really were not systematized and there were very wide international variations. In the United States there was a lot of use of weight-height tables like the insurance company tables that you have probably seen. There

is a whole set of issues of skinfolds measurements, different kinds of prediction equations; a lot of different kinds of weight-height indices. There is the Broca index, ponderal index. You can see these used in different literature and they are used in different metric systems as well so you never knew whether it would be kilograms and meters or centimeters or pounds and inches. So, if you look at the literature back in the '70s, say, and before it is very difficult to make any comparisons. There are a lot of different definitions that were being used and there were a lot of differences between countries as well.

I think during the 1980s epidemiologic consensus began to form around body mass index, which is also called Quetelet index after the great Belgian statistician in the 19th century. So, you can see that this index has been around for a long time and has been used somewhat, but it began to be really more the index of choice. An NIH consensus conference in 1985 recommended the use of body mass index. But at that point the cut-off values still

were somewhat varied.

The 1959 Metropolitan Life tables in the U.S. had a range of desirable weights for a given height. There was a practice that had grown up of taking the midpoint of that range as kind of the ideal weight and then saying if you are at or about 120 percent of that midpoint, then that was the beginning of the definition of overweight of the median frame weight range.

At the NIH consensus conference, in '85, there was data presented from NHANES, as I have already shown you, about the 85th percentile values for men and women age 20 to 29. Those were a value of 27.8 for men, 27.3 for women. The consensus conference decided to adopt those as some kind of definition of overweight because they actually correspond pretty closely to the Met Life, to the 120 percent definition based on Met Life. We, in fact, used these values as recently as 10 years ago. We would have been publishing data using those particular cut-off points.

Meanwhile, BMI cut-points of 25 and 30

began to be recommended by expert committees. These were not suggested originally by these expert committees. I think the earliest suggestions I am aware of were by George Bray and George Garrow, back around 1980 probably or perhaps before. But these were thought to be more systematized. There was a 1995 report from an expert committee of the World Health Organization that suggested these cut-off points. That was followed in 1998 by the Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults that NHLBI put out, which is really more or less the basis for our current use of these values.

Why these values? Here is what it says in the 1995 expert committee report that they proposed a classification with cut-off points of 25, 30 and 40. This is based principally on the association between BMI and mortality.

They go on to say the method used to establish these kind of points has been largely arbitrary. In essence, it has been based on visual

inspection of the relationship between BMI and mortality: the cut-off of 30 is based on the point of flexion of the curve.

So, in this report and in others there is not a careful study of the criteria for using exactly 25 or 30 as opposed to, say, using 30.5 or 27.8. These are kind of general and, as I say, largely arbitrary. Here is kind of a typical relation between mortality and BMI curve that would have been available to that committee. This is from the American Cancer Society studies.

You see a couple of things here. First of all, the point of lowest mortality tends to hover around a BMI of 25. You see this curvolinear, somewhat U-shaped relationship with much higher risk out here. Also, body mass index is not a physiologic measure; it is just an index and you can kind of intuit that the choice of cut points of 20, 25, 30, 35 and 40 are because these are round numbers and they vary by 5. These are not really physiologically based cut points. So, these are approximations. They are very useful

approximations, by the way. We are very glad to have internationally standardized definitions that we can all use. Now you can compare one person's data with another person's data so these are quite valuable to have.

The 1998 NHLBI clinical guidelines also offer the same definitions. Here overweight is 25 to 29.9 and they say the rationale was based on epidemiological data that show increases in mortality with BMIs above 25. This increase tends to be modest until a BMI of 30 is reached. So, you see that this language also is somewhat imprecise.

I think this is on the following page. They describe quite a few studies. Very often the point of minimum mortality is around a BMI of 25. This is a study of NHANES I where they show the lowest mortality in the range of 25-30, and they found, by race and sex, the lowest mortality at 24.5 for white men, 26.5 for white women, and even higher values for black men and women. There is other information presented in the same NHLBI report which also has somewhat similar analyses.

So, definitions of overweight have changed quite a bit over time. We have pretty much settled down now to using these standard definitions but that is a little bit of the history.

Getting back to definitions, overweight is a BMI of 25-29.9. These are slides like the ones I showed you but now these are really just that range. There are two things you can see from this. One is that the prevalence of overweight by these definitions has really changed very little over time. It is almost constant. Another thing you can see is that the prevalence of overweight by these definitions is quite a bit higher in men than it is in women, which is less true of the prevalence of obesity. It is about 38-40 percent for men and about 25 percent for women.

Just looking at the numbers of people, and I am going to try to divide this by separate categories. One is BMI to under 27 and 27 up to 30 because that is one of the cut points used in the current guidance document. This is just to show you the number of people in the U.S. population who

fall into these various categories. I also included the next lowest category as kind of a comparison point. In this lowest category of 23 to less than 25 the numbers of men and women are approximately equal, about 14 million in each. In the range of 25 to under 27 there are a few more men than women. There are about 16 million men and 12 million women. As you go up to the range of 27 to 30 there are more people in this category, which is actually a broader category, of course, also. There are 21 million men and about 17 million women.

Looking at that by age as well, I have divided this into 4 age groups, 29-29, 40-59, 60-79 and 80 and above. You can see that for a BMI of 25 to 27, men and women both in that BMI range are in the age groups 20 up to 59. When you get to the 60-79 year-old age range there are fewer people but you see that in the younger ranges there are more men than women in these categories. When you get up to this age range there are actually almost equal numbers of men and women in the older ages.

The same is true for the next category of a BMI of 27-30. So, there is a definite age pattern with these numbers.

Now I am going to talk about comorbidities. There are five listed plus "other" in the guidance document: hypertension, hyperlipidemia, glucose intolerance, cardiovascular disease, sleep apnea and other obesity-related conditions. I don't really have good data to show you on cardiovascular disease or on sleep apnea or the other conditions so I am just going to talk about these three from what we have, hypertension, high cholesterol and glucose intolerance.

One thing I was asked to do is to consider the question of the point of inflection of the curve of the relationship of these comorbidities to BMI. So, I have presented the data this way and I have a whole series of slides, all laid out the same way.

The yellow line is men--this is for men, 20-39; the green line, 40-59; the pink line, 60-79; and then 80 and above. This shows the body mass

index categories along this axis and the prevalence. There are a couple of things you can see from this. First of all, you don't see a very clear point of inflection, for example, between 23-25, 25-27. Here you see a little increase but in this case it was a decrease here and an increase there so these bounce around somewhat. So, you see a gradual increase in the prevalence of these conditions with the BMI level in all age groups. You don't visually see an obvious point of inflection.

The other thing to notice is that although we talk about these as obesity-related comorbidities, this shows you pretty clearly that they are also age-related comorbidities and, in fact, the prevalence of any of these conditions in people with a BMI of 30 who are young is far, far lower than the prevalence even in people at the lowest BMI level who are older. So, you need to keep that in mind. Again, there are other risk factors for these conditions and age, in particular, is a very strong risk factor.

This is the same picture now for women. Again, you see at the old age range a very high prevalence of hypertension at all BMI levels. You see in most age groups a slight increase in the prevalence by BMI level and you don't see a strong inflection point. By the way, I defined hypertension as a measure of blood pressure systolic over 140 or diastolic over 90, or using medications for hypertension.

This is for high cholesterol, which I defined for this purpose as total cholesterol of above 240 mg/dl or using medication. Here you see a somewhat similar picture. The prevalence is not as high even in the oldest age group and our data are somewhat sparse in the older age group. It may be one of the reasons this curve is not estimated that well. Again, you see some tendency for increase in cholesterol with BMI, also a tendency to increase with age--not a terribly clear inflection point.

Here is the same information for women. Again, sort of the same comments would apply.

Finally diabetes--this is just based on diagnosed diabetes and this is self-report of diagnosed diabetes so this is not based on measurements of glucose tolerance or looking at undiagnosed diabetes. This is people who say that they have been told that they have diabetes. I also excluded people who had age at onset below 30 and have used insulin since diagnosis, approximately since diagnosis, to try to limit this proximally to type 2 diabetes. Again you see the increase with BMI. You see the age differential and you, again, don't really see a strong inflection point. The same thing for women.

This is just the prevalence of any comorbidity. I should say any selected comorbidity because I am only looking at three. This is by age and body mass index group for men. This has somewhat smoothed out the lines because there are more comorbidities involved. Again, there is this big age differential--you know, fairly smooth curves; they go up and down some but there is no obvious inflection point between 25-27 and 27-30 or

23-25.

This is the same diagram for women. Again, big age differences; increasing prevalence of comorbidity with BMI group; fairly smooth lines.

So, how many millions of people are we talking about? I will show you some other data but this is when people have 2 or more comorbidities by BMI categories. For comparison purposes, I put a lot of BMI levels in here. In this range, which is the range of interest for this purpose I think, there are roughly speaking about 4 million people in the U.S. who have a BMI at that level and have 2 or more comorbidities. That is in contrast to about 6 million in the 27-30 range who have 2 or more comorbidities. So, there is a ratio here. This is about two-thirds of that. I have left out some comorbidities so presumably these numbers could be higher so this is just selected comorbidities.

For comparison, even at the next lower level there are almost 3 million people who would fall into that category, even the lowest BMI

category. So, these comorbidities, again, are not limited only to people in these overweight and obese ranges. At the BMI level of 30-35 the numbers are really much higher. Also, the numbers of men and women are pretty equal in these categories of interest in the overweight range.

There is a difference by age again. This shows the same slide but now it is just limited to people in the age range of 20-59. Here there is about one and a half million people who fall into this category, which is BMI 25-27 and one or more comorbidities, and now the numbers of men and women are no longer equal. There are about twice as many men as women in this younger category.

This is for ages 60 and above. Remember, the total here is a little under 4 million so almost 2.5 million of those people are in the age range of 60-70 and now we see that there are, not unexpectedly in this case, more women than men in this age range in this BMI category with comorbidities. That is true along the whole spectrum of BMI levels.

This is sort of changing the design here but this shows you the number of million of people with 1 or more, 2 or more or 3 comorbidities. This is for BMI 25-27 so this is 1 or more, 2 or more or 3, and this shows the total with the different components of the bar showing the age ranges. So, what you can see is that, for example, is people with one or more comorbidity about equal numbers of people in the 40-59 and 60-70 age ranges and those make up the majority of people with a smaller contribution from people 20-39, even though many people in the population in this 20-39 age range don't fall into the comorbidity range.

So, we see about 12 million total with one or more comorbidities as compared to 18 million in the higher BMI range. When we get down to 2 or more comorbidities, which is the number I just showed you, this is approximately 4 million. The largest group is going to be people in the 60-79 age range and people above 60 make up the majority of this group, although not everybody in this group. That is true also for BMI 27-29. So, the

age structure of these age groups is not the same as the age structure of the population.

What about weight loss for people with BMI 25-27? I have tried to review the literature. I have probably not reviewed everything, by a long shot. As far as I can discern, there is not very much information about the benefits of weight loss in this particular BMI range. Most studies of weight loss don't include that many people in this level. Again, up to 10 years ago we would not have considered people in this range to be overweight so that might be one of the reasons why they were not really going to be included. Some of them may actually explicitly exclude people when they study a BMI of 27 or a BMI or 28.

That is also true of studies of the benefits of weight loss in the control of conditions such as hypertension or hyperlipidemia. They may explicitly exclude people who have BMIs as low, so to speak, as 25-27 or may include few, if any, participants.

In kind of a mirror image, I also read an

article which was complaining that drug trials for hypertension are conducted in people who are overweight but not obese so we know very little about it. So, basically, trials of weight loss and hypertension are conducted in obese people and in trials of drug use and hypertension are studied in overweight people but not the converse. So, we may have missing information on both sides of that.

The NHLBI clinical guidelines recommendations for a BMI of 25-29 overweight recommend treatment only when patients have 2 or more risk factors or a high waist circumference. Other than that, weight maintenance is actually recommended. So, the guidelines here for overweight treatment do not recommend treatment for everybody but just for people with other risk factors. They also mention--I didn't put this on the slide--that treatment of the other risk factors is also just as important and should also be considered.

You will see this statement on another slide, but there are a lot of studies that show

that short-term weight loss has beneficial effects on risk factors such as high blood pressure and cholesterol. That is really very well established. Most studies suggest that these are monotonic relations but there is no obvious threshold. So, you would infer from this that weight loss is very likely to improve blood pressure and other risk factors, certainly in the range of BMI of 25-27 as well and perhaps at any weight level. We don't really know but there is not that much evidence on the specific BMI range. This is a fairly reasonable inference.

How much benefit would that have? What would be the net result? That is very hard to judge in the literature. This is one very approximate way of looking at it. You have already seen these data but in a different format. What is the prevalence of having 2 or more comorbidities by age group for BMI 23-25 versus 25-27? If you think that weight loss in the BMI group 25-27 puts you into this next lower group, which is a very plausible assumption, roughly speaking what would

the expected prevalence be?

You can see that effect--this is an approximation again--by just comparing these 2 bars which show the prevalence in the 23-25 BMI group versus the prevalence in the 25-27 for different age groups. In the youngest age group in which BMI is probably a stronger risk factor, relative risk for hypertension associated with BMI stronger are stronger in the youngest group, you see a pretty big potential difference of about half the number of people in this lower BMI group. The number with 2 or more comorbidities is about half. So, that would suggest that you get a fairly noticeable prevalence effect by this kind of change in weight. At the older age ranges the prevalence is high.

So, just looking at these data you would suspect that if you had people with a BMI of 25-27 and they reduced their weight to 23-25 it is not likely that they are going to end up down here where the 20-39 year-olds are. They are more likely to be approximately where people in their same age group are. So, the prevalence of having 2

or more comorbidities is likely to be high even after weight reduction. So, while there is likely to be a beneficial effect, the net effect on prevalence may not be that great.

Weight loss is just kind of part of the therapeutic armamentarium for treatment of various conditions. There is a whole non-pharmacologic treatment or therapeutic lifestyle changes which include weight loss, physical activity and healthful eating habits, which may mean more fruits and vegetables, less sodium, less saturated fat, a whole different range of possible changes. These are an important part of the treatment of diabetes and cardiovascular risk factors obviously. Drug treatment is also often used in managing these conditions.

So, you might ask what is the relative contribution of weight loss in this panoply of treatments. As far as I can find out, that is not well established. For example, what would be the probability that non-pharmacologic treatment alone versus drug treatment would have on management of

hypertension? There are review articles and summary data on this but they tend to start at a higher BMI level, at BMI of 27 or above or 28 or above. So, it is somewhat difficult to assess.

Also, for example, there is one paper by Ed Gregg using the national health interview survey data that suggests that the intention to lose weight is associated with improved mortality regardless of actual weight loss, and the intention to lose weight may be accompanied by some of these other changes, such as increased physical activity and changes in eating habits. So, it is hard to judge and usually weight loss by itself is not the only part of it. Therapeutic lifestyle changes include more, and clinical trials will also look at lifestyle changes. So, they include more than weight change and try to assess where weight change itself falls in the pictures. I couldn't find any data that really spoke very clearly to this issue.

There are a couple of concerns. This is from the Look Ahead Action for Health and Diabetes study, I guess. This is from their website. This

is the sentence I already had on the other slide. Although we know that weight loss improves risk factors and clearly improves blood pressure and glucose tolerance, there are these observational studies that suggest some association of weight loss with increased rather than decreased mortality.

These studies do not differentiate intentional from unintentional weight loss so they definitely have limitations but they can't be completely ignored either. Because of this, there is actually a randomized clinical trial of intentional weight loss going on. There are some questions we don't really have the answers to about this possibility of increased mortality with weight loss so that is one concern, looking at weight loss in this BMI range.

Another possible concern is, again, that a lot of the people who are in this BMI range who have comorbid conditions are elderly and more of the elderly, not surprisingly, are women rather than men and there are, you know, some possible

adverse effects of weight loss in this age range in the elderly and particularly perhaps for women. One of these is the possibility that weight loss as adverse effects on bone health and can result in lower bone density or greater risk of hip fracture.

This is a report from the study of osteoporotic fractures where these women were close to this range and the median and they had an increased risk of hip fracture with weight loss. In fact, this study found also an increase in thin women as well, although the increase was not as great. They did look at intentionality versus unintentionality or lack of intention to lose weight. In this study, and this is not the only study on this topic but just something to kind of keep in mind as a possible issue, regardless of current weight or intention to lose weight there was an association of weight loss with hip bone loss and risk of hip fracture. So, they concluded that even voluntary weight loss in overweight women increases hip fracture risk.

Just to summarize, definitions of

overweight have varied a lot over time, and epidemiologically useful consensus definitions do not necessarily represent physiological differences.

The prevalence of selected comorbidities rises with BMI and doesn't have, at least in my analysis, clear inflection points. There are about 12 million adults with a BMI 25-27 with at least one selected comorbidity and about 4 million have at least 2 selected comorbidities. So, it is a large group of the population.

Half or more of the adults with BMI 25-27 and selected comorbidities are age 60 and above. Weight loss, lifestyle changes and drugs are all used to manage these and other comorbidities. So, weight loss is part of a whole package of possible treatment modalities.

Weight loss is associated with some possible adverse consequences in observational studies. So, I would conclude that the benefits and risks of weight loss for people with BMI 25 to under 27 have not been clearly established. Thank

you.

DR. BRAUNSTEIN: Thank you. Are there any questions from the panel members? Dr. Follmann?

DR. FOLLMANN: I just had a comment. I hadn't seen the relationship between BMI and overall mortality before and I was really struck by the nadir at 25. Many of these documents we have been reading before this meeting were talking about a cut point of 25-30 for definition of overweight, and it just strikes me as maybe curious as to why you would recommend or why people would consider having someone who has to be above 25.1, which is close to optimal, lose weight. So, I was wondering if you could comment on that.

DR. FLEGAL: Well, I guess I think of this from an epidemiological perspective. We have prevalence estimates that use 25 and, you know, different studies show the nadir at different points so I don't think you can say that it is exactly at 25. But the recommendations of NHLBI are really not to lose weight at a BMI of 25.1 unless you have comorbid conditions. So, avoidance

of weight gain is probably more important in that range.

DR. BRAUNSTEIN: Yes?

DR. RYDER: Yes, I just have one quick question. On the two graphs that I you showed earlier on the age-adjusted trends in obesity, you used two categorical definitions, one of 25 and one of 30 with somewhat different patterns.

I have a two-part question. One is if you use 27 instead of 25 or 30, because I have seen that put forward, would the display be more like 30 or more like 25?

DR. FLEGAL: I think it would be more like 30 but I haven't actually looked at data.

DR. RYDER: And the second part is the average weight in the United States over this time period I believe has been going off in somewhat of a linear way, or maybe even more than a linear way. Has the distribution pattern, Poissant distribution, been maintained or is it just one arm skewing out?

DR. FLEGAL: That I can't answer.

Basically, the whole distribution of body mass index is shifting to the right a little bit. But the distribution is becoming much more skewed so there are much larger changes at the higher tail of the distribution. The median has shifted somewhat but the 90th percentile has shifted a lot. So, the distribution is both shifting to the right and becoming much more skewed.

DR. RYDER: Thank you.

DR. CARPENTER: I was struck by the large impact of age on the comorbidities and, at the same time, struck by the fact that in your later slides you demonstrate that the effect on comorbidities with weight loss is much greater at the young ages. I wonder if anybody has looked at the duration of carrying a certain BMI as being more important than the current BMI as a risk factor for comorbidities.

DR. FLEGAL: There are studies like that. I don't think they would explain those age differences. I think basically a lot of people, even at the lowest BMI in the age range of 60-79--you know, a lot of people have hypertension

regardless of BMI. So, any duration or changes can't affect that. You know, at every BMI level you have like 70-80 percent of people with hypertension so, although duration may very well have an impact, I don't think that can be the explanation for those prevalence figures.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: Have there been studies done that look at the pattern of weight gain over, say, a 10-year period and how that might affect mortality? I am thinking of someone who, say, weighs 200 lbs at 40 and goes up to 250 lbs in a steady linear fashion as one kind of trajectory, and the other where they repeatedly diet and their weight fluctuates a lot over that 10-year period but they end up at the same weight. So, steady versus erratic weight velocities--have there been studies looking at the risk associated with those two possible trajectories?

DR. FLEGAL: Well, there have been studies of weight cycling. Sue Yanovski probably knows more about that than I do. But I believe that a

kind of consensus is that weight cycling probably doesn't have a large impact on mortality. Is that right, Sue?

DR. S. YANOVSKI: Yes, the difficulty with these kinds of studies is that they are all observational studies, and weight cycling in itself is associated with a lot of psychiatric morbidity, a lot of other comorbidities and it is really difficult to tease out cause and effect in those kinds of studies.

DR. FLEGAL: Again, there are observational studies that suggest that weight loss is associated with increased mortality. There are a lot of questions about intentionality; why do people change their weight. As Sue was saying, there are other issues. So, this whole area is a very tangled and confused area to really sort out.

DR. BRAUNSTEIN: Dr. Hirsch?

DR. HIRSCH: I think you have just about answered what I was going to ask. The 1997 recommendation concerning the issue that a randomized clinical trial of intentional weight

loss is the only way we could prove whether there are dangers inherent in weight loss--no such trial that fits any of those issues has been carried out. Is that true?

DR. FLEGAL: Of intentional weight loss--

DR. HIRSCH: Yes, randomized, prospective trial. You are saying that is the only way you could find out what the inherent harms of weight loss might be.

DR. FLEGAL: Look Ahead is the only one I am aware of. Is that right, Sue?

DR. S. YANOVSKI: Yes. NIDDK is sponsoring the Look Ahead clinical trial, which is 5000 individuals with diabetes who are randomized to intentional weight loss or a controlled condition.

DR. HIRSCH: But no data are available?

DR. S. YANOVSKI: Not yet.

DR. BRAUNSTEIN: Why do you think the mortality curve is J-shaped? That is, that the mortality goes up as you start getting to a lower BMI at a time when all the comorbid risk factors

seem to be lowest?

DR. FLEGAL: Well, again, there are a lot of issues that are really unresolved. It could be that at older ages there is some association--at all ages there is an association of low BMI with mortality as well as with high BMI. It may have to do with issues like not having adequate nutritional reserves; people going in for surgery at age 65 and you lose weight in the course of being in a hospital and deplete your nutritional reserves. You may be at a higher risk of hip fracture. The pattern of the causes of mortality may be different at different BMI levels at different ages. There are also issues of smoking. Most of these studies adjust in some way for smoking but smokers tend to have lower body mass index and be at higher risk. So, there are a lot of different issues. I don't think it has really been sorted out very clearly in the literature.

DR. BRAUNSTEIN: Thank you. We will move on to Dr. Frank Greenway's discussion of the current status of weight-loss drugs.

Current Status of Weight-Loss Drugs

DR. GREENWAY: I was asked to speak on the safety and efficacy of the drugs that we have for weight loss at the present time. Obesity, before the 1985 consensus conference, was felt to be bad habits rather than a chronic disease, which is the way we now understand it. At least, it was my understanding that eating habits can be retrained over a period of a few weeks and that this at least was another reason why the older recommendation for obesity drugs was over a shorter period of time.

The drugs approved before 1985 were, therefore, approved for periods up to a few weeks, and tested over that period of time. Mazindol and fenfluramine are no longer available; phentermine and diethylpropion are. Dr. Colman already reviewed the analysis of the FDA information on new drug applications that were reviewed in the 1970s that showed that these drugs approximately doubled the weight loss seen with the placebo groups.

Just a few overview comments about treating obesity as a chronic disease with

medications, first of all, the drugs work only when they are taken and I will show you a slide to demonstrate that. The average weight of the participants in those studies is 100 kg. So, one can look at these weight loss graphs as percent weight losses or kilograms of weight loss since it is 100 kg.

The placebo group in these trials has always required some type of treatment because IRBs feel that placebo groups need to get some form of treatment as well. So, people in these trials are really getting two different treatments. Weight loss in these trials usually plateaus at about 6 months. The primary criteria for approving drugs in Europe is a 10 percent weight loss that is greater than placebo. A primary criterion in the United States is a weight loss that is 5 percent greater than placebo and is statistically significant.

This is a slide of a study done in a practice situation where patients were given fenfluramine, a drug no longer approved. They were

seen monthly for a year. As you can see, the weight loss plateaus at about 6 months. The one-year people in this trial had their drug discontinued but they would continue to be followed for the following year. When they were followed off the treatment the weight loss just about went away by the time they got to the second year.

Another point I wanted to make was about the ancillary treatment that goes on in these clinical trials. Back in the early '70s behavior modification was a new treatment. There was a trial that was done to approve mazindol and two of the sites did it in the standard way, which is demonstrated on this slide. Everybody got a tear-off diet sheet and the placebo and drug groups were given pills each week and were weighed each week. As one can see, the placebo group really lost no weight over 6 weeks and the mazindol group lost 6.5 lbs over that period of time.

In another site in that trial behavior modification was superimposed upon all groups. The mazindol group in that site lost 8.5 lbs rather

than 6.5 lbs but the difference between drug and placebo was reduced considerably, to the point where, at least in this particular site, the difference was no longer significant.

To sort of carry that forward, because this is sort of the difference between the European and U.S. kinds of criteria, here you can see that an orlistat trial in Europe had 11 percent weight loss but only a 2 percent difference from placebo. This is because there was presumably a larger ancillary program that was superimposed upon this weight loss program.

This is a sibutramine trial that was done in the United States where the difference was to get a spread between the two groups. You have a 7 percent weight loss with sibutramine and a 2 percent loss with placebo, and there was, therefore, a 5 percent difference.

In talking about the safety and efficacy of the drugs that are presently available, the Rand Corporation was commissioned to prepare an evidence report on the pharmacologic treatment of obesity by

the agency for Health Care Policy and Research of our federal government. Some new meta-analyses were done during that process using the studies that were at least 6 months in duration. Although this hasn't yet been published, they have given me permission to present some of that data.

There are several categories that one can put the drugs available into. One would be phentermine and diethylpropion which are approved for obesity but for short-term use. The second would be orlistat and sibutramine which are approved for obesity for long-term use. Then there are drugs that are approved for other indications, not for obesity, things that are approved for depression, like fluoxetine and bupropion; things that are approved for epilepsy such as topiramate and zonisamide which also give weight loss. Then, there are 2 drugs that are in phase 3 clinical trials, Axokine and rimonabant which have some public information available on them.

The data presented here on efficacy presents the data in the way the FDA evaluates

drugs, that is, the difference between the placebo group and the drug group. In trials of phentermine up to 6 months in duration, using 30 mg/day, the difference between drug and placebo was about 3.5 kg. With diethylpropion, in studies that went up to about a year, the difference was 3 kg.

One might ask how can one, in this day and age when we understand obesity to be a chronic disease, find a use for these medications that are only approved over a period of a few weeks. This is a study that was done comparing the green line, which shows continuous use of phentermine, against the yellow line, which showed 1 month on 1 month off; 1 month on, 1 month off.

As you can see, the line is more jagged but they end up at approximately the same place at 9 months compared to the red line, which is placebo. So, there are still ways that these drugs can be useful.

Orlistat, at 120 mg 3 times a day, gave a 2.5 kg difference compared to placebo at 6 months in the 11 studies in this meta-analysis, and about

2.75 kg at 1 year in 21 studies.

Orlistat is an inhibitor of pancreatic lipase. It causes a third of dietary fat to be lost in the stool. The relative risks for diarrhea were 3.4, for flatulence 3.1, and dyspepsia 1.5. So, one can see that these side effects result from the mechanism of action.

These trials showed a reduction in total LDL cholesterol and in blood pressure. There was a slight reduction in glucose and glycohemoglobin in diabetics, and it was shown that one could prevent diabetes in those with impaired glucose tolerance.

Sibutramine, in doses of 10-20 mg/day, showed a 3.5 kg difference from placebo at 6 months in 12 trials, and about a 4.5 kg difference at 1 year in 5 trials. Sibutramine is a norepinephrine and serotonin reuptake inhibitor. It had dose-related dry mouth, insomnia and nausea associated with it. The heart rate went up 4 beats/minute in these trials, and there was no consistent effect on blood pressure or lipids. There was a slight improvement in glucose and

glycohemoglobin in diabetics.

One could logically ask, since we have these two drugs that are approved for long-term use in obesity and they work by different mechanisms, could one combine them and get better weight loss. This is one trial that tried to address that issue. The yellow line shows sibutramine treatment for a year. You can see that the weight loss plateau'd at 6 months and remained stable for the next 6 months. When orlistat was added to sibutramine there was no further weight loss.

Fluoxetine is a medication that was approved for depression, not for obesity. It was studied for obesity, however, and at 60 mg/day, a higher dose than is typically used for depression, it caused about a 4.5 kg difference from placebo at 6 months. But, as you probably will notice as something different compared to the other slides, there is less difference at 1 year than there was at 6 months, in this case 3 kg.

Fluoxetine is a reuptake inhibitor of serotonin. The relative risks of nervousness,

sweating and tremors was 6.6; of nausea and vomiting 2.7; fatigue and somnolence 2.4; insomnia 2.0; and diarrhea 1.7. There was regain of weight between 6 months and a year. That is presumably the reason that it was not approved.

This is a slide to graphically demonstrate that fact. You can see that the weight loss came down and plateau'd at around 6 months, but in the last 6 months of that year there was obvious weight gain in the fluoxetine group and not in the placebo group.

Bupropion is a drug that is approved for depression and smoking cessation. At 200 mg twice a day in 2 6-month trials there was about a 2 kg difference from placebo. In one trial at 1 year there was about a 5 kg difference.

Bupropion is a reuptake inhibitor of dopamine and norepinephrine. The 6-month studies were both in depressed patients. The 12-month study was in obese patients that were not depressed. So, these may represent 2 different groups in terms of response. The relative risk for

dry mouth was 3. There was also an increased incidence in insomnia, and there were no increases in pulse or blood pressure in those studies.

Topiramate is a drug approved for epilepsy, not for obesity. At 192 mg/day there was a trial that showed a 6.5 kg difference between that drug and placebo. The mechanism or weight loss with this drug is not clear. The relative risk of paresthesia was 4.9. Taste perversions was 9.2. There were other central nervous system and gastrointestinal side effects with this medication.

Zonisamide is another anti-epileptic drug, not approved for use in obesity. A 16-week trial showed a 5 kg difference between that drug and placebo.

Axokine is a large protein that is injected subcutaneously and is in development in phase 3 for the treatment of obesity. There is one study that is in the public domain that shows a 3.5 kg difference from placebo at 1 year. Axokine appears to activate the leptin pathway distal to the place where leptin acts since it acts in

animals that don't have leptin. It has injection site reactions, nausea and a dry cough associated with its use. Over 30 percent of the people in the trial that I mentioned developed antibodies to Axokine. Those patients who developed these antibodies lost less than 1 percent of their body weight compared to placebo at a year.

Rimonabant is the other medication on which there is public information in the phase 3 trials for the treatment of obesity. The one trial that was reported talked about uncomplicated obesity. It was a 16-week trial and I took the liberty of projecting the weight loss consistent with other weight loss curves of these types of drugs. If one projects that out to 6 months, one gets just slightly less than a 5 kg difference, assuming no weight loss in the placebo group which was not reported on that website.

There is a second trial that used rimonabant in dyslipidemic patients. The difference from placebo was 5 kg at 6 months and 6.5 kg at a year.

Rimonabant is an antagonist of cannabinoid-1 receptor. In other words, it blocks the receptor that is thought to be effective in causing the munchies when people smoke marijuana. Nausea and diarrhea were greater than 5 percent above placebo. There was a 10 percent increase in HDL, a 15 percent reduction in triglycerides and a reduction in the 2-hour post glucose load insulin, and no significant effects on pulse or blood pressure in these dyslipidemic patients.

I put in this slide to put into context the blue line, which is a typical drug where there is weight loss of 10 percent, compared with the gastric bypass which has weight loss of 30 percent which is durable over 14 years.

In summary, there are short-term weight loss medications that are approved for treatment of obesity, such as phentermine and diethylpropion. There are drugs that are approved for the long-term use in the treatment of obesity, that is, orlistat and sibutramine. There are other medications approved for epilepsy or depression, i.e.,

bupropion, fluoxetine, topiramate and zonisamide, which are not approved for use in treating obesity but which seem to give weight loss. And, there are two drugs, Axokine and rimonabant, about which there is public information that are presently in phase 3 trials for the treatment of obesity.

In conclusion, all these drugs give between a 2 and 6.5 kg greater weight loss than placebo in trials that last up to a year, and the amount of weight loss appears to be medically significant. The weight loss between these different drugs is not different statistically and the choice, therefore, revolves around side effects. The weight loss and the difference from placebo are two different things, which I hope I demonstrated, and data beyond 2 years essentially does not exist, with a couple of exceptions. Thank you.

DR. BRAUNSTEIN: Thank you. Questions from the panel? Yes, Dr. Woolf?

DR. WOOLF: There was a report in "New York Times" on Monday, I think it was, of results

of a one-year or a two-year trial in Europe with a drug that they didn't specify, other than saying it was a receptor blocker of some sort that had, I think, 19 lbs weight loss and 3.5 inch reduction in waist and a 24 percent increase in HDL. Do you know anything about that?

DR. GREENWAY: That was rimonabant. I saw that article and that was about rimonabant.

DR. WOOLF: Sorry?

DR. GREENWAY: I read the article and it was reporting on rimonabant, a new study of rimonabant, not the one that was reported by Frank.

DR. WOOLF: Thank you.

DR. GREENWAY: Actually, those results are on the website. I checked it yesterday, 1 year, 52 weeks, 5 and 20 mg.

DR. BRAUNSTEIN: Yes?

DR. ARONNE: Frank, can you talk a little bit about the problem with dropouts in weight-loss drug studies, and some of the pros and cons of the type of analyses used, last observation carried forward versus completers?

DR. GREENWAY: Well, it seems as though people in weight-loss studies appear to have a feeling of being stigmatized when they drop out of studies because they don't want to come back. It is very difficult to get final data on people who drop from weight-loss studies. Weight-loss studies that go out to a year usually have something like a 30 percent dropout rate.

The traditional way of analyzing these studies, as Susan suggested, has been the last observation carried forward, and what that does is it dilutes the effect of the drug because it assumes that the reason the people dropped out is because they didn't lose weight. Actually, what the physician treating a patient is interested in is more what happens to the patient that I treat who stays in treatment, rather than the more public health perspective of this last observation carried forward which looks at the entire group. If you treat everybody, what does the total group gain from this experience? So, from the way in which these medications are used, it is much more

informative to me, as a clinician, to have the analysis of completers rather than the last observation carried forward.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: Just a quick question about Axokine. You said it worked distal to leptin. Do you know if it works distal to the leptin receptor or just distal to leptin? Is its actual site of action known?

DR. GREENWAY: The site of action of Axokine is in the leptin pathway. It is probably in that signaling pathway but it is distal to the site where leptin acts.

DR. BRAUNSTEIN: Frank, can you describe, in the studies that were carried out for one year with these drugs, what the effect was on the comorbid states and whether there were any differences among the drugs? For instance, did some lead to lowering of blood pressure and others didn't? Did some lead to lowering of cholesterol while others didn't? Or were they all fairly consistent?

DR. GREENWAY: You are asking me what was the effect on comorbidities in these studies?

DR. BRAUNSTEIN: Yes.

DR. GREENWAY: Of the two drugs that are approved for treatment of obesity in the United States, orlistat seems to have a disproportionate beneficial effect on lipids, probably because it enforces a low fat diet. Sibutramine doesn't have the expected beneficial effect on blood pressure that one might expect, probably because of its norepinephrine reuptake mechanism of action. Otherwise, one gets the expected benefits that one would expect with weight loss with these drugs.

DR. BRAUNSTEIN: Other questions?

[No response]

Thank you. Our next speaker will be Dr. Laura Governale, who is going to speak about patterns of weight-loss drug use.

Patterns of Weight-Loss Drug Use

DR. GOVERNALE: Good morning. To begin, I would like to briefly state that the Division of Surveillance Research and Communications Support in

the Office of Drug Safety is responsible for the procurement, management and analysis of drug utilization databases for the FDA's use. The information contained in these slides has been approved for this meeting.

The topics I will be discussing today are the patterns of prescription weight-loss drug use and the patient demographics associated with weight-loss drug use. For this presentation weight-loss drugs are defined as dexfenfluramine, sibutramine and orlistat and amphetamine congeners such as phentermine and dimetrazine diethylpropion, phendimetrazine, diethylpropion, benzphetamine, mazindol and fenfluramine. We did not include amphetamines in this analysis. Also not covered in this analysis are over-the-counter drugs and nutritional supplements. The analysis is conducted using proprietary databases at the agency's disposal.

Two databases were used in this analysis from IMS Health. IMS health is a pharmaceutical marketing usage company that collects prescription

drug use information worldwide. The agency uses these databases as well in order to obtain drug use information and trends in the U.S. The two databases from IMS Health were the National Prescription Audit Plus and the National Disease and Therapeutic Index.

NPA, or the National Prescription Audit Plus, measures the retail outflow of prescriptions from pharmacies into the hands of consumers by formal prescriptions. The number of dispensed prescriptions is obtained from a sample of approximately 22,000 randomly selected pharmacies around the country and projected nationally. The pharmacies in the database account for approximately 40 percent of all pharmacy stores and represent approximately 45 percent of prescription coverage in the U.S. The pharmacies include the following retail channels such as chain, independent, mass merchandisers and food stores with pharmacies, and also include mail-order and long-term care pharmacies.

The National Disease and Therapeutic Index

is a survey of roughly 3000 office-based physicians around the country. The data gathered in NDTI are designed to provide descriptive information on the patterns and treatment of disease encountered in this setting. The data are collected and projected to provide a national estimate of use. However, in certain instances the small sample size tend to make these data unstable and sometimes these results should be interpreted with caution.

Patterns for prescription weight-loss drugs dispensed were obtained from NPA Plus. Here I will present the trends in prescription weight-loss drug use dispensed from 1966 to 2003 and also the method of payment for these prescription weight-loss drugs from 1999 to 2003.

This slide, which is based on NPA data, represents the total number of prescriptions dispensed for prescription weight-loss products from 1966 to 2003. The total number of prescriptions represents new prescriptions as well as refill prescriptions.

The yellow-shaded area here represents the

total added prescription weight-loss products of all the individual weight-loss products as shown here. The individual lines represent individual active ingredients in some of these weight-loss drug products. Again, this slide does not include any amphetamine products.

As you can see, over the last 38 years there have been fluctuations in prescription weight-loss products. As you can see, there are two major spikes in prescription drug use. These fluctuations in use have been largely due to two or three prescription drugs at any given time.

The first spike, which occurred during the early 1970s, around the decade of the '70s, was most likely due to the enactment of the Controlled Substances Act in 1970. This was also presented by Dr. Colman in a previous presentation. This legislation in essence restricted the production and distribution of amphetamines which, throughout the 1960s, were commonly prescribed for weight loss. When these restrictions were placed on amphetamines the amphetamine congeners were used

more frequently.

Also in 1973, the agency declared that amphetamine and amphetamine-like compounds were effective for the treatment of obesity. This led to a large spike in use for diethylpropion and phentermine products. The number of prescriptions here peaked at 12.5 million in 1976.

However, we see a decline in use around 1979. In 1979 there was a Federal Register notice calling for the removal of the obesity indication in amphetamines. This led to a sharp decline in use in weight-loss drugs, namely, for phentermine and diethylpropion. However, the proposal to remove the obesity indication from the amphetamines never materialized. Since then, the use of weight-loss products had steadily declined until the mid-1990s.

I will focus now on the last 13 years for prescription drug trends. Looking at the last 13 years, the number of total prescriptions dispensed for weight-loss drugs reached its lowest point around the 1990s, early 1990s, with approximately

3.3 million prescriptions dispensed.

Then, in early 1995, 1996, we began to notice an increase in usage. This was most likely due to the result of a publication, in 1992, of a series of papers that concluded that the combination of phentermine and fenfluramine, or phen-fen, was safe and effective for long-term weight loss. In 1996 the FDA approved dexfenfluramine for the treatment of obesity. The number of anti-obesity prescription drugs dispensed reached its peak in 1996 with 21 million prescriptions. The compounds responsible for this increase include phentermine, fenfluramine and dexfenfluramine.

Again, dexfenfluramine was marketed under the name of Vidoxx and fenfluramine was marketed under the name of Pondimin. During its peak use in 1996 fenfluramine held 33 percent of the market share with 7 million prescriptions dispensed, whereas dexfenfluramine held 11 percent of the market share with 2.3 million prescriptions dispensed. Phentermine held 52 percent of the

market share with approximately 11 million prescriptions dispensed.

This large spike in use was followed by a market decline over the next two years when, in 1997, the FDA announced a voluntary withdrawal of fenfluramine and dexfenfluramine following increased reports of cardiac valvulopathy in patients treated for obesity. The total number of prescriptions dispensed went from a peak of 21 million prescriptions down to approximately 7 million prescriptions ion 1998, which represents approximately a 67 percent decline. Since then the number of prescriptions dispensed for weight-loss drugs has declined to approximately 5.8 million prescriptions in the year 2003.

Orlistat was released into the market around 1997, and sibutramine in 1999. Currently, or in year 2003, they hold second and third place in the market with 1.3 million prescriptions dispensed for orlistat or 22 percent of the market share, and 760,000 prescriptions dispensed for sibutramine, which represents 13 percent of the

market share.

Phentermine continues to predominate the market with approximately 3 million prescriptions dispensed, which represents over 50 percent of the market share. Other products, such as the amphetamine congeners, have steadily declined in use since the mid-1990s and collectively account for less than a million prescriptions per year.

This slide, in contrast to the previous slides, represents only new prescriptions dispensed. Furthermore, this analysis excludes the mail-order and long-term care channels. Therefore, the numbers of prescriptions reported in this analysis are smaller than in the previous slides.

This graph is an analysis of method of payment for prescription weight-loss drugs. As you can see, the number of new prescriptions paid by cash has declined steadily over the past 5 years, from approximately 5 million in year 1999 to 2.6 million in year 2003. However, the number of third-party payment for new prescriptions has remained steady at approximately 1.1 to 1.6 million

prescriptions over the 5-year period surveyed. The drop in cash payment, in effect, has increased the proportion of third-party payment for these drugs from 20 percent in year 1999 to approximately 30 percent in year 2003. So, the main message from this slide is that cash payment remains an important mechanism for the payment of these weight-loss prescription drugs.

Next I will discuss the patient demographics associated with prescription weight-loss drugs. The data are based on IMS Health, National Diseases and Therapeutic Index. Again, the data are projected nationally. However, it does not represent disease burden, nor is it representative of all disease states in the nation. Rather, the data reflect a population of ambulatory patients, visiting physicians and office-based practice settings during which a weight-loss drug is mentioned during the visit. Again, due to the limitations in data sampling in this database, any perceived trends must be interpreted with caution.

The topics I will be discussing for

patient demographics include the principal diagnoses associated with prescription weight-loss drugs, the gender distribution, age distribution and race distribution.

This table represents the principal diagnoses associated with prescription weight-loss products for ambulatory patients. Not surprisingly, obesity is the diagnosis most often mentioned with weight-loss drug products, with approximately 89 percent or 1.8 million projected diagnosis visits.

This slide represents the number of mentions associated with the use of weight-loss drugs as reported by office-based physician practice settings. This is a measure of drug mentions again and is not reflective of disease burden in the nation.

As you can see, females account for a clear majority in use for prescriptions of weight-loss products, with an average of 2.3 million drug appearances or 85 percent over the time period surveyed.

Taking a closer look at the most recent calendar year, we see that the adult age group, 18-44, accounts for the largest majority of drug use for prescription weight-loss products, with approximately 1.2 million or 62 percent of total drug appearances. This is followed next by age 45-64 category, with 624,000 mentions or 32.6 percent of total drug appearances in the year 2003. In conclusion, the majority of weight-loss drug products is in the young, female, adult and middle age adults.

This graph represents the race distribution of patients associated with the use of prescription weight-loss drugs as reported by office-based physician practice settings. Again, the reporting in this database, NDTI, is reported by the physician and not is not self-reported by the patient. The key take-away from this graph is that a proportion represented by each race group has remained constant over the time period surveyed. Approximately three-quarters of use is from Caucasian patients.

Now that I have represented the data, I will present the limitations on each of these databases. The NDA Plus data provide only limited demographic information on prescription use. Therefore, we did not use this database for this analysis. Instead, we used NDTI to obtain demographic information which has these limitations: As you can see, the small sample size makes some projections unstable. Again, the data are not generalizable to all of these patients. And, due to the limitations, any perceived trends must be interpreted with caution.

In conclusion, over the last 38 years there has been a fluctuation in the total number of prescriptions dispensed for prescription weight-loss products. These fluctuations have been largely due to two or three drugs at any given time.

The second point is that cash payment remains an important mechanism for payment for these products. Also the primary users of these products are Caucasian women between the ages of 18

and 44. That is the end of the presentation.

DR. BRAUNSTEIN: Thank you. Any questions from members of the panel? Yes?

MS. COFFIN: On your slide that talks about the race distribution of the patients you can see huge differences and, of course, the Caucasian patients are shown as the largest amount. How does that normalize to the population as a whole? Is the population as a whole from '98 to 2003 more greatly Caucasian than it is Asian American or African American?

DR. GOVERNALE: Again, this database is not supposed to represent any epidemiology of obesity. It represents patients visiting office-based physicians and it could reflect just that there are more Caucasian patients visiting these physicians.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: Do you know if the heavy use of cash for these drugs is because they are being excluded by drug plans that the patients have? Are they being excluded from the formularies that the

patients are covered on? Is that why cash is so prevalent?

DR. GOVERNALE: I think if I heard your question, it is why are most of these products not covered?

DR. WOOLF: Yes, is the reason that cash accounts for three-quarters of the method of payment because they are being excluded from drug plans?

DR. GOVERNALE: Yes, that is the limitation with these products. Most of these products are not covered by third-party payers and, therefore, that is why they are being paid for by cash.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: I was interested in your demographics. I may be making wrong inferences but it seems to me if the largest use of these drugs in the real world is by younger white women, that may be more for cosmetic benefits of weight loss. This is a question then for Dr. Greenway. I didn't get from your presentation the demographics of the

subjects that are studied in the typical weight loss trial. Are they different from the people who are using these drugs as we heard from this presentation?

DR. GREENWAY: The patients in the regular weight-loss trials primarily have a BMI between 30 and 40. So, they aren't in the trials because they have just cosmetic concerns, but I think that what you have observed is correct, that obesity is stigmatized in our society, particularly stigmatized in regards to women, and that is probably the reason that we have 80 percent of these obesity trials that are composed of women. Clearly, 80 percent of the population isn't women.

DR. WATTS: To extend that though, is there a particular age of the subjects in the studies that you showed? Were they different, older, from the use of these drugs in the real world?

DR. GREENWAY: The average age of the people in the trials is usually around 40. So, they may be slightly older than this group but I

think they are probably fairly representative.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. S. YANOVSKI: These data did not report out BMI. They might have the physician diagnosis for obesity correct but you couldn't tell how many of the patients in these studies had BMIs above a certain range. Is that correct?

DR. GOVERNALE: Correct. There is no linkage of BMIs to the diagnosis of obesity.

DR. S. YANOVSKI: So, in preparation for this I pulled an article by Laura Kettle Conning and colleagues at CDC that looked at use of prescription weight-loss pills in U.S. adults from 1996-98 that I think addresses your question. They used the behavioral risk factors surveillance survey and they looked at all patients who reported use of prescription weight-loss drugs. They then looked at the proportion of patients who reported using prescription weight-loss drugs who had a BMI of less than 27, which was the lower limit for indication with comorbidities. What they found was that 5 million U.S. adults had used prescription

weight-loss drugs in that 2-year period. Of that group, 25 percent reported that they had a BMI of less than 25. So, it looks like there is substantial use of these medications for cosmetic purposes.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: I just want to pursue Dr. Woolf's question about the reason that the cash payment is decreased. Do we know that there has been a systematic change in policy of third-party payers as to what they will approve for weight-loss drugs? Perhaps you don't know but other panelists may know.

DR. BRAUNSTEIN: What will the effect of the recent change in coverage of the drugs by Medicare have on all this? I guess that is part of the question.

DR. SCHAMBELAN: Well, Medicare or other payers.

DR. GOVERNALE: We did not look into the reasons for why some of these prescription drug products are being covered or not covered by

third-parties, but that could be a very interesting question to look into for future analyses.

DR. BRAUNSTEIN: Dr. Aronne?

DR. ARONNE: While there hasn't been a systematic change in the number of plans which are covering drugs, what we have seen is that practitioners of obesity medicine where we focus on obesity to treat someone's diabetes, sleep apnea or other complications, is a steady increase in the willingness of insurance companies to pay for drug therapy in an appropriate setting. So, with prior approval, if the patient is in a medically supervised program, the insurance companies will pay for the drugs. Right now in the New York area it is more than 40 percent. The last number I heard was that 44 percent of patients who have insurance get coverage for these types of drugs.

DR. BRAUNSTEIN: Any further questions?

[No response]

We will take a 15-minute break. Thank you.

[Brief recess]

DR. BRAUNSTEIN: We are changing the order a bit. We are going to ask Dr. Richard Atkinson, who is director of Obetech Obesity Research Center, to speak on the role of drugs in the treatment of obesity: current and future. Following that, we will then move to the open public hearing, followed by Dr. Orloff's talk.

Role of Drugs in the Treatment of Obesity: Current and Future

DR. ATKINSON: Thank you, Dr. Braunstein. Thank you, Dr. Orloff and Dr. Colman for inviting me to speak. I am coming today wearing two hats. One is the president of the American Obesity Association and the second is a physician/clinician who has literally treated thousands of obese people over the years.

From that perspective, I have looked into the eyes of these people and seen the pain and heard their pain as they talk, and I have failed them and I think we have all failed them. The physicians and scientists have failed them. The drug companies have failed them and the government

has failed them. That sounds like a negative message and I am going to spend a little time talking about why I think we have all failed. But I think the promise of the future is really very bright and I will try to end up on that.

I always like to start off with something that is not unique to me; I probably stole it from someone, but obesity is a chronic disease of multiple etiologies characterized by the presence of excess adipose tissue. Everybody has excess adipose tissue but the critical word I think here is "disease." I think we have heard in this discussion this morning even some questioning of the idea of obesity as a disease. But I believe obesity is a chronic disease and if you think of other chronic diseases, try to think of one that is not treated with drugs.

If obesity is a chronic disease and most other chronic diseases are treated with drugs, why not obesity? We know that the biochemistry of obese individuals is different from that of lean people. That is very well known. Bob Eckle and

others have some data that when obese people lose weight their biochemistry does not become the same as lean people's. For example, lipoprotein lipase, the major clearer of triglycerides out of the bloodstream, in adipose tissue lipoprotein lipase goes up; in muscle it goes down. So, people who were formerly obese are poised to regain their fat. What do we do with drugs? We change the biochemistry. So, the rationale for using drugs is to change the biochemistry of the bodies of obese people.

There have been, as you have heard, a number of barriers to the use of drugs. The first one I am going to put up here is discrimination against obesity. I am going to spend several slides talking about this.

When Dr. Orloff asked me to talk, we talked about the fact that we were going to have a very nice bunch of scientific presentations and I am going to come with a more emotional part with this presentation. But as president of an organization that is advocating for these people, I

want to point out some of the discrimination against obesity. The fact of physician and clinician ignorance of obesity, an particularly of obesity drugs; economic factors; policy and political barriers, and I have come much more to appreciate that. We have had several meetings with people from the FDA, NIH and others and I have come to appreciate more some of the barriers. There is a lack of advocacy about obese people and, finally, currently there is a modest effectiveness of obesity drugs, as we have heard.

I am going to talk a little bit about discrimination. Obesity is the last bastion of socially acceptable bigotry. If you are a radio announcer or a TV announcer and you tell a joke, a race joke or an ethnic joke, or a joke directed against homosexuals, you will get fired. Fat jokes are told all the time. Look in your comic pages and virtually every day there is some slam against fat people and nothing is done.

This discrimination against obesity is in the people who are in our field. Stan Heshka and

David Allison are two very good friends, two very bright people, good scientists, but "labeling obesity a disease may be expedient but it is not a necessary step in a campaign to combat obesity and it may be interpreted as a self-serving advocacy without a sound scientific basis." Well, those are pretty strong words for somebody who is in the field.

There is a lack of medicalization of obesity. Think about obesity compared with some other chronic diseases. For example, newly diagnosed type 2 diabetes, newly diagnosed hypertension--a very high percentage of those patients will respond very well to diet and exercise. it goes away. I did a study about 20 years ago and it goes away in 80 percent of the people. But the first words our of the mouth of a primary care physician are not "I'm going to put you on a diet and exercise program;" it is "I'm going to put you on drugs."

The primary treatment for obesity is diet and exercise and drugs are an adjunct. As we have

heard from Colman's talk, that has been true for many, many years. Many patients must demonstrate that they have failed diet and exercise before they can get either drugs or surgery. There is no other disease where that happens.

Physician and clinician ignorance--obesity, obviously, is not thought to be a real disease. As many of you know, we have been doing some work on viruses that cause obesity and I have gotten up and had people shake their fist at me and say, "you're trying to give these fat people an excuse." Wow! Physicians are uncomfortable about counseling overweight or obese patients. I have a talk on discrimination against obesity to document many papers in the literature where this has been shown.

Physicians and clinicians are not knowledgeable about nutrition, physical activity, and particularly about obesity drugs. This is a disease that is killing 400,000 people per year according to the CDC. At the University of Wisconsin I was able to get a clinical nutrition

course on the curriculum and we had exactly three lectures on obesity. Since I left, that has now been cut to one. That is pretty much all they get about obesity in the whole curriculum.

Physicians are unaware of referral information. If you have a fat person, what do you do? They feel helpless and there is a feeling that if you refer a patient to an obesity physician you are sort of sending them to a charlatan. There is a bias. We have heard a little bit about that today, that drug treatments are dangerous, ineffective and somehow not worthy.

There are economic factors that are barriers to obesity drugs. I was flabbergasted to hear Lou Aronne's comment that in New York 40 percent of third-party payers are starting to pay for drugs. That is super. We looked in Wisconsin and in our population it was between 10-15 percent. They had a very high percentage of HMOs and these HMOs simply didn't cover obesity or obesity drugs.

Some of the reasons for that are that the treatment is fairly expensive. This, after all, is

a chronic disease. The insurance companies and employers are worried about breaking the bank. There are a large number of overweight and obese people. We heard Katherine Flegal's talk. Over 30 percent of the entire adult population is obese, has a BMI of 30 or above. So, one, there is a large population that might want to use those drugs or use that treatment and, secondly, given a choice, they will.

We heard from Susan Yanovski about maybe as many as 25 percent of people that are using these drugs are using them for cosmetic purposes. That is a little bit of a discrimination in itself. There is a whole industry that makes drugs for cosmetic purposes, like skin rashes and so forth and so on. So, what is so bad about somebody wanting to lose some weight when, if you are overweight, you have a harder time getting a job, getting promoted in a job, finding a spouse. If you are a small kid other kids don't want to play with you. It is not just a cosmetic problem; this is a socioeconomic huge discrimination problem

against obese people.

For many of the insurance companies and insurance plans and HMOs savings in the future costs are too remote compared to current expenses. Their bottom line is a year or less. If it doesn't pay for itself in a year, let's don't pay for it.

Turning to the government, honest to God, at a Harvard CME course put on by George Blackburn, I am happy to say a former member of the FDA, he made the statement, "gaining weight doesn't hurt you and losing weight doesn't help you." I am embarrassed to say I got into a shouting match with him in front of 400 people.

Obesity drugs I think have been held to a different standard in the past than drugs for other diseases. I will just bring up the phen-fen debacle versus troglitazone. Within two months of the first unconfirmed, uncontrolled case series that was prematurely reported by The New England Journal--it wasn't even published yet but what was released as a press release--within two months of that fenfluramine and dexfenfluramine were taken

off the market. It was not really sure that anyone had died from fenfluramine or dexfenfluramine. Sixty people had died from troglitazone and it stayed on the market two more years.

Now, the cynic in me says that is because diabetes is a real disease and obesity is not. That may not be fair and there are other factors, but from my side, coming from an advocacy organization, it looks like that is discrimination against obesity. I am not saying that fenfluramine and dexfenfluramine should not have been taken off the market, but the timing was interesting.

The recent experience of obesity drugs--dexfenfluramine had quite a hard time getting approved. Sibutramine was initially turned down and only upon appeal was approved. Orlistat had what apparently was a spurious association with cancer so they had to go back and do a great many more trials to look at the patients to show that there was not a correlation with cancer.

As many of you know, and as many of you here have participated in, the American Obesity

Association has sponsored a series of meetings with people from the FDA, the NIH, other government agencies, scientists and many representatives of the pharmaceutical industry who have obesity drugs or are interested in obesity drugs. And, one of the things I have been impressed with is that the people at FDA have a huge load on their shoulders because if anything goes wrong, it is their problem. We have, you know, 100 million people who might be wanting to take these drugs and if even a few of them start to have problems, it is the FDA's fault for having not been more careful.

Fenfluramine had been on the market since 1973. It was not until 1997 that it was found to have cardiac valve problems. The problem with pulmonary hypertension, as Eric noted, was there but it was really pretty rare. So, I have a much better understanding of the pressures, both political and from media and from scientists, on the FDA and why they simply have to be cautious.

From the Medicare/Medicaid perspective, we have already heard today that until just a month or

so ago the language in the Medicare and Medicaid regulations was "obesity is not a disease" despite the fact that it was called a disease in 1985 by an NIH consensus development conference. Apparently, efficacy standards, in contrast to drugs and treatments for most other chronic diseases, will have to have some sort of proving that this treatment works. Now, as I said earlier, we have failed these people but obese people fail themselves. The expectations and the behavior of obese people contribute to the problem because many do not believe they are worthy or respect. Obese people discriminate against obese people actually more than thin people discriminate against obese people. They do not bind together for action. Trying to get people to join this advocacy group has been absolutely amazing. I thought everybody in the world who was obese would sign up. They don't. They are ashamed to be associated with the world of obesity. They simply do not act as advocates.

Other barriers to obesity drugs are

limited choices and poor efficacy. There are only two drugs still on patent. Why haven't the drug companies done more in the past? They are certainly doing it now. There are really only three categories of drugs, as you have heard, the adrenergic agents, sibutramine which is in a category by itself and orlistat which is in a category by itself. We still have an infantile understanding of the etiology of obesity and mechanisms of action of drugs. We heard about topiramate. We don't have a clue as to how it works. It causes weight loss but we don't know how it works.

As we have heard, typical weight-loss agents, single agents at least, cause only about a 10 percent loss from initial body weight, and there has been very limited use of combinations of drugs. I will come back to that.

This is the data on dexfenfluramine, the index study from Europe, the best study that dexfenfluramine had, and there was about a 10 percent weight loss at a year.

Sibutramine, about an 8 percent or 9 percent weight loss at a year with 15 mg. Sibutramine out over 2 years, again over in Europe--again, this is about a 13 percent weight loss. This is the Storm trial.

With orlistat, about a 10 percent weight loss at one year. This is a 2-year trial. The 2-year data was about 8 percent.

If you are a 220 lb woman and you lose 22 lbs, your physician can tell you all he or she wishes, "oh, you're healthy; your blood pressure's better; your blood sugar's better, your lipids are better." That woman or that man who is obese is still suffering the slings and arrows of discrimination by society. As a matter of fact, when we showed the data from 2000, John Monroe's group in BMJ and in Practitioner back a long time ago, these were 36-week trials and the percent weight loss was about 13 percent in each. That is pretty much all there is with phentermine which is the most commonly used drug.

That is sort of, if not the bad news, at

least the mediocre news. Let's look at what is going on for the future. I apologize, I am sure some of the companies out there have some areas that I have left out here. But we know gut peptides are a very fierce focus of action with CCK analogues and enterostatin and so on; opioid antagonists, the ones in phase 3 trials; various neurotransmitter agonists and antagonists; thermogenic agents, the Holy Grail--increase your metabolic rate, keep eating and increase your muscle mass and reduce your fat mass. Growth hormone and growth factors have been disappointing to date but maybe there is something there. Things that enhance lipid oxidation I think will be of particular interest; and nutrient partitioning agents will be very interesting agents for the future. I am sure this isn't all. There are many more areas in which we may be able to affect food intake, body weight or body composition.

These are just some of the potential agents. Again, several people and particularly Frank have talked about bupropion, topiramate and

zonisamide which are already out there. There are several in clinical trials, and then there are a number of others here. From my understanding, there are about 350 different drugs in the pipeline.

This is the data on bupropion. Frank already showed this, about a 10 percent weight loss at a year.

Topiramate--I put this slide up because it shows 5-year data in epilepsy patients. As Frank showed you, it has a pretty reasonable comparison against placebo at 6 months.

This is the data from Gadde on zonisamide, again showing a 32-week weight loss of about 9 percent.

However, single drugs are not likely to be very effective or much better than about 10 percent or 15 percent because there are so many redundant systems regulating food intake and body weight, something so critical to life as that. So, I think I am not sure we are even born yet with our use of drug combinations. I talked about the infancy of

drubs. Obesity is a chronic disease. Most chronic diseases are treated with drugs. Most chronic diseases require more than one drug. How many chronic diseases can you think of that are treated with just one drug?

You heard about phentermine and fenfluramine. Combinations of drugs may have additive or synergistic effects. As Weintraub showed with phen-fen, some of the side effects may even be offset.

Here is the original Weintraub data showing about a 15 percent weight loss at a year. As you know, he took those data out to 4 years. He had a pretty good dropout rate but still had efficacy.

Here is another combination of ephedrine and caffeine. Either one alone is not terribly effective but the combination causes about a 16 percent weight loss that persisted out to a year. That is, of course, not on the market anymore.

Here is some data that we did at the University of Wisconsin comparing phen-fen to

phentermine and fluoxetine and the slope is about the same. These are 6-month data. Again, we had a pretty good dropout. We did not have a control group.

This meeting is all about the guidances and what is going to happen to the guidances. So, let me put on my helmet, get my lance out and tilt at this windmill for a while to talk about some of the things that I think would be very useful to have from an obesity advocacy point of view.

Obesity is a major public health problem. We have an epidemic here. There have been 10 times more people dying of obesity-related causes than are dying of AIDS in this country alone. Why shouldn't obesity drugs be fast track as they are for many other drugs? As Dr. Greenway pointed out, in virtually all the drugs that we see the weight loss plateaus certainly by 6 months.

Why should we need to show efficacy? Why should the trials go out past that? Why not have safety? You know, safety is what is really important. If you show efficacy, and almost all

the drugs show a 5 percent weight loss in 6 months or better, virtually all the safety issues have been seen by then, and when we have a drug on the market--fenfluramine--for 20-some years and we don't pick up that it has a problem, it is just a crap shoot. Why not go ahead and allow the drug companies to cut those massive costs of research to get the drugs on the market earlier, and then have a much more rigorous long-term safety evaluation as the drugs are on the market and they can begin to recover some of their costs?

This extended run-in period--I see very little usefulness for the run-in period. I am raising some of the questions that were brought up at the discussions that we have had, four discussions so far. One of the things that most people feel is really pretty useless is a run-in period. In one of the original guidances people were supposed to show weight loss and only those people who showed weight loss would then be allowed to go on to the clinical trial. That makes no sense at all. We know that long-term diet and

exercise don't work. The question is do drugs work long term? Trying to get people to change their behavior is very, very difficult. If you can change their biochemistry maybe we can get somewhere.

Frank Greenway showed a trial on mazindol with and without behavior modification, and when you throw in behavior modification you reduce the apparent efficacy of the drug but you can only lose weight so fast. If you starve yourself you can only lose weight so fast. So, as you have a better diet and exercise program you wash out the effect of the drug. Why have a run-in period at all?

Another thing that I think would be useful--I was quite interested in Eric's comments about what used to be the acceptable standard, any statistically significant difference from placebo. Drugs almost certainly will have to be used in combination. Unfortunately, sibutramine and orlistat don't work in combination but phentermine and fenfluramine did. I, and I know others in this room, have used phentermine and topiramate together

and appear to get a little better weight loss than with either one alone. That has not been studied in any organized fashion. So, if safe, these drugs not only cause modest weight loss, many hold promise that they could be used in combination with other drugs and I would love to see that in the guidances somehow. Varied indications for use are justified. Others have shown that rapid weight loss initially is associated with better response of blood pressure, blood sugar. Jim Anderson has done two meta-analyses showing that rapid weight loss early, no matter what the time period, no matter what the outcome measure--the people who have lost a lot initially have at least as good or better outcome variables. So, maybe drugs that only cause a short-term weight loss might be useful and then you switch to something else.

So, I think there are many varied indications for use. Some for short term; some for long term; some for use after a very low calory diet, and perhaps the committee could consider some of those indications.

One of the things that David Orloff and I spent some time talking about on the phone is how desperate the American public for drugs to treat obesity. So, I think rational expectations for the media and for patients--current drugs are only modestly effective. Drugs in the pipeline appear to be similar in terms of efficacy. The maximum weight loss that I have heard is about 17 percent.

When companies over-hype the weight loss or try to convince people that a 5 percent or 10 percent weight loss is wonderful, it is not. So, I think over-hyping is bad on the part of the drug companies. On the other hand, over-caution by the FDA and scientists is detrimental. Hundreds of thousands of people are dying of obesity-related causes. Some drugs cause some problems. We have to be safe but there is that tradeoff and Eric's balance at the end I thought was particularly appropriate. The media has not always been responsible. In fact, I would say the media has been predominantly irresponsible. I still remember the Redux revolution--the cover on Time magazine,

this is going to solve all your problems, America. The general public is desperate. They need perspective and understanding of obesity as a disease. Physicians have not really given them that perspective. Unfortunately, I think long-term lifestyle changes are needed. Trying to change behavior is very difficult but that is what we are stuck we right now.

For the future, I believe drugs of the future of obesity treatment has the offer of virtually every other chronic disease. Obesity is due to biochemical differences. Drugs change biochemistry. And, why am I so optimistic? Frank Greenway showed you the data on obesity surgery is somewhere between 25-40 percent of anethole body weight. Surgery doesn't work because it makes a little gastric pouch. It works because it changes the biochemistry of the body. There are starting to be lots of papers on changes in metabolic rate and multiple different hormones. And, if surgery can do it I have no doubt that the smart people at the drug companies are going to figure out how they

can reproduce that kind of weight loss with one drug or combinations of drugs. The surgery changes biochemistry.

At least 350 drugs are in the pipeline, I understand, and I think that bodes very well for the future. Combination treatment I think is going to be necessary, and I think the future is extremely bright.

So, I will just end up by showing the slide for the American Obesity Association. It is a lay advocacy group. Its mission is to improve the quality of life of obese people. I guess you got copies of these slides but this is my contact information, here. Thank you very much.

DR. BRAUNSTEIN: Thank you, Richard. Questions from the panel? Let me start off with one. You mentioned that fenfluramine had been on the market for some time before the valvulopathy was uncovered. If we look at the previous speaker's slides on the use of fenfluramine, it really didn't pick up greatly until the Weintraub papers had come out. So, I wonder if what we are

talking about in terms of safety is a numbers game; if you really do need a large number of patients to pick up some of these potentially disastrous complications. I would like your thoughts on that.

DR. ATKINSON: Yes, I notice there was something like 70,000 prescriptions of fenfluramine per year over a long period of time. That went up to several million later. But Weintraub's paper came out in 1992. By 1993 those numbers were going up dramatically and it still took until 1997 before it was identified, and there were millions of people taking it obviously, and fenfluramine and dexfenfluramine had been used in Europe. Obviously, dexfenfluramine had been approved 10 years earlier. So, it is not just here. It was all over the world that it was being used and it wasn't picked up.

So, you know, I think drugs are going to have consequences and obviously we need to look very carefully at the drugs and study them, but I would argue for shorter initial trials and more intensive longer-term trials. I noticed in one

slide that the FDA was not charged with showing the safety of drugs after they have been approved. That probably ought to change.

DR. S. YANOVSKI: I would just like to comment on your excellent question about dexfenfluramine and why it hadn't been picked up earlier with the fenfluramine. Before the Weintraub papers came out these drugs were used only exclusively short term, often 30 days or less and it was never more than 90 days. It was only after the Weintraub paper came out that they started getting used for months and months and, in some cases, even years. Since there was a length of treatment response relationship with the valvulopathy, that is likely why it wasn't seen earlier.

DR. ATKINSON: Yes, that is an interesting point, however, there were a number of people that were reported that had valvulopathy who used it for a relatively short period of time. It is probably an idiosyncratic reaction.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: I am unclear. Are you proposing that drugs for the treatment of obesity be held to a different standard in terms of evaluation of efficacy and safety than drugs in general? At least the drugs that we discussed in this committee before have had trials longer than 6 months, and certainly the clinical trials that I participated in have been longer than 6 months. So, are you proposing a different standard for obesity drugs, or that the FDA change its modus operandi?

DR. ATKINSON: I couldn't hear that very well, but what I heard is am I proposing different standards for obesity drugs? I think there are different standards for different drugs. For example, drugs for Alzheimer's disease, drugs for AIDS, after relatively limited safety and efficacy evaluations, are allowed to go on the market. The point I am making is we have an epidemic of obesity and a third of the population is affected. I think it is not unreasonable to say how can we improve the delivery of drugs, new and better drugs and

more drugs so we can try some of those combinations? No, I don't want to have different standards but I think there are different standards for drugs and I would like to put obesity with sort of the ones that get handled expediently.

DR. BRAUNSTEIN: Dr. Schade?

DR. SCHADE: I have a question about weight loss. If one assumes that the drugs overall result in, let's say--I am going to be optimistic--10 percent weight loss, if you look at the mortality or morbidity curve, if somebody has a BMI of 35 and they lose 10 percent of the weight so they drop to a BMI of 32, is their mortality then exactly the same as a group that doesn't lose weight but has a BMI of 32?

DR. ATKINSON: Yes, that is a very good question. I don't know the answer to that. Katherine Flegal's data were mainly focused on the lower BMI groups. As you start up, when you start getting to 30 and above, those curves start going up fairly dramatically I think, if that is right, Katherine. But I can't tell you that if you have

lost 2, 3 or 5 BMI units, do you then assume the mortality and the morbidity of people who have never been above that. I just don't know that.

DR. SCHADE: Well, the reason I ask that is when we treat diabetes we treat hemoglobin A1C and we assume, through our treatment, that we then reduce the hemoglobin A1C and we can plot on the curve the benefit. I just wondered whether the curve for obesity is similar.

DR. ATKINSON: Yes, and I think that is good. As you heard, there are some trials that are ongoing to try to look at these sorts of things. Again, this is a disease that affects--what?--100-some million people in the U.S. and we know almost nothing about it.

DR. BRAUNSTEIN: Dr. Aronne?

DR. ARONNE: Can I comment on the last question? I think that the benefit from small amounts of weight loss is disproportionate to the amount of weight lost because of the initial loss of visceral fat. When you look at the composition of weight that is initially lost, it is the

riskiest fat that is lost first so small amounts of weight loss appear to have disproportionate benefit, out of proportion of what you would expect from that small amount. What some people have suggested is following something like the C-reactive protein and that in the future that could turn out to be our version of the hemoglobin A1C because it is a measure of the inflammatory burden of fat, and a lot of people believe that visceral fat is where a lot of the C-reactive protein is coming from.

DR. BRAUNSTEIN: Dr. Orloff?

DR. ORLOFF: Can you reiterate your position on the run-in aspect of trial designs, and specifically address whether you are proposing that all run-ins of any duration, of any type, be dispensed with?

DR. ATKINSON: No, certainly not. I think a run-in period in the trials that I have designed and gone out and done, investigator initiated type clinical trials, we have put in a 2-week run-in period that was not a treatment period but we

stretched out the initial evaluation. What that does is get out the people who are not serious, who don't want to come or it is too difficult to come, or whatever. But in terms of requiring a weight loss or requiring people to show that they can adhere to a diet before they are allowed to go on drugs, that is not true for other kinds of diseases, for example, diabetes and hypertension, and there may be companies that would want to do that and would want to have a run-in, or that would be what they think their drug is going to be useful for--in other words, get the weight off and then this is going to be their weight maintenance drug. Fine, they can have a run-in. But I think the mandate that all companies have to have an extended run-in I don't agree with.

DR. ORLOFF: Again, a bit more clarification. Do you still advocate diet and exercise and continued reinforcement of those lifestyle aspects for treatment of obesity in the context of the trial?

DR. ATKINSON: Yes, I guess it was fairly

dramatically shown here. Dr. Greenway showed the difference in weight losses that are achieved in the United States versus over in Europe. The companies design the trial to get well over whatever the standards are. So, I think that can be manipulated.

I make the statement often that everybody, whether they are skinny or fat, needs to have a good diet and lifestyle. I think as people come in they need to be informed of what is a healthy lifestyle and the exercise and the vegetables, and all those things. Again, I am speaking for myself not for anybody else, but I think the idea of allowing the drug companies individually to figure out where in the spectrum they want to put that is not unreasonable, but at least some lip service ought to be given, if for no other reason, because people will do things very differently. I mean, they have to be given something because, as anybody here who has ever taken care of obese people knows, they get all excited about how they are going to lose weight and they may even go on a starvation

diet, and all kinds of things. So, you have to have some guidance.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: I guess one thread that is running through your talk is that obesity is a disease. So, if obesity is a disease and I am thinking of weight loss in someone as a surrogate for clinical endpoints--if obesity is something more about being concerned about your body image, then maybe weight loss is a proper primary endpoint. So, with your advocacy for short duration trials where, you know, you might have transient effects that can't be maintained so you will end up with no net weight loss over a long period of time, I don't see how that is really helping combat obesity as a disease. So, I worry about the surrogacy issue of weight loss in this population, and particularly when you are suggesting just to do short-term studies.

DR. ATKINSON: Again, I was having a little trouble hearing, but the idea about obesity as a disease and if people lose weight and then

can't keep it up, is that a negative? Well, people have cancer and they can't keep that off and it comes back. Yet we still approve drugs for cancer. Many of you on this panel are diabetologists. I was a diabetologist before I was an obesity doc. None of the oral agents work for more than a few years and then pretty much, if the patient has bad diabetes, we put him on insulin. Again, are we going to hold obesity to a different standard? I don't think it is fair.

DR. FOLLMANN: So, basically you are thinking even if you keep weight off over a relatively short period of time it should have clinical benefits. Is there evidence for that?

DR. ATKINSON: Yes, there are a few papers looking at rapid weight loss, and even out at a year, as compared to the slow weight loss on diet, where the people had better glucose tolerance. The same thing was shown with hypertension, and there may be other studies that Lou or Susan can come up with. People certainly feel better and their mental outlook is improved. Lots of studies have

shown that weight loss is associated with that. Yes, when they regain their weight they feel bad again. I don't know how to get around that. We need better drugs that are effective longer term.

DR. BRAUNSTEIN: Dr. Flegal?

DR. FLEGAL: I just wanted to follow up on the question asked a while ago about change of a BMI from 35 to 32 and its effects on mortality. I know you can't hear me--by the way, it is very hard to hear from the podium. That is why all of us are acting like we are deaf when we go over there. Although the literature certainly suggests that your blood pressure improves more rapidly or goes down further than you would expect from the weight loss, the observational epi. studies do show that mortality is not necessarily decreased and may, in fact, increase with the weight loss. So, the changes in cardiovascular risk factors are improvements but mortality data in the observational studies, which have a lot of limitations, don't actually show that. In fact, your mortality may be increased.

DR. ATKINSON: I would just make one comment about that. There is almost no data to show that losing weight improves mortality. There is a paper from 1963 of Metropolitan life tables that showed that but I am not sure I believe that. But Corey's data from surgery is the one paper that shows that if you lose a lot of weight you have an improved mortality. So, again, we need better drugs and bigger weight loss.

DR. HIRSCH: I can tell you that the people who are BMI 35 and go down to 32 are really different from those who are 32. This is not humorous; it is a rather subtle matter. That is, those who come down to 32 don't stay there. They go back to 35. Those who are 32 stay there. And, that is a key difference. That is a very interesting mixture of behavioral, biochemical, social and I don't know what else. But until we understand that we are going to be in some big trouble in trying to figure out how to handle weight loss.

The other thing I would comment on is the

phen-fen business. It is a very interesting matter. If you look carefully, as I have a number of times, at the Weintraub papers, please keep in mind that this was not the great pharmacotherapeutic trial of all time and we were undone because of adverse effects. Not at all. The dropout rate was enormous in that study. And, of the few survivors remaining after four years, even they were working their way back up to their starting weight.

Insofar as the adverse effects were concerned, you have to remember that we were coming into the age of echo cardiography. This was getting more and more commonly done with a greater recognition of this. So, there was a sort of cultural change in medicine that permitted a more rapid uncovering of the valvulopathy that may or may not have been all that significant as time has shown but, nevertheless, occurred with these drugs.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: To go back to the issue of surrogate endpoints again, I certainly can't argue

with the value of weight loss for someone who is overweight but I am interested in knowing--and this has been explored a little bit--the differences in quality of life for people who have lost weight, and I don't think any of the speakers have addressed that, and differences in surrogate endpoints, which was touched on. Some drugs may have the same weight loss but different effects on blood pressure, lipids, and so on. And, if we are really concerned about the medical consequences of the epidemic of obesity, evidence that short-term interventions or any intervention will have an impact on anything other than the scales I think is of critical importance.

DR. ATKINSON: There is certainly a lot of data showing short-term dramatic decreases in blood sugar, insulin levels, blood pressure, triglyceride levels, sleep apnea. A number of the complications of obesity get dramatically better with weight loss and, surprisingly, without a huge amount of weight loss. I mean, you take somebody with a BMI of 45 and they go down to 30 or 38 and their sleep apnea

goes away; their diabetes has gone; their hypertension is much better; their incontinence is better; their arthritis is better. So, those things certainly occur.

Yes, as they regain their weight it comes back. Many years ago there was the wonderful paper on glucose tolerance tests and the one who started with 100 kg and lost down to 60 kg, she had frank diabetes and everything got--she was perfect; she was normal. Then, as she gained weight her insulin started going up and finally her glucose went back up and she was back to having full diabetes. Did she delay anything from her two or three years of being normal? I don't know.

DR. WATTS: We have all seen dramatic improvement in individuals who lost weight. My question is have these changes been validated in large-scale trials? As to the quality of life, I would be interested in knowing if at the end of, say, a 6-month program the people who lose weight have an improved quality of life and then, when they regain it, is their quality of life worse for

having succeeded and then failed than having not tried at all?

DR. ATKINSON: Just to get one thing straight about yo-yoing, for example there have been now several meta-analyses looking at the effect of repeated cycles of dieting and does that make your diabetes or your hypertension, your whatever, worse--in other words, you would have been better if you had never done it, and that does not appear to be the case.

Certainly, there are many studies showing that your quality of life improves with weight loss and, yes, it goes back to what it was when you regain the weight. You know, I don't know where to go without saying, you know, when you have any kind of disease and it gets better for a while and then it gets worse, yes, it gets worse again.

DR. BRAUNSTEIN: Ms. Coffin?

MS. COFFIN: I have a couple of comments. At one point you actually warned drug companies and the media about over-hyping things. I want to caution that the 400,000 people that are dying of

obesity-related diseases leads people to believe that if they were to walk in any hospital all they would see would be obese people and that is not, in fact, the case. So, you need to be careful, again, with how you are doing that because then an obese person says, "oh, I walk into a hospital and there are lots of thin people there that are just in poor health." So, be careful with that.

As far as people always gaining weight back, I don't think that that is necessarily the case. I don't think that we have the studies to prove it one way or the other. Again, you have huge dropout rates. People are very ashamed about dealing with their obesity. I would relate it to the mental health drugs and how we treat mental health drugs and you wouldn't think of putting someone who is severely depressed on a medication without also putting them on behavioral changes as well. There is value in the process of learning to deal with lifestyle changes. I think if you use drugs alone you are going to see 6 months and you will bounce back because you haven't learned the

process of becoming a more healthy person. If you go through rehabilitation if you break your leg, you rehab and you learn how to deal with that injury. So, you use the drugs to start out.

You suggest using the drugs, like in diabetes, where you start with drugs and also lifestyle changes. What that could do is that could give a patient some initial success which then bolsters their motivation but, without that lifestyle change, if the lifestyle change isn't an adjunct and there isn't a process or a protocol to get those folks off the drugs, then, yes, you are going to find that they bounce back. So, those would be some of my comments as far as that goes.

DR. BRAUNSTEIN: Dr. Aronne?

DR. ARONNE: I was going to point out, as far as the mortality issue is concerned, that the paper that was just published in September in The Annals of Surgery that looked at 1000 patients who had gastric bypass and other obesity surgeries in Canada versus 4000 controls showed striking reduced mortality in the surgical group compared to the

control group. The numbers they reported were 89 percent reduction in mortality in the treated group compared to the control group. So, it suggests that there is a difference.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: Listening to your discussion, there seem to be two aspects to your presentation. One is the image of the obese person in society and that would take, I would guess, 50 percent weight reduction, somewhere between 30-50 percent. That is very different than the weight reduction to improve comorbidities, which may be 10 percent. So, really the question is will one drug fit all sizes? Are we going to have to have different standards for different things? I mean, if we say that image is something that our society needs to pay for, that is a humongous issue. If we are talking about improvements in comorbidities, that is still a very large issue. In your discussion I don't see that difference. I see we have to treat obesity because we are discriminating against obese people. Yes, that is true but it is going to be a tough issue to

get a handle on.

DR. ATKINSON: That is one of the barriers. It certainly is going to be very expensive, but expense has not kept us from treating many other diseases that are not as common as obesity that are also very expensive.

To give you an idea about how painful it is and the reason that I keep pushing more than 10 percent weight loss, Coleen Rand did a study asking obese people who had had surgery and had lost large amounts of weight what price would they pay to stay thin. They were asked if, "I give you two million dollars will you let me hook you back up and you will regain your weight?" A hundred percent said no. "If you knew the price of staying skinny was to go deaf, would you rather be deaf and skinny or fat again?" A hundred percent wanted to be deaf; 89 percent wanted to be blind rather than fat again.

So, that level of pain--I think we in the health professions need to address that. It is not a cosmetic issue. All those things I said are

true. There are many, many studies showing that it is harder for people to get a job, to get promoted, to get married, and so forth. This is not simply a cosmetic issue.

DR. BRAUNSTEIN: Richard, thank you very much. We actually need to move on to the public hearing to try to stay somewhat on time. We haven't received any outside requests. Many different individuals and companies have sent in documents for the committee to review before the meeting in response to the information in the Federal Register. Is there anybody in the audience who would like to address the committee? Not hearing any, we will go on to Dr. Orloff's presentation about the 1996 FDA draft guidance document and he will also deliver the charge to the committee.

Charge to the Committee

DR. ORLOFF: Thank you. First thing, I want to apologize in advance. I was making some last minute changes to these slides before the break or during the break and the last ones outline

the questions for our discussion that I intend to go over now. We will then put them up. If they are hard to read now, I promise I will have them fixed during lunch.

My purpose here, as Dr. Braunstein has said, is to go over what we believe are the important aspects of the 1996 guidance, many of which have been touched on already but to make sure that I have gone through the rationale behind those aspects of the guidance, you know, from a scientific, and clinical, and regulatory standpoint, and then to move to a discussion of some of the issues that were raised in the comments that we received in response to our Federal Register notice soliciting those direct comments, and then from that, I will translate those into items for discussion.

Our 1996 guidance, first of all, identified patient populations based upon evidence that these were populations at risk from chronic adverse sequelae of obesity. As you can see, these included, and still do in our drug labels, patients

with BMIs from 27-30 with comorbidities, for example hypertension and diabetes, or patients who are more obese than that, that is to say, greater than 30 kg/m2 and they didn't necessarily have to have comorbidities.

Again, the identification of patients at significant risk goes to some overriding principles that I will touch on probably multiply in this presentation. The first is that, regardless of how long these trials are and how many patients we treat, we are always going to have limited information at the time these drugs go to market, and these are chronic use drugs, albeit presumably for eventually a life-threatening condition but not immediately life-threatening. So, we need to be sure that we have identified patients who are at substantial risk from the disease before we confer risk of drug. All drugs are associated with some risk.

I should also mention, in follow-up to some of the conversation that was occurring earlier, that this is a standard that is not unique

to the obesity drug group. This is a standard that we apply to all chronic use drugs for what are deemed, at least at the time that the therapies are initiated, as non-life-threatening conditions.

Obviously, the guidance also includes as an aspect of study design the run-in phase, which was touched on in Dr. Atkinson's talk. The rationale beyond that run-in phase for the trials of new obesity drugs were, number one, to identify placebo responders in order to avoid the unnecessary treatment with drugs of patients who were likely to do well on diet and lifestyle changes alone. That is in keeping with what we believed at that time and I think the committee agreed with really a central tenet of medical management of any chronic condition or disease, that if you can do it with other than the most invasive or potentially the most toxic intervention, then that should be your approach.

With regard to the duration of phase 3 studies, again touched on a few minutes ago, we noted, and it is really hard to toss it off to

bias, that there is an unavoidable fact of historical bad luck with anti-obesity drugs. Their mechanisms of action, perhaps the underlying risks of the patients, the fervor with which new obesity remedies are met by the continuously growing population of obese patients, all lead perhaps--I guess in retrospect we could say--to decisions with regard to approval and method of use that in the end are not necessarily advisable.

Also, it is important to point out that to this date we have really a dearth, if not a complete absence, of hard outcomes data from trials of obesity drugs. With the exception of the recent Sandoz trial which looked at an aspect of perhaps irreversible morbidity--probably not irreversible but significant morbidity associated with obesity, that is to say the development of frank diabetes, we don't have much in the way of hard outcomes data with regard to sequelae and we certainly don't have mortality data.

So, in the absence of these data going into development, we held a standard of a first

year placebo-controlled study in order to provide proof of principle of efficacy and, obviously, also to provide a comparison group for the assessment of causality with regard to adverse outcomes observed in the context of the study.

That was to be followed by a second open-label year optional open label. It could also be placebo-controlled in order to establish durability of efficacy and tolerability, because tolerability clearly, even if it is not toxicity per se that leads to intolerability, does impact the ultimate effect of the drug. And, to establish long-term safety.

Our efficacy criteria have been mentioned here and we actually had two efficacy criteria. There are two efficacy criteria from which a sponsor can choose essentially, post hoc for that matter, in order to propose that their drug, indeed is effective. Those criteria are, number one, a mean placebo subtracted weight loss of greater than or equal to 5 percent from baseline, or a categorical analysis, as we refer to it. That is

to say, the proportion of subjects who lose greater than or equal to 5 percent of baseline body weight is greater, simply statistically significantly greater in the drug versus placebo-treated group.

At this point, I don't think anyone here, at the FDA, believes that these are too stringent criteria for the establishment of efficacy, and we note that the EMEA criteria that are still in place are more stringent still with 10 percent cuts for both of those criteria.

With regard to patient exposure, again something that came up in the conversation just past, the fact is that the size of patient exposures is in the end arbitrary. There are really no fixed constructs for how to establish the size of a patient exposure, aside from mathematical ones and the statistical principles that allow you to determine that a given exposure can exclude a certain rate of adverse events. Unfortunately, we, or anybody else for that matter, don't know how many patients you really need before you can see that horrible adverse event that might crop up when

it goes into the marketplace.

Our patient exposure criteria were a total of 1500 patients completing 1 year and a placebo control exposure, and then at least 200-500 patients completing the second year exposed to drug. Obviously, in some cases I believe that second year has been placebo controlled.

I note also that these standards are in excess of the standards laid out in the ICH E1A document which talks about safety exposures in the development of drugs for long-term use in non-life-threatening conditions. Specifically, the numbers in that document are 300-600 for 6 months and 100 for 1 year--it is not listed here, but with a total of 1500 patients exposed totally, including in single dose biopharmaceutics studies.

To digress for a second but I think important to this conversation, the ICH E1A document goes further into discussing how to essentially tailor the exposures in clinical programs to a particular drug or indication. Although those minimum numbers that I cited on the

last slide, 300-600 for 6 months and 100 for 1 year, are by many taken as the standard across the board, the document clearly states that larger and longer exposures are merited, or maybe be merited, if the benefit of the drug is, on the one hand, small, for example related to symptomatic improvement or for the treatment of a less serious disease experienced by only a fraction of treated patients, as in perhaps a prevention type intervention and of uncertain magnitude. Specifically, they cite reliance on a surrogate. Again, I point out that we don't have hard endpoint data with obesity drugs generally or even, for that matter, with any specific obesity drugs in terms of mortality.

Our experience, again tempering our approach to these products, as mentioned by Dr. Atkinson, is with only modest efficacy of drugs that we have approved and evaluated to date and, as far as anyone around here knows, not anticipation, frankly, that there is anything in the pipeline that is going to be dramatically more effective

than what we have seen already. Anyway, I have already made these points so I am going to move on--I don't need to say this; I don't need to say that; I don't need to say that.

So, we put out our request for comments on the guidance and a number of issues were raised. I am going to walk through some of these and I have noted what issues were not addressed in the proposals. This should, I hope, segue into my outlining our topics for discussion. I apologize because I don't believe the order here is necessarily going to correlate with the order of the questions but maybe we will get lucky.

The first comments related to the broadening of the target population. We will include in this first one pediatrics/adolescents. It is noted by the petitioners, if you will, that this is a burgeoning problem, I guess in a sense echoing the problem that was first evident in adults, that is to say, childhood obesity long-term population-specific risks, as well as non-population-specific risks. One of the issues

that is raised as a simple statement is that the most appropriate endpoint in growing children should be body mass index rather than weight. I don't think anybody has any quarrel with that.

I have underlined here "no specific criteria for selection" were proposed. So, one of the things that we ought to think about is what are the entry criteria, if you will, or the eligibility criteria for adolescents and children into trials and, therefore, for selection for treatment.

The other one with regarding to broadening the target population is lowering the BMI limit, again something that was discussed by Dr. Flegal at least with regard to the epidemiologic data. This really, in my mind, at least in part comes down to targeting prevention of weight gain, something that I will mention in a second.

The petitioners talked about high risk treatment and prevention in this lower BMI subpopulation, although the definition of high risk is not given, which is an issue we need to discuss. They point out that there are observational data,

if not controlled trial data, that drugs are effective. That is to say, they are associated with weight loss in excess of placebo in subgroups of patients in larger trials who have lesser degrees of obesity.

Finally with regard to broadening the target population, there has been a lot of talk, not just in the comments we received but for several years, about essentially targeting some of the comorbid features of obesity, for example diabetes, metabolic syndrome, perhaps dyslipidemia, perhaps hypertension, as primary targets for anti-obesity therapies. One thing we want to talk about or hear about is sort of general opinions on that but also what would be the criteria for using obesity drugs as primary therapies in those diseases.

With regard to study design, we talked about run-in, and the only thing that wasn't mentioned was the means of assuring standard of care in the context of the trial. We will want to hear more discussion of the importance of the

run-in from the standpoint of inference of efficacy, but also I think when I queried Dr. Atkinson, whose thoughts I believe are consistent with the petitioners on this issue, he was not excluding diet and exercise as a standard of care intervention in clinical trials.

The duration--Dr. Atkinson raised this in his presentation. The comments that we received actually proposed one year of controlled efficacy but safety at one year as well. There were questions about the utility of an additional year if there were no safety concerns raised after one year.

There is no approach given, and I think that is something that bears discussion, to assessing the need for additional time or patients. For example, there are always issues about durability of efficacy which, in some respects, is a simpler problem. But the necessity and appropriateness of longer term and larger safety exposures--let's just say it is hard to come up with any rationale for a specific fixed duration.

FDA always errs on the side of caution and so larger and longer is the way we go. But if we are going to go shorter or at least allow for shorter and smaller, we have to be able to have some constructs to guide us and to guide sponsors in those instances where longer and larger exposures might be necessary. So, for example, preclinical findings, mechanism of action, the information that would lead to presumptions with regard to the types of toxicities, that is to say, acute, idiosyncratic versus chronic, cumulative dose related, as being two diametrically different situations which would clearly direct different approaches in development.

Combination studies really is the next issue and we will want to talk some about the efficacy criteria for such studies. I will say a bit more in just a second when we get to those questions.

A new efficacy criterion was proposed. We are actually at a loss to make anything of it at this point. It was simply a total weight loss of greater than or equal to 5 percent from baseline at

12 months, seemingly ignoring any placebo effect.

Other criteria proposed are in keeping with our current criteria. Then, there was a proposal actually to raise the bar on what would constitute a categorical win. I am not sure exactly where that comes from, although it would clearly put certain drugs in a loftier or in a more favorable position from a regulatory and marketing standpoint.

With regard to efficacy criteria, there were requests to define weight maintenance, prevention of weight gain, drug-induced weight gain and, as I talked about earlier, the efficacy criterion with regard to BMI change in pediatric patients. I already talked about safety exposures.

So, by way of summary, if I haven't lost everybody in this rambling, let me go through what I would like us to talk about now. With regard to lowering the entry criterion to a BMI of greater than or equal to 25 kg/m2 when accompanied by comorbidities, we need to ask what evidence supports treatment or prevention in this

population; what magnitude of effect would be deemed clinically significant; and what assurance of safety is required to treat lower risk patients. Is this one of those instances, for example, where you need larger numbers and longer exposures?

With regard to pediatric and adolescent patients, what factors should be weighed or addressed in assessing risk versus benefit, again, in this population who, no matter how great the problem is, I think it is agreed have a relatively low short-term risk of at least what are deemed the classic comorbid features of obesity or chronic sequelae of obesity, I should say.

Then with regard to obesity associated with metabolic derangements and cardiovascular risk factors as primary targets of drug therapy, I think we just need to hear some discussion there.

The run-in I have already raised. With regard to combination drug regimens and designs, I just want to say a few words by way of background. The combination drug standard for the Food and Drug Administration or approval standard is a simple

one. It requires that (a) and (b) together, the two drugs in combination, be better than either one alone. But that can be a fully additive combinatory effect. It can be a synergistic or less than additive effect. It can be a multiplicative effect. I think a simple question for approval of a combination drug regimen is what is the incremental effect of adding one drug to another that should be deemed clinically gainful? As I suggested, should it be an expectation of additivity? Should it be simply statistically significant increased efficacy over one drug alone? It is something we need to think about.

With regard to obesity prevention, weight maintenance and prevention of weight gain, and Eric Colman in his presentation actually showed you the indication sections for sibutramine and orlistat and those terms did find their way into those labels. I will confess here that we did not have a standard of evidence which we applied to the data that were proposed to support those indications.

I guess I would begin by asking at this

late stage whether those, for an individual drug, are expected to be distinct clinical effects and/or distinct pharmacological effects. If they are deemed to be, are studies needed to document efficacy and safety for each of these indications? I would propose, based on pure sort of logic, intuition, common sense, that in fact these are not likely to be distinct clinical and pharmacological effects but I am interested to hear comments.

With regard to proof of treatment or prevention of drug-induced obesity, this is something that gets raised a lot. It is obviously a subset of a much larger obese population due to other causes and, yet, it is a problematic issue for patients who take, for example, anti-diabetic agents and who are faced with weight gain even as they are attempting to control their diabetes. But I think if we start to look at this from a regulatory standpoint and, frankly, from a standpoint of establishing a science-based clinical rationale for these interventions, there are some questions that come up. For example, do we know,

across all the drugs that are associated with weight gain, what are the risks associated with obesity associated with those drugs? Is it run-of-the-mill risks associated with obesity? Are they in some instances, because of the nature of the drug, less prone to at least the long-term sequelae? I think the classic example is the diabetes drug one.

There are clearly also going to be issues of interactions between the obesity drug, the disease and the medications that are used to treat the primary condition that may impact the safety and efficacy of both agents, but let's just say for the sake of discussion, talking about impacting the safety and efficacy of the primary therapy. An example might be weight gain associated with neuropharmacologic intervention and the use of an obesity drug that might work, at least in part, through a central mechanism. What standard of evidence is necessary to support intervention with an obesity drug in a population of patients who have developed obesity using neuropharm. agents?

With regard to the reduction in the number of patients, again, there is no rationale based on the magnitude or the nature of expected efficacy or documented efficacy. There is no rationale based on the size of the target population. Something I didn't mention earlier is that it always has given us pause, and I think a lot of our advisers, that the population that ultimately will take obesity drugs is absolutely massive.

As I think Richard Atkinson said, we do live in constant fear of even a very low incidence adverse event, but serious adverse event, rearing its ugly head postmarketing when the drug goes from an exposure of a few thousand to an exposure of not just a few million but millions upon millions. It is important for purposes of this discussion to understand that try as we might, and with as much money and emphasis that FDA places on postmarketing safety surveillance of drugs, the best way to understand drug safety still is in the context of an adequate and well-controlled investigation. Spontaneous adverse event reporting in

postmarketing has severe limitations, for obvious reasons. I would say that as a rule the instances in which spontaneous reports are truly useful are when the adverse event is so wild and unexpected and idiosyncratic that there is an unavoidable conclusion of association. For example, rhabdomyolysis with statins. That is not often the case with drugs, and in a disease where many of the drugs may confer or interact with regard to cardiovascular risks, targeting a population whose underlying disease puts them at risk for such, as in the blip in the sibutramine marketing that occurred in Europe on the basis of a couple of cardiovascular deaths, it is really impossible to render conclusions about causality in those cases.

With regard to the second year of an open-label study, again I mentioned this, there is no rationale based on the nature of drug toxicities acute versus cumulative.

There were some other suggested changes that we just wanted to hear comments on, which I believe I mentioned before--categorical weight

loss, absolute difference criterion; metabolic syndrome as a therapeutic endpoint. I have mentioned drug combinations. Then, something that came up before, it is worth conversing a little bit about cosmetic weight loss, under which I include psychosocial benefits, socioeconomic benefits and quality of life.

As I promised, I will clean those up before the discussion because, since these do not conform to the printed versions of the questions that you got or the issues, we are going to plan to just put them up on the screen as we talk. Thank you very much. If there are any questions that I can answer now, please go ahead.

DR. SCHAMBELAN: Dr. Orloff, with respect to the question of the numbers of individuals in a phase 3 study and/or the duration of the study and the fact that relatively rare events often don't emerge until postmarketing surveillance phase 4, does the agency have any idea of what the effective cut point is whether going from 500 to 1000, how many detections of what ultimately turns out to be

a side effect that makes a drug unapproved--how often does that occur or one year versus two years? You kind of alluded to that and I wonder if there are any data.

DR. ORLOFF: I don't believe there are any data. This comes down to experience and ultimately I do think we have to look at things like drug mechanism, preclinical toxicity, and then integrate that information into a construct that is based upon the severity of the disease being treated, the magnitude of the effect observed, the size of the population that is going to get it. Those are the factors. We don't actually have the data. The experience is, remarkably enough, that there is something that works in our system. We do have drugs out there for chronic life-long use, but at the end of the day, despite having only been studied in a relatively small number of patients, appear to be quite safe and extremely useful products. For example, statins I think are a huge success and boon to the public health. Anti-diabetic agents, troglitazone not

withstanding--the number of approvals in recent years have apparently made quite a difference in the experience of patients and physicians who are addressing that disease.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: I have two questions for clarification. One, in the original document they talk about 1500 being a desired number for the initial efficacy study. Do you know how that number came about? Secondly, you talked about two different criteria for approval and then you alluded to the fact that these could be chosen after the fact and I wonder if you could amplify on that a little.

DR. ORLOFF: Eric, 1500?

DR. COLMAN: I have to say that I don't know exactly how the 1500 was derived. My sense is that in large part it was arbitrary but I don't know that for certain. The second part of your question had to do with?

DR. FOLLMANN: Well, there are two criteria for efficacy. Does the sponsor need to

prespecify which one they will be using before the study is done, or is that left unclear and then decided upon after all the data are in?

DR. COLMAN: I have seen companies choose one or the other as the primary efficacy outcome. In some cases, if a company prespecifies that they will only use the mean difference between groups of 5 percent and they don't make it on that but they have, as a secondary outcome, the categorical and that does make it, then we would be inclined to consider that drug efficacious.

DR. BRAUNSTEIN: In my distant cobwebs, having sat through our original meeting, I recall a statistical analysis that basically said that if you have a double-blind, placebo-controlled trial with half of the patients on placebo and half of the patients on active drug you need a certain number--it may have been 750--in order to pick up an adverse event at a 1 percent rate and to show that it was different from placebo. It was something of that nature that the number came from. Dr. Woolf?

DR. WOOLF: Two questions. One relates to the current criteria that 1500 patients must be in a randomized clinical trial for 1 year. I am assuming that half would be on active treatment and half would be on placebo, or is it 1500 in each arm?

DR. ORLOFF: It is 1500 on drug, I believe.

DR. WOOLF: Secondly, with other medical conditions which are serious public health hazards that don't kill you in the next 6 months, what are the typical sizes of the clinical trials that currently come into the FDA for approval?

DR. ORLOFF: What was that?

DR. WOOLF: For hypertension, hyperlipidemia?

DR. ORLOFF: Actually, let me take diabetes. All right? This is public information that has been presented at the Drug Information Association. The agency, our division specifically, is overseeing development, if that is the right term, of some several dozen peroxone

proliferator activated receptor agonists for diabetes. Those drugs have substantial and worrisome preclinical toxicities. For what it is worth, they also appear in many instances to have cumulative toxicity in animals. The two marketed products, rosiglytazone and pyloglitazone, have reasonable safety profiles. Although they are as yet not well understood reasons, there are patients who develop problems specifically related to fluid retention and congestive heart failure. I don't think there is any good evidence that either of those drugs has a direct cardiotoxic effect per se, which is a distinction between what is observed in humans and what is observed in preclinical models.

Suffice it to say, the level of concern is such with those drugs that we are asking for very large, on the order of several thousand, patient exposures beyond a year and a half. We are talking about, you know, 500-plus at two years. So, this standard for obesity drugs is actually below that.

For dyslipidemic agents, for some of these programs, for example, the Lipitor program I

believe had a total of 4500 patients who were treated with at least a single dose of drug in that program with active treatment. They had something approaching a thousand who were treated for a year and a half, I believe. But going way back, our division--because this ICH guidance is pretty long-standing now; I don't know what the date of it is--but we have always maintained that a higher standard is needed specifically addressing those conditions that ICH laid out. That is to say most simply, if are approving based on a surrogate, you don't really have a handle on what the ultimate benefit of the drug is. So, for lack of a better expression of it, you damned well better be sure that it is as safe as you can know.

DR. WOOLF: As I recall, I believe when we discussed Crestor more than a year ago, that was defined as the single biggest statin submission and it was several thousand.

DR. ORLOFF: I believe with Crestor there were 4000 starts on the 10 mg dose.

DR. BRAUNSTEIN: Dr. Ryder?

DR. RYDER: I just wanted to add just a couple of points. The first point is that there have been several recent symposia on the application of quantitative assessment tools to the question of risk management. There was a combined PhARMA-FDA symposium last fall. The bottom line is that it very much depends upon what you want to look at and what the background rates are. I mean, I can speak a little bit more about hepatotoxicity because we have, although still poor understanding of background rates of hepatotoxicity--I am not sure about hepatotoxicity in the obese population perhaps, but it does depend upon what you are looking for.

Dr. Braunstein, my recollection is your recollection as far as the ICH goes, and these go back some time, these numbers came out of the desire to speak with some certainty about ruling in or out events that occur with about a percent frequency, something akin to that.

The last point that I wanted to make is one that I think Dr. Orloff just mentioned. I

think it is very important to keep in mind whether you are talking of an absolute minimum that you must have in terms of exposure, regardless of the details of the preclinical toxicology or the specific characteristics of the product that you are investigating, as opposed to the size of a program that ultimately you design, along with FDA and external consultants and a number of other agencies throughout the world today, that has to answer a couple--many sometimes--key questions--efficacy; perhaps comparative efficacy; and, of course, answer a number of safety issues that have come up during preclinical testing or early clinical testing. So, it is different when you talk about a basic minimum versus what ultimately happens when you get findings. Dr. Orloff mentioned some of the findings with the PPODs that we are all struggling with, but probably every development program has issues like this.

DR. BRAUNSTEIN: Yes, Dr. Carpenter?

DR. CARPENTER: Given the suggested directives for developing pediatric studies for

these types of drugs, what is the history and the experience with study population size and duration of therapy in pediatric/adolescent studies with some of the other drugs you have mentioned as precedents?

DR. ORLOFF: The pediatric studies, by and large, are smaller and they are of limited duration. In our division, for the lipid-altering agents, LDL lowering specifically, the target population is restricted within the pediatric age group to those patients who have heterozygous FH and who, therefore, have a vastly increased lifetime risk of cardiovascular disease related to marked hypercholesterolemia. The proof of principle of efficacy and safety in those patients is deemed not to take all that long, let's say, or that many patients.

Our diabetes programs, likewise, are relatively small. I guess I would offer that, you know, once we have examined or feel comfortable with the safety profile--not necessarily the absolute safety but the safety profile so we know

what the expected adverse events are with a diabetes drug, for example, then it really becomes a matter of proving or of demonstrating the extent of its efficacy, tolerability and then safety along those same parameters in a pediatric population. So, again, not a big intellectual leap; not a big scientific leap.

I should mention that I want to be careful that I don't give the impression because I don't believe it is the case that this relates somehow to a bias against obesity per se, but there is broad agreement about the importance of early intervention in diabetes, control of hemoglobin A1C, control of metabolic derangements to reduce long-term sequelae.

Likewise, with marked hypercholesterolemia, there is a very clearly understood association between level of cholesterol and time with extent of cardiovascular disease and, therefore, clinical cardiovascular risk. We believe, based upon large experience with the drugs that we have used to target those two

diseases--let's say we understand in most cases very well the pharmacologic mechanisms by which those drugs alter the metabolic profiles of the patients being treated.

I am not sure we always have that with obesity drugs. If we could get to a place where we were comfortable with pharmacologic mechanisms and, therefore, we had a greater comfort level with the reliability of our limited observations with regard to safety, then I think using such drugs for prevention, if you will, or for early intervention becomes less of a leap.

DR. BRAUNSTEIN: Thank you. Yes?

DR. SCHADE: I have one question. The reduction in the number of the population that we study from 1500 to, say, 500--I can see one of the rationales would be that studies would be significantly less costly. There are I think several arguments that can be made not to reduce. The obvious one that has been made is that maybe you would pick up more safety issues with a larger population.

There are other important issues that haven't been raised. One of the issues is if you have a large enough population you can look at subgroups. That can be important for example in a diabetes prevention program because there were 1000 people receiving that and it was clearly shown that it did not work well in the elderly population, at least compared to the younger population. So, if you have a large enough group you can actually say something about the drug in different groups within the larger population.

I think the argument to reduce the number, let's say from 1500 to 500, may relate to the cost of doing the trial. But what I haven't seen is a slide from the FDA, or maybe FDA has some data, that if you reduce the cost of the application and the trial, it will really result in more or better drugs being released. In other words, the argument throughout all the material that you gave us to read was that one of the problems is that it is so expensive to put a new drug through the process. In fact, if we do reduce the cost, does the FDA

feel that we will get more and better drugs or whether we will just simply generate more profits for the companies? That is not necessarily bad; I am not implying that it is bad, but maybe we will get more and better drugs. I think that is a key issue and I haven't seen a slide presented showing the cost of putting a drug through versus the number of drugs that are actually approved.

DR. ORLOFF: I can't really help you there. I don't believe we have such data. Agreed, the longer, the larger the trial, the more intensive the monitoring, the more expensive it is. Dr. Atkinson proposed, sort of in broad terms, that the pre-approval experience and, therefore, costs be limited, with a commitment to investment in better understanding of the overall profile of the drug, risk versus benefit, in phase 4. FDA doesn't have much regulatory leverage and, thus, we have less in the way of capabilities to protect the public health in phase 4. I think that it really violates some central tenets of our procedures to wing it at the time of approval.

DR. BRAUNSTEIN: I have two announcements, before we break for lunch, for the committee members. Number one, please hold on your calendars December 13 and 14 of this year for another meeting of the committee. Secondly, there is an area in the hotel restaurant reserved for the committee if you want to eat in the restaurant.

We will take a 45-minute lunch break and convene again around 1:05 or 1:10. Thank you.

[Whereupon, at 12:25 p.m., the proceedings were recessed for lunch, to reconvene at 1:15 p.m.]

A F T E R N O O N S E S S I O N

Committee Discussion

DR. BRAUNSTEIN: Good afternoon. We will open the afternoon session. Dr. Orloff, do you want to lead us through the format?

DR. ORLOFF: This is where we start so you can take it if you have any questions or clarifications and I will just run up to switch slides.

DR. BRAUNSTEIN: Terrific. Thank you. What we will do is we will go through the questions that have been posed by the FDA for us to discuss. We will have sort of a general discussion where people raise their hands to have some input or ask questions. Then I am going to go around and ask everybody to sort of weigh in on these issues. Again, there is no voting but it is to give the sense of the individual members' of the committee input to the FDA about what their feelings are concerning these questions.

The first is populations. At the present time the recommendation is for a BMI greater than

or equal to 27 with a comorbidity and greater than or equal to 30 without comorbidity with be appropriate populations to treat. One of the queries that we have is should the recommendation of a BMI less than 25, when accompanied by a comorbidity, be considered? Or even should there be exclusion of a comorbidity requirement when considering a BMI that low?

So, let me open this up for discussion. What evidence supports treatment or prevention in this population? What magnitude of effect would be clinically significant? And, what assurance of safety is required to treat lower-risk patients? Dr. Levitsky?

DR. LEVITSKY: Well, I will throw my voice into the ring here. I thought about this a bit and there clearly is no evidence to support treatment or prevention in this population from what we have had presented and what we know so we can't look at evidence. There probably ought to be, and there probably should be but there isn't.

So, what I did was to look at magnitude of

effect and assurance of safety, and I chose the one treatment that we know has a huge magnitude of effect and is not so safe, and that is surgical bypass. Surgical bypass is the only thing that really works in people with severe exogenous obesity and it is associated with, I guess, a 3-5 percent risk depending on how sick someone is when they go to bypass.

The decision there has been made, and it is probably reasonable, that if you have very, very severe, life-threatening obesity associated with comorbidities that that risk is worth it. Therefore, what I would suggest is that we need to stratify studies based upon degree of risk, and I would like to have assurance of much more safety before one dropped the BMI down to the 25-27 kg/m2 range. Therefore, I would like earlier studies done on the people who have higher risk, where the risk is available in the literature now, and if these agents are proved to be very, very safe in the initial studies, then I think one could move on to studying a population which at this point at

least has cosmetic obesity, not obesity associated with other risks, although I believe they probably do have other risks that we just haven't defined yet.

DR. BRAUNSTEIN: Yes, Dr. Schambelan?

DR. SCHAMBELAN: I just have a question. Do you think the evidence is there to support treatment for a BMI greater than 27 anymore than there is for 25?

DR. LEVITSKY: No, I suppose you would have to get up around 30 before we have really done the studies.

DR. BRAUNSTEIN: Yes?

DR. ARONNE: I think that there may be subgroups of the population who would fit into a category of being someone worthy of treatment as a substitute for another treatment modality. For example, someone of Asian descent who has a BMI of 26 and has a large waist circumference and has type 2 diabetes, in my opinion, treating their obesity would be a good idea. I think that that might be an appropriate case of an indication for obesity

treatment, rather than just treating the diabetes. So, I think that there may be situations where it could be proven that there is health benefit. Someone with metabolic syndrome--mainly these would be I guess a subpopulation who have metabolic syndrome and a large waist circumference even though they have a relatively low BMI. So, there are people in that category.

One of the problems is that when we set a guideline, then the insurance companies follow this like it is chiselled in stone in the basement and it is difficult to dissuade them. So, I think it could be that companies should be encouraged to study people in this other category so that we can finally get data to see if there is medical benefit from treating that part of the population.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: It raises an issue that Dr. Schade brought up earlier, the value of larger sample sizes which will allow you to do stratification and look at subpopulations. In terms of magnitude of effect, it is hard for me,

from seeing any of the data so far, to think that weight change alone would represent a satisfactory endpoint for me. I would like to see either quality of life improved or improvement in surrogate markers--blood pressure, lipids, C-reactive protein, and ideally some evidence that weight reduction achieved by medication confers some improvement in morbidity or mortality. I think the lower you drop the level of intervention the greater the need for safety data which, again, requires large sample sizes to achieve.

DR. BRAUNSTEIN: Dr. Orloff?

DR. ORLOFF: I wanted to clarify something that I forgot to mention earlier and this reminded me. Our standard for approval or approach to the evaluation of these drugs includes an evaluation of the effect of drug-induced weight loss on comorbid features--hypertension, diabetes, dyslipidemia. As some around the room know, the issue related to pulse and blood pressure was salient in our evaluation of the overall risk/benefit of sibutramine because, indeed, there is a

subpopulation of patients who received that drug who, in contrast to actually getting a benefit on those comorbid features of obesity, seemed to have some deterioration in those features despite perhaps weight loss.

So, anyway, I wanted to make clear that we do have that system in place now and that will always be the case, that we are looking at the weight of evidence and we approach the weight loss criterion in light of the other aspects of the drug's effect.

Finally, with regard to sibutramine lest anyone go away thinking that sibutramine was approved despite the fact that everybody who loses weight gets problems with pulse and blood pressure, in fact, the two effects are dissociated. So, we believed that monitoring for that potential adverse effect is sufficient to accomplish safe use of the drug.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: Can I get you to clarify? If you have an enrollment criterion that includes

comorbidities as one of the requirements, is comorbidity just an item of interest or is it an endpoint as well?

DR. ORLOFF: I believe therapy are believe they are evaluated as secondary endpoints. To the extent that this is all based upon surrogates, if you will, the true endpoint of interest is long-term serious morbidity and mortality. We don't have any of those data. Weight loss in someone who is obese and at risk and has, let's say, the panoply of cardiovascular risk factors associated with classical type of obesity, it is supposed to affect salutary changes in those risk markers. So, we look at those as secondary endpoints and our overall evaluation of the drug is clearly tempered by the results of those secondary endpoints.

DR. BRAUNSTEIN: Let's go around and I will ask members of the panel to specifically respond to question number one with the three points here. We will start with Dr. Hirsch.

DR. HIRSCH: I will be happy to start with

that, but let me just say as a prelude to what I am going to say, and I will be very brief about this, if there were really a new and very efficacious drug available to treat obesity we would be living in a different time and I think the considerations might be somewhat different. But I think people tend to confound the issue. What has happened in this whole obesity research scene is that it has become evident that there is a very, very complicated mechanism whereby body fat storage tends to be controlled over long periods of time, and it is controlled in a bad or deleterious way in those people whom we designate as being obese. All sorts of new peptides and new mechanisms are being uncovered by the wonderful activity of molecular genetics and cell biology, etc., etc., that fills up our interest, and so on, but in the treatment arena, even though these new peptides and their agonists and antagonists are bandied about and tried, nothing new has happened. Fundamentally, every obesity treatment that we have, and those that I know of in the pipeline, are sort of counter

forces, are techniques of making this mechanism not work quite so well, but are not aimed at the pathogenesis of obesity or the new understanding of it.

So, in some respects, what we have here is a bunch of drugs that act somewhat like jaw wiring of years ago. I mean, no one thinks, for example, that pancreatic lipase dysfunction is a cause of obesity. On the other hand, its inhibition, which ordinarily would be considered an adverse effect, does have an effect on this body weight regulation mechanism. So, for this reason, all the drugs we look at and hear about all hit the 5 percent, 7 percent, 8 percent, or whatever it is, per year weight loss as compared with placebo because they all operate in this same counter force kind of way.

Now, I am not denying the use of these things, but nothing new or special has happened that makes me want to change the guidelines we have. So, I think, in answer to your question, it is not a good moment to lower the BMI of 27 with comorbidity, etc., and to markedly widen this

population on the basis of new information. We don't have any new information about the pathogenesis of obesity that is yet relevant to its treatment.

DR. BRAUNSTEIN: What magnitude of effect would be clinically significant?

DR. HIRSCH: I think 5 percent over the year is fine. I think the categorical thing, I would worry about that. I think that is a snare and a delusion and any statistician knows that post hoc you can always find a category that you can make significant. You can pick between 8-11 percent, 3 percent, whatever it is. So, if you do categorical things, they must be stated ante hoc and you must examine the distribution, that is, the mathematical distribution of the weight loss.

Consider, for example, the situation in which you want to use categorical things and somebody's average weight isn't quite what you wanted but the 5 percent level is met. That could theoretically be brought about remotely because the drug you are using actually caused some other

people to gain weight and balance off the mean. So, one must be statistically extremely careful about categorical things. I would think 5 percent of the mean over the year is a good thing, except in the most special of circumstances.

DR. BRAUNSTEIN: This is 5 percent below placebo?

DR. HIRSCH: Below placebo, yes. Five percent weight loss, that is right.

DR. SCHAMBELAN: I would concur with the notion of not lowering the bar for enrollment. Since I wasn't part of the decision to make 27 the cut-off, I am not even sure why that is the current cut-off. Certainly, I would continue to require comorbidity rather than to eliminate it, as was suggested by at least one of the submitted documents.

I think 5 percent seems to make sense. There is some evidence that is a health benefit. Obviously, we want to make sure safety is assured. I think when we get to talk about the numbers of people in trials perhaps we will have a different

chance to weigh in on that.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: In response to the first question, I don't think we have really seen evidence to support looking at this population. The curve that I really focused on was that J-shaped curved of BMI and mortality, and that was just in the overall population. So, to proceed and try and go in this direction you would want to see, you know, evidence that BMI greater than 25 and a comorbidity really is where the dose-response curves start to take off and we haven't really seen that yet today.

In terms of what magnitude of effect would be clinically significant, I would feel more comfortable with the 5 percent benefit compared to placebo along with some improvement in the comorbid profile, if you could call it that.

The categorical criterion that was being discussed earlier doesn't really talk about an absolute magnitude. It just says that the percentage of success on drug is larger than the

percentage of success in some control--you know, it is statistically significant where success is defined as a 5 percent improvement from baseline. So, you could have a situation where a drug, where a company does a huge trial, wins on this "success" endpoint because the trial is so large when it is a very small actual difference between the two groups. So, that is why I favor the first criterion that was discussed.

Finally, in terms of safety, I think for low risk populations, as was mentioned earlier, you want to have more assurance about them for a couple of reasons. One is because you are worried about the risk/benefit relationship, but also you are worried I think that this could be applied to a much larger population out there, and I think our concern about safety should be magnified if the drug is going to be extremely widely used.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. J. YANOVSKI: I concur that in general there is no good evidence to support dropping the criterion for routine study of such medications or

use of such medications at 25 kg/m2 even when accompanied by comorbidities. In part, that is because when we look at the lower part of the curve the prevalence of comorbidities is not so different below 25 as it is between 25-27. I think those numbers are not that different. So, then it runs the risk of people feeling that we should use weight loss even in lower BMIs and there is the greater probability of abuse, I think, when a larger population is approved for use. So, for both of those reasons I would concur that we should not decrease routinely the criteria, and certainly there is no evidence that would support it existing now.

However, there may be special populations in whom it may be appropriate to study, particularly if we are going to consider a criterion for prevention of weight gain. For instance, in an individual with a BMI of 25 who is about to undertake or is currently undertaking psychotropic therapy with known complications of weight gain, it might certainly be reasonable to

find out if any of the agents that we are studying would be of value to prevent that weight gain and the development of a high BMI. Maybe there will be other criteria. So, I think there ought to be the possibility of special populations being studied, but it should not be a blanket statement for anybody with a BMI of 25 even when included with comorbidities.

The question of magnitude effect--I think we may be confusing two issues. One is in general what magnitude of effect we want in obesity drugs for obesity with a BMI over 27 or 30. Then the question is, if you are going to consider people who are over 25 kg/m2 who are not obviously yet obese, then a smaller magnitude of effect or prevention of weight gain may be appropriate as an outcome. So, the statistics for that are going to be different and will probably require even larger sample sizes if we are going to look for smaller differences. So, I think that those are going to be population-specific statistics really. So, the sample size questions are going to be based on what

is the probability of severe weight gain, for instances, after psychotropic use.

So, I think there are unique issues when we talk about folks who have not yet reached a point with any elevation in mortality in general, and we need to then look at specific populations if we are going to use anybody under 27. And, I think the 27 and above criteria basically comes out of the fact that we used to define overweight at that point. That is why the cut point came about. It is clear. But the J-shaped curve does support the notion that the higher the BMI, the more risk we should take in using medication so, as a result, I don't see any reason to decrease the criterion.

DR. BRAUNSTEIN: Dr. Levitsky?

DR. LEVITSKY: Well, the BMI is a surrogate marker for obesity obviously. It is a pretty good one but it is not a perfect one and, therefore, I don't think we should reduce the BMI criterion yet. And, I think all studies that are done with new drugs should be done as treatment studies initially, with prevention studies being

secondary after safety has been assured.

DR. BRAUNSTEIN: Ms. Coffin?

MS. COFFIN: I am actually going to go against the curve here. I think that the 27 is in the guidelines because that was the use back when the draft was put together in '96. Since then, across the board, it has become more of a standard out in the community, that if you have a BMI of 25-30 you are considered overweight and if you have a BMI of 30 or higher you are considered obese. I do think then that the consistency for the consumer is important. So, drugs to treat people that are overweight with comorbidities should be consistent with the definition of being overweight, and drugs that are consistent with treating people that are obese, those with a BMI over 30, should be then in there. I would not, however, suggest removing the comorbidity from those folks who are overweight because I believe that there are quite a few folks out there that can be overweight but still healthy and so only those that are having other symptoms or other comorbidities should be considered for drug

treatment, and 5 percent seems to be a reasonable magnitude. So, I would suggest lower, just for consistency.

DR. BRAUNSTEIN: I actually am also going to weigh in against some of my colleagues and suggest that we do lower it to 25 or above for the following reasons. Number one, the J-shaped curve does seem to have the cut point at around 25. So, above 25 the mortality goes up; below 25 the mortality seems to go up also. But that is one reason.

The second reason is that Dr. Flegal showed in her summary data that there wasn't much difference in the comorbidity prevalence between a BMI of 23-25, but around 25-27 it starts to go up, especially in men. There is more of an upswing. It is not a clear-cut cut in the data but if you look at her combination of any comorbidities, it does go up between 25-27. So, I think that, in and of itself, would be justification.

Thirdly, we are seeing increased prevalence of obesity in the American population.

There is increased recognition that about 25 percent or so of the population will have the metabolic syndrome which has been clearly associated with cardiovascular disease and other problems. So, I do think that lowering it to 25 is reasonable.

Having said that, I would like to keep a minimum of 5 percent difference between placebo and active agent. The Europeans use 10 percent. We have had 5 percent. There is data in the literature, for instance in women with polycystic ovary disease that a 7 percent reduction in weight decreases the oligomenorrhea, increases ovulatory rates, decreases hirsutism. So there is clearly beneficial effect of 7 percent so I assume that anything over 5 percent is going to be better than less than 5 percent. But I would like to see as a minimum 5 percent being maintained.

As far as assurances of safety, obviously we want the drug to be ultimately extraordinarily safe. As Dr. Ryder will probably comment--I don't mean to steal your thunder but I do want to make

the point that you made. Sometimes we have to look at drugs with a risk/risk evaluation rather than a risk/benefit evaluation. I will let you expand on that. But, basically, my understanding of that is that if you have a disease that has a high mortality or morbidity rate and you have a drug that has side effects but the risk of the side effects, overall risk to the person's well being is less than the risk of the disease then it is worthwhile using that. As you start getting down to a BMI of less than 27, yes, the risk/risk probably becomes more difficult to assess and, therefore, one would want to see a larger database of safety in that population. Also, I do agree that there should be a comorbidity less than a BMI of 30. Dr. Greenway?

DR. GREENWAY: I also agree with lowering the BMI to 25 with comorbidities. I say that for a couple of reasons. One is that the BMI of 27 cut point I think is mainly of historical interest, as Dr. Flegal described. I think that the standard across the world now is that being overweight is

between 25-30 and I think it would make sense to have this standardized. Secondly, it is not just a matter of making it standardized, there is also an increase in risk that starts with a BMI of 25. Clearly, with diabetes weight loss is beneficial and even with insulin resistance it is going to prevent diabetes. So, I think that there are reasons to lower the BMI to 25.

I agree that a 5 percent weight loss is what is clinically significant and that should be a lower limit. Obviously, the lower the risks of the population, the greater the safety of the medication needs to be. So, anything that is used for obesity is obviously going to have to meet a higher level of safety than many other diseases that are more immediately life-threatening.

DR. BRAUNSTEIN: Thank you. Dr. Flegal?

DR. FLEGAL: I guess I didn't realize I was actually going to be called upon to answer these questions. My inclination or my personal view would be that it is not the best idea to lower the cut point to a BMI of 25 because I think these

cut points are very arbitrary and, yes, I think standardization is a good thing and it is really helpful to us to have standardization for our purposes, but I don't think they should be mistaken for clinically significant cut points, and I think without a lot more evidence about that range of 25-27 it would not be the best course to lower it at this point. You know, if you read the literature on how these cut points are determined, it is really a very arbitrary process so I don't think it should necessarily be the standard followed to set standards for everybody else and for other, different kinds of purposes. That would be my only comment I think actually.

DR. S. YANOVSKI: I have mixed feelings about this. I thought a lot about it over the weekend and, on the one hand, more than 60 percent of the U.S. population right now has a BMI of over 25. That is an enormous number of people. Of those who have that BMI between 25-30, a number would be overweight but not really over-fat, particularly among men. Men are not the ones,

however, who are going to be mostly using these products. As we saw today, they are young white women.

I think some of my concern stems from the fact that lowering the BMI threshold, if one were really going to prescribe it for those with metabolic syndrome or diabetes it wouldn't worry me as much as the fact that I know these medications are going to be misused and taken by a number of people who don't have comorbid conditions and I think we have to be aware that that is going to happen regardless of our best intentions.

At a minimum, I think it is not a bad idea; it is a good idea to have these medications studied in that population, and potentially I could see them being approvable in, for example, someone like Lou Aronne pointed out, someone with a BMI of 26 who is Asian and likely to have more visceral fat who has metabolic syndrome. I think maybe provisions could be made to come in for specific types of indications or studies for very high risk populations.

When I think about people with this BMI between 25-30, where I really see most of the money, would be in weight gain prevention for people who are at really documented high risk. I think Jack might have pointed out somebody who is about to start an atypical anti-psychotic where we have a good idea that they are going to be gaining large amounts of weight, increasing the risk for diabetes. So, I see more of the money in prevention of weight gain in specific populations at high risk, or perhaps a treatment indication at very specific targeted populations at high risk, but I have a lot of trepidation about a general lowering of the BMI threshold to 25, both because I think we don't have a lot of data on how much benefit we are going to get there and because of my concerns about risk of misuse.

Regarding magnitude of effect, I am going to disagree with Dr. Hirsch, my esteemed colleague, on not having categorical definitions. First of all, I don't think any of the drugs we have today--I am not sure any of them would meet the 5

percent across the board difference from placebo. We are going to find responders and non-responders and I think that having the categorical variables and allowing a drug to be approved that may have a standard number of responders is important. Now, the magnitude of responders versus non-responders in the studies that I have seen is often pretty substantial. It might be 35 percent versus 17 percent in the placebo group. There is often a doubling of the responders. I think it would be a good idea to actually quantify the difference between placebo and active treatment groups in the percentage of responders and non-responders, not just make it statistical significance.

Regarding assurance of safety, again I think that when you are looking at a lower risk population you have to have even more assurances of safety.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: The drama increases with the decreasing amount of data we have to make our decisions. I have to weigh in, after certainly

submitting that this is a hunch and an instinct as opposed to a great deal of data analysis, that it is difficult to justify dropping the BMI, primarily for reasons that have been stated. I think the single piece of data that sticks in the mind that I have seen today is the J-shaped curve, and there may be small differences between 27 and 25 but I am hard-pressed to consider that they are clinically significant, certainly not as significant as the ascension between 27 and 30 in terms of complications or mortality on that curve.

I agree also with Dr. Yanovski that I would include the categorical proportion of responder criteria in addition to the 5 percent delta between placebo and treatment. It seems to work in the way that we have been talking about the previous data. And, I think it is absolutely clear that safety is a primary mission of this whole process and in a low risk patient it becomes an even higher profile issue and we should stick with extremely high assurance of safety in that group.

DR. BRAUNSTEIN: Dr. Wierman?

DR. WIERMAN: I would say that the whole discussion today reminds me of the discussion of what were our LDL requirements 15 years ago. Our goal, you know, started at 120 and then went to 100 and currently is quite a bit lower than that in different at risk populations. I think what we have to decide now though is where are we right now on that curve. I thought the curves looked fairly linear, without any obvious huge cut point on many of the curves that were shown this morning. But because we don't have outcomes data related to mortality or even morbidity, I think that I personally would not lower the BMI cut point with comorbidity to 25 yet until we get more outcome data, unless there were special populations such as have been outlined--patients with metabolic syndrome; patients with perhaps postpartum hypoglycemia, etc., that could be studied in that range. All the other comments I agree with.

DR. BRAUNSTEIN: Thank you. Dr. Woolf?

DR. WOOLF: I would like to keep the cut point at 27. Surely there is no shortage of

subjects. We are not talking about an orphan drug here. In fact, we are talking about just the reverse. If it hadn't been for historical purposes, I probably would propose increasing the level rather than decreasing it. There is no increase in mortality with a BMI of 25. The J-shaped curve takes off somewhere between 25-30 and goes up. So I would much rather start where I know it is going up rather than supposing where it is going up. So, I really want to keep the current guidelines where they are.

I would like also to keep both criteria. I think it is important to know what proportion of patients actually benefit over placebo from this drug. It may be that the decrease in weight is only 2 percent but, in fact, if 25 percent of the population or, let's say, 30 percent of the population really loses 5 percent and there is another 10 percent that gains weight, we are obviously not going to keep people who are gaining weight on the drug; you would stop it. So, I think that having both criteria is important. But I

agree with Dr. Hirsch that it ought to be prespecified rather than post hoc. And, as everybody else has said, where the benefits are weak at best, you have to err on the side of safety, and the bigger the study the better.

DR. BRAUNSTEIN: Thank you. Dr. Watts?

DR. WATTS: I am on the fence as far as changing. I think studies certainly need to be done looking at the effectiveness of weight-loss strategies and for prevention of weight gain for patients who have BMIs between 25-27. But whether the criterion for approval should be dropped, I have reservations about that.

Magnitude of effect--I think there needs to be significant weight loss and there needs to be change in some surrogate marker, insulin resistance or some other comorbidity, and the further you drop the bar for initiation of therapy, the greater assurance we need about safety.

DR. BRAUNSTEIN: Dr. Schade?

DR. SCHADE: I have a little different opinion. I believe we should keep the BMI of 27

for the arguments made, but I think we should get rid of any comorbidity stipulation. The reason for that is if you keep a comorbidity it implies that the treatment for the comorbidity should be weight loss and it is very clear, I think as Dr. Orloff stated, that the drugs that induce weight loss may or may not affect the comorbidity. In fact, I would make the plea that weight loss is a poor way to treat comorbidities and, compared to five years ago we have very good drugs to treat hypertension; we have very good drugs to treat hyperlipidemia; and we have very good drugs to treat diabetes. Waiting for a clinical trial to improve comorbidities is a huge clinical mistake. Comorbidities need to be treated aggressively and they need to be treated now.

So, if you design a clinical trial to look at the effect on a comorbidity, assuming a patient has it, I don't think you could ever get it through my IRB because those patients ought to be treated immediately for their comorbidity. You should not wait six months or a year to see if this

weight-loss drug affected this comorbidity. That would be a huge clinical mistake. I think having comorbidities in there makes it impossible to assess because if the trial is designed correctly and people are treated appropriately those comorbidities need to be treated. And, I think it is a huge mistake to include comorbidities in any kind of criteria for a weight-loss drug because, in fact, it will be obscured by the treatment of those comorbidities with much better agents. So, I will put a strong plea in to take out the comorbidities because I think it is a totally outdated concept because we have much better ways to treat them.

I think the magnitude of the effect--5 percent is okay. That would certainly be a minimum as being clinically significant. Let me say a word about assurance. What do we need for assurance of safety? I can tell you what I think we need. I think we need time. We need experience. I was a principal investigator in a diabetes prevention program and in that program we had 3000 patients and we used two drugs, one was troglitazone and one

was metformin. The troglitazone at that time had just been released or was just made available from the Japanese groups, whereas with metformin we had 30 years experience in Europe. At the end of the trial troglitazone was off the market. People had died from it. Metformin basically was considered an extremely safe drug.

So, if you want to know the answer to number three about assurance, there is no substitute for experience in use of these drugs in large populations. So, that is basically what we need before we start treating lower risk populations.

DR. BRAUNSTEIN: Thank you. Dr. Aronne?

DR. ARONNE: As far as the first question is concerned, I think the reason we don't have evidence to support treatment or prevention in a population with a BMI of 25-27 is because we haven't approved drugs for that category so there is no way to drive a company to study their drugs unless you give them a chance to get the drugs approved. I believe that if we include that group,

perhaps as a separate category to seek approval with maybe a different set of safety standards, that that will drive industry to study it very carefully. I think that the criteria in that group needs to be not just weight-based but proof of health benefit, but my belief is that that health benefit will be forthcoming if the weight is lost.

I think the magnitude of effect that is clinically significant--I think that both the 5 percent placebo subtracted weight loss and the categorical weight loss are good measures of that. Then, as far as what assurance of safety, I think in the lower BMI group I would want to be sure that this is safe using more stringent criteria. I think the longer a drug is around, clearly that is a good way to start. But I think that clearly you are going to need bigger studies if you are going to use a drug in that lower BMI group.

DR. BRAUNSTEIN: Dr. Ryder?

DR. RYDER: Yes, just two quick comments, one just to continue on the theme that Dr. Braunstein mentioned. I am on a one-man personal

crusade for replacing benefit/risk, which I think really doesn't help discussions or I haven't found that, with risk/risk. I know that it is somewhat cute but it just reminds people that it is, in fact, the risk of the illness, the risk of the condition and the associated conditions versus the risks of the product. I think that is important to keep in mind. If you have the comorbidities, the comorbidities themselves do have risks or treatments for the comorbidities have risks. Every treatment, whether it is surgical, pharmaceutical, that I am aware of has at least some risk. So, just to keep that in mind.

I don't have any specific comment on the 25 or the 27. The other comment that I wanted to make was that I do think it is important, as several committee members have mentioned, to open up the concept of having some population-specific development paradigms. There are some very unique circumstances, whether it is drug-induced weight gain or something else, there are other populations that are somewhat unique and maybe to allow people

to study these would be a good thing because we could increase our information base.

DR. BRAUNSTEIN: Thank you. Dr. Orloff?

DR. ORLOFF: Just two points. One is the issue of enrolling patients with comorbidities with an eye towards examining the effects of drug-induced weight loss on those comorbidities. Even in the day of effective treatments for the associated metabolic derangements in obesity, trials can clearly be designed to examine things like drug dose, addition or subtraction of medications in the regimen, as well as the clinical parameters per se that are being treated, whether it be diabetes, hypertension or dyslipidemia. So, we don't actually view that as a limitation, and that is essentially what is being done now as we move forward in this field. And, I can't remember my other point so we will move on.

DR. BRAUNSTEIN: Before going to the second question, are there any other issues that any members of the panel want to raise about question number one? Dr. Carpenter?

DR. CARPENTER: Just very quickly, talking about using drugs for some clinical situation in which people might gain weight, I think with the psychotropic agents, fortunately, there are some choices. You can use one or another kind perhaps to minimize that. But a population that is very vulnerable and where it is a real issue are people who are, hopefully, stopping cigarette smoking and that might be a kind of area to look at drug treatment possibilities. I think that holds some people back to not smoke because of the weight gain.

Finally, in talking about the hazards of different groups, there is one group that I think is particularly vulnerable and we should be very, very careful in all our thoughts about it, and that is adolescent girls or women who are sensitive to feeding disorders because the specter of bulimia and anorectic diseases, and so on, looms high in that group. So, that is a particularly hazardous group I think to deal with in terms of drug treatment. I would just like to bring up their

particular vulnerability.

DR. ORLOFF: I know what I wanted to say. I want to make sure that the discussants, as well as the audience listening, the public, don't lose sight of the fact that this whole discussion--again, this was stated in some of the remarks earlier--this whole discussion is taking place in the context of a pharmacopeia that is really inadequate. I think that is the most accurate way of saying it. The effects of our current crop of drugs on weight loss as well as on comorbid features of obesity are far from ideal. Clearly, in a risk/risk, risk/benefit sort of construct we can't forget that.

Now, clearly, if a drug comes along that preliminarily shows a huge amount of weight loss benefit and an accompanying appropriate, graded reduction in comorbid features, then I think that creates a whole new arena for discussion.

DR. BRAUNSTEIN: Yes, Dr. Carpenter?

DR. CARPENTER: Another suggestion for perhaps a minor component of this BMI cut-off,

given the data that was shown earlier regarding the striking effect of age on the comorbidities, is that it may be useful for some of the studies to look at some parameter that would identify interaction of age and BMI, not just segregating out the adolescent population but through the decades in terms of where these drugs may be most useful and most helpful. So, it may be that BMI, in fact, would end up being a moving target across the decades.

DR. BRAUNSTEIN: We will move on to the second question. I will start with Dr. Ryder this time and go around in that direction. Actually, before we start with Dr. Ryder, let me open it up for general discussion and then we will go to the specific panel members. For the pediatric/adolescent age group what factors should be weighed or addressed in assessing risk versus benefit?

DR. J. YANOVSKI: This is something we have spent a lot of time thinking about, and there are very divergent opinions in the community about

what should be, for instance, the necessary enrollment criteria for such patients.

First just to remind everybody that when drugs are approved for adults, they are approved down to age 16. So, this age group we are talking about is 12-16, I guess, that we are calling adolescents, and then pediatrics below that. Obviously, in both populations, younger populations, there are significant amounts of linear growth going on and, as a result, the use of the BMI without correction for age and sex and maybe even race is inappropriate as the metric so we need to use something like the body mass index standard deviation score. So, as an entry criterion we have promoted certainly BMI-SD over the 2 SDs or a little less than that, 95th percentile, as an entry criterion, following which we have also suggested that comorbid conditions be required to be present, besides overweight, in such patients because they are a population that is not making up their own minds so they need additional protections beyond those afforded adults. So, the

risk of the disorder should be greater than necessary perhaps for adults. So, we have suggested that comorbid conditions should be present, that high BMI be present and, indeed, the list of comorbid conditions probably should be prespecified as to which ones would be considered acceptable.

The weight loss in adolescents, because of the developmental changes in height, needs to be interpreted carefully because, in fact, the BMI standard deviation score can drop even while the weight increases, depending on how the height increases. So, measures of body fat should also be included, but the problem being, again, that there are no good consensus definition of what is truly over-fat--modern definitions, anyway. We have a lot of things we use but no consensus on what is over-fat for children and adolescents in terms of the number of kilos of fat mass, for instance, or percentage body fat. That makes it difficult but I think those should be part of the criteria for assessing the outcomes.

As a result, the physicians also have to, of course just as in adults, make sure that they study the patients in whom the medication will be used and so over-sampling for a particular population, such as Hispanics and African Americans that are at a much greater risk, particularly females in adolescent ages, is necessary. Then, sufficient sample size to discern benefit among those groups may also certainly be needed because we expect different medications perhaps to have different efficacy.

Then, the improvement in comorbid conditions I think is a secondary outcome of weight reduction in these individuals, but obviously is of importance in deciding how beneficial it is. When we decide to treat an adolescent we are suggesting that they are going to be treated for the rest of their lives or certainly for long term since, at least in this room, I think there is a consensus that such treatment for obesity needs to be continued because efficacy rarely continues after the drug is discontinued. So, we have to be doubly

careful that the medications we use are sufficiently beneficial that they are worth starting at all. So, I think large populations of younger children should be studied before such drugs are approved.

DR. BRAUNSTEIN: Dr. Levitsky?

DR. LEVITSKY: A question actually for Jack, what would the comorbidities be that you would accept for this? Hypertension, type 2 diabetes, what else?

DR. J. YANOVSKI: The list that we have suggested includes hepatitis, diabetes, hypertension and significant dyslipidemia. Now, the reason why it is particularly interesting in pediatrics is that, for instance, there is no consensus for the treatment of dyslipidemia in the absence of FH. So, that comorbid condition, which we really believe is going to lead to cardiovascular risk, is not being treated routinely with a statin. Similarly, blood pressures that are in the intermediate range, which we may expect to cause trouble later on, are not being aggressively

treated in adolescents. So, we have suggested that those kind of comorbid conditions should be entry criteria. Someone suggested insulin resistance, measured either by high fasting insulin but, unfortunately, in adolescents almost everybody, because of puberty, will have a higher insulin level so that may be a less stringent criterion. Also, obviously sleep apnea and the other disorders that are seen would certainly be acceptable comorbid conditions.

DR. WOOLF: I would be extremely concerned about treating kids who have either not entered puberty or are in puberty, rather than post-adolescent, let's say, 16 year-olds. We have no idea what these drugs will do to these kids as they grow up or to their offspring. So, we are not talking about a potential generational effect. So, I would much rather have--unless I were assured to the contrary--very strong data that we are treating kids who have comorbidities. We know that fat kids lead to fat adults but we can treat them when they are adults.

Another thing that I think is important is that we get them away from their computers and away from the couches. There is a recent study that exercise an hour a week leads to significant improvement in weight. I mean, it is trivial exercise. So, I would be much more concerned about treating younger kids because we just don't know what it is going to do.

DR. BRAUNSTEIN: Let me go around and those of you who want to add comments, feel free to add comments. Dr. Ryder?

DR. RYDER: My only comment would be one that Dr. Levitsky and others have already mentioned, that just in general as a starting place, you expect to have a little bit more certainty around the product specification because we generally accept a different level of risk when we treat pediatrics and adolescents than adults. So, it would be just a little different starting place typically, and this is just a general statement across just about all products, and I have heard a lot of people say that I think.

DR. BRAUNSTEIN: Dr. Schade, any other comments?

DR. SCHADE: I just have a couple of comments. One is that although we can wait until they are adults to treat them, I just want to remind everybody, and I am sure everybody knows that atherosclerosis has been well documented in the 21, 22 and 23 year age group from autopsies from soldiers who have been killed. So, we are dealing with a disease that we know starts very early on and these people may not even live to their 40s or 50s if they have significant risk factors. So, we can't always wait.

On the other hand, I am very concerned about treating patients with weight-loss drugs rather than treating directly the comorbidities in this age group, and I would actually raise the BMI to higher than 27 for treating these children because I am worried about these drugs causing changes in memory and in intellectual function and things that we don't know about. So, I am more conservative about treating these adolescents with

weight-loss drugs, whereas I am much more aggressive in treating the comorbidities directly because I know atherosclerosis is a huge issue.

DR. BRAUNSTEIN: Dr. Watts, anything?

DR. WATTS: The issue about the run-in period is going to come up later but I think it is particularly relevant here where you are hoping to find some change that will have long-term effects rather than a period of pharmacologic intervention that will then be stopped. So, I think in the pediatric/adolescent weight-loss studies there needs to be more attention to run-in phase behavior modification.

For drugs that have CNS effects, I am concerned that we need to be alert and develop tools to measure changes in school performance, intellectual function both during the time that the intervention is being given and in the time after the intervention is stopped, not just in scholastic behavior but in personal relationships with peers and with parents, and would hope, with the lack of long-term data for the adult studies, there would

be some way to try to improve the gathering of long-term data from these studies. I agree that a higher BMI starting point for children would be at least an initial step compared to the BMI starting point used for adults.

DR. BRAUNSTEIN: Dr. Woolf, any further comments?

DR. WOOLF: No.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: Just a brief comment on the story with pediatrics here. I think that unlike the story we heard earlier from Dr. Orloff regarding the pediatric population perhaps being a small subset of a study with a drug that would expand the indication, we are really talking about a completely different set of studies that have to be done in this group because of the complexity of the issues, the long-term cumulative effects of the drugs, the developmental components both neurologically and growth related that are going to be part and parcel of studying this group.

I think the problem that Dr. Yanovski

raises of trying to assess a moving target in terms of linear growth still going on--it is all going to create an environment for a completely different design and intensity of study than what we have previously been discussing, and I think it is going to require a substantial discussion that perhaps has some issues that are parallel to what we have been talking about in the older group. But I think it may be best to explore this in detail as a separate issue down the pike.

DR. BRAUNSTEIN: Dr. Flegal?

DR. FLEGAL: I have just a couple of comments. One is that, given the way the definitions of overweight for children based on the 95th percentile are involved, it might be advisable to have a higher standard than that to indicate treatment, and I would not recommend using Z-scores for that because I know how growth charts are constructed and I know the Z-scores are not going to work out at the tails, but maybe some absolute amount higher than the 95th percentile.

Just one more comment, and I don't know

very much about this area but it seems to me that the indications for treatment of high BMI as a risk factor should be commensurate in some way with the indications for treatment of other risk factors in this age group, including blood pressure and high cholesterol. I think it would be ironic if you ended up saying that for one of these conditions we go in and have drug treatment but for the other ones we avoid drug treatment. There should be some common denominator in how these are handled.

DR. BRAUNSTEIN: Dr. Greenway?

DR. GREENWAY: Well, I have just two thoughts that I think are different about this group. One is that I think they experience a lot more social ostracism than people in even older age groups and, yet, there is the whole issue of mental growth and physical growth and development in this population that has to be taken into consideration.

In addition, I think there are a lot of methodologic issues that haven't been sorted out with relationship to how to assess this whole area in growing people. At least I have no idea how to

do a power analysis on a Z-score.

DR. BRAUNSTEIN: I basically agree with the comments that have been made. I would like to reemphasize what Dr. Carpenter said, that this population of patients needs to be studied separately from the adults so that when one designs a study it shouldn't be including individuals from ages 14 to 70. The adolescent and childhood obesity problem needs to be treated on its own accord with appropriate controls and studies of growth parameters, psychological parameters, etc. Ms. Coffin?

MS. COFFIN: I have a question for the industry representative. I heard earlier that the average age of the participants in the studies is about 40 years old, which is actually even a little on the old side for the participant users or the end users of drugs currently. Is the industry interested, excited, chomping at the bit to test drugs on adolescents? Because my understanding is that it is a terrible group to test because there are so many complications.

DR. RYDER: I have never run a clinical program so I can't speak for the emotional state of the people who are running the programs. I do know that industry is certainly interested in bringing new treatments to people who need them, and it sounds to me like people need new therapies for the treatment of obesity, whether they are 12, 14, 18, 30, 40, 60, 80 or whatever. So, I am sure that the industry supports the intervention of new treatments.

That said, I will go back to my prior comment--Dr. Levitsky made it, Dr. Carpenter just made it, many have mentioned that you have to have a different set of certainties around you product specifications because you are going into a population where typically we accept a little bit less risk. You have to perhaps notch it up in terms of the certainty that you want in not bringing harm, and all these considerations. Dr. Carpenter said very nicely that it is a somewhat different population.

MS. COFFIN: Thank you very much. I would

agree that this is definitely a different population and would like to see this handled in a separate guideline or a separate study, but I would also say that prevention early on, as Dr. Woolf mentioned, is important, and more education that you can provide to adolescents. Right now we are actually requiring a physician sign-off to get into behavioral changes for treatment of obesity and overweight for adolescents and pediatric participants. So, we are looking for the medical field to give us a little bit more direction.

DR. BRAUNSTEIN: Dr. Levitsky, any other comments?

DR. LEVITSKY: I am going to comment on a few different things that have been said. One is that industry had been given encouragement to do these studies, obviously, because they get their drug with their patent a little longer if they do. So, they will be done, I am sure, although they will be more complicated.

The second thing is that I am a little bit concerned about the level of concern about doing

studies in adolescents because of worries about passage onto the next generation. I recall that those same arguments prevented studies in women for many years. So, I guess that we have to worry about it but recognize, nonetheless, that these kids do need to be studied.

The next thing is that I would categorize pediatric studies in several groups. One of my colleagues, a pediatrician, when he sees a patient, a little child who is overweight and whose parents are complaining about it, always pats the kid down and then says, "I can't feel any money in his pockets. How is he getting the food?" So, there is an age at which this is not a pediatric problem; this is a family problem and I don't think that we need to look at the drugs for those kids. I have certainly been very successful with Prader-Willi syndrome kids as long as the parents understand it. But there is also an age at which children become free range and at that point testing these drugs is important and starting at the 12-16 year range is certainly appropriate. That is also nice because

it is a range that, although neuronal connections and growth are still going on there, they are not so intense as in the early ages. So, I think it is feasible to conduct these studies.

The last point is one of Dr. Yanovski's actually. If you use the 90th percentile for BMI using the new fudged growth charts, which don't have the weight data that are presently available but use the old weight data because children have gotten fatter than are on the new growth charts, you really are working around a BMI of 30. So, that is probably pretty reasonable, isn't it?

DR. BRAUNSTEIN: Thank you. Dr. Yanovski, any other comments?

DR. J. YANOVSKI: I guess just to address one last point to remind everyone that, indeed, there are data suggesting that pediatric aged, or at least adolescent aged BMI predicts additional morbidity many years hence independent of adult BMI, and so there really is a very good rationale for successful treatment.

Then, to make a plea that the studies in

pediatric populations include long-term follow-up. It is not enough just to show efficacy for 6 months or even a year or maybe even 2 years if we are going to suggest that young children, particularly young children, take medications for 50 years.

DR. BRAUNSTEIN: Dr. Follmann, any comments?

DR. FOLLMANN: I would just echo that in the pediatrics and adolescents you want to study those that have the very highest risk and they deserve special studies.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: I would also emphasize the need for these being separate studies, and then I would add that the lifestyle modification be a major component of the approach taken in this population, whereas that may not be as much the case in adults.

DR. BRAUNSTEIN: Dr. Hirsch?

DR. HIRSCH: I think that the very young women that I am most concerned about would probably be the biggest users of such a drug, if it were

made available to them, because they are so involved with food intake and worry about it, and whether they are obese or not, and so on. I think that the menarcheal years of young women--they are so susceptible to all sorts of influences and there are all sorts of important developmental things occurring, and this explains a lot of the feeding disorders we have and even to consider them as targets for the kinds of drugs that are currently available I don't think is the right thing to do.

DR. BRAUNSTEIN: We will go on to the third question. I am told this is the third out of 11 questions so what we are going to do is still stick with sort of general discussion to begin with and then go around, but if you don't have anything to add or don't want to add anything, please feel free to pass.

The third question is obesity-associated metabolic derangements, cardiovascular risk factors as primary targets of drug therapy, when is an obesity drug a primary therapy for diabetes, hypertension and dyslipidemia. Yes, Dr. Woolf?

DR. WOOLF: I think that is sort of a silly question. If you are going for an indication for a secondary problem, then go for the indication. So, if a drug is going to treat hypertension, then go for the hypertension indication; and if you think it is going to treat dyslipidemia, then go for the dyslipidemia indication and then weight loss is a secondary issue. So, I am going to turn it around--

DR. ORLOFF: I am going to clarify it a little bit. This is a thorny issue with industry. Basically what it gets to is a question that has been asked of us, and that is--well, let's put it this way, we have taken a position that if the effect on the comorbidity is simply consistent with the weight loss effect of the drug, given that for half of these drugs we may not know what the mechanisms of action are but we certainly don't have any evidence that there are independent effects on the comorbid features, at least for some of the drugs, although that might be different in the case of dyslipidemia. But just because you do

a study in patients who have diabetes and show that when they lose weight with your weight-loss drug their diabetes gets a little better, does that then become a primary treatment for diabetes? That is the question. How do people suggest we think about those issues?

DR. BRAUNSTEIN: Dr. Yanovski?

DR. S. YANOVSKI: There are a couple of issues within your issues. One is that I think if a weight-loss drug causes improvement in the comorbidity, even if the mechanism of that is through weight loss, that is fabulous. We know that weight loss improves dyslipidemia and hypertension.

Now, there is a question as to whether you would get a similar effect through behavioral weight loss. I think as a physician, what I would want to know in the PDR or anything else is that this drug caused improvement in these risk factors and that it was consistent with the amount of weight loss, or that there was actually an independent effect. So, I think you just tell the

physicians so that they could let their patients know, yes, your lipids may improve; your blood pressure may improve consistent with the amount that it would improve if you had behavioral weight loss treatment or non-drug treatment.

Now, if you are going for a primary indication--I actually saw a beautifully written little statement in here that it should be considered efficacious as a primary indication for the comorbid condition if it is clinically relevant for the disorder, in line with accepted clinical practice, and has similar magnitude and durability. So, I think you could go for a weight-loss indication or a primary comorbidity indication. But just because it is working for weight loss, I see that as a plus not a minus.

DR. BRAUNSTEIN: Dr. Aronne?

DR. ARONNE: I strongly agree with Dr. Yanovski's point, and want to point out to you one of the absurdities right now. If you prescribe a drug that causes weight gain and complicates someone's diabetes in other arenas but it gets the

glucose under control, that is an approvable drug. In fact, those drugs are approved even though they are causing weight gain, increasing visceral fat, increasing C-reactive protein, for example. But a drug that causes weight loss is not approvable because it causes weight loss as its mechanism of action, even though it will improve other comorbidities at the same time. That, in my opinion, is an inherent absurdity in the rules as they stand now. I see weight loss as a valid method to achieve these. In fact, I look forward to the day, 5, 10, 15, I don't know how many years in the future, when one obesity drug will be used to treat all those at the same time. So, instead of treating all the comorbidities with 5, 6 or 10 drugs we will be using 1 or 2 or 3 obesity drugs to treat the whole picture. So, I agree strongly with what Dr. Yanovski says and I think that her statement is a nice summation of it.

DR. BRAUNSTEIN: Let's go around and see if anybody else has anything to add to this. Dr. Hirsch?

DR. HIRSCH: If it worked it would be great. They don't lose weight and they don't do any other thing.

DR. SCHAMBELAN: I concur.

DR. FOLLMANN: I think it is basically impossible to try and sort out, say, if a drug has its entire benefit through weight loss. If a drug has a benefit on weight loss and hypertension I don't see how it is possible to describe what percentage of the benefit, in terms of blood pressure reduction, is due to the drug's weight-loss ability or some other mechanism, and I wouldn't even try to discern that or worry about it. I would just say it reduces weight and it reduces blood pressure.

DR. J. YANOVSKI: I just want to make an obvious reminder to the committee that we have approved a drug for diabetes that, in fact, causes weight loss. It is called metformin and at least part of its action, undoubtedly, is due to the fact that it induces some weight loss. So, the proof of concept has already been done. I don't see any

reason why a drug that has an indication for--oh--pulmonary hypertension couldn't be approved for erectile dysfunction or vice versa. We know there is a drug that is of that nature. Similarly, the same thing could be true for a drug that happens to decrease body weight and might also be very effective for hypertension or dyslipidemia.

DR. ORLOFF: I want to just clarify one thing, Glenn. For the record and to make sure the committee understands, what we are talking about here really are issues around labeling because we have criteria for approval for weight-loss drugs and we have approved drugs using those criteria.

The question is whether the weight-loss drug, by its reduction in weight, makes your diabetes a little better, whether that means you then write in the label that it is indicated for the treatment of diabetes, essentially. We include all this information in labeling in adherence with the principle that our labels should convey all the information we have on the expected benefits and risks of the drug. So, whether it makes your

comorbidities better or worse, you know, the information goes in. Likewise, for the diabetes drug that induces weight gain the labeling, I believe, expresses what the magnitude of weight gain was in the clinical trials.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: Can I ask a question? So, are you concerned about the use of the agent in somebody who is not obese, who doesn't meet that criterion but for the treatment of diabetes alone? That cannot be handled in the label in some way?

DR. ORLOFF: I suppose. I mean, I think that is a potential confusion. Let me just say that I think the best advice we got essentially from Dr. Yanovski on this is that if an obesity drug wants to be a diabetes drug, then it should be taken through its paces according to the same standards that are applied to a diabetes drug. Likewise, for a lipid-altering drug or an antihypertensive drug. The fact that in the trial that was designed as a weight-loss trial in obese diabetics, just the fact that their obesity got

better and their diabetes got better doesn't necessarily equal a primary therapy.

DR. J. YANOVSKI: Right. So, if they want to pursue an indication, they should do exactly the same studies that are required for any other drug for diabetes, any other drug for hypertension, etc.

DR. LEVITSKY: And there may be some reasons why this would be reasonable. There may be companies that wish to differentiate themselves that way so I think that is a perfectly reasonable approach.

MS. COFFIN: Just to add that the labeling does make a difference with insurance and what they do cover and what they don't cover, and you need to keep that in mind.

DR. BRAUNSTEIN: I agree with Dr. Yanovski's approach.

Design, run-in prior to randomization, pros, stratification, etc., exclusions, responders, limit of duration. This is the present guideline 6-week dietary, behavioral type of run-in. So, we will open this up for general discussion first.

Should the run-in requirement be maintained or deleted?

The comments received, primarily from industry, suggested that we delete this, the primary reason being that almost all the patients entering this trial will have already tried diet and exercise and have failed, and since all the patients are being treated in a double-blind, placebo-controlled manner with the same type of dietary and exercise instruction, there is no need for a pre-treatment run-in diet and exercise period. So, that is what the basic area of the question revolves around. It is open for comments. Yes, Dr. Ryder?

DR. RYDER: I just have one request really of the FDA. I do not have any empiric data personally from my experience to bring to the committee, but we did run into an issue like this using an overactive bladder drug that I was involved with. I was wondering do you have any information where companies have had different run-in periods in different programs, and have you

see selectively better results or different results compared to, say, a placebo arm? Do you have empiric information that would be helpful in telling us whether using different run-in periods--you know, people have run different programs in the past and I was just wondering if you had any experience. I don't.

DR. ORLOFF: I can't speak to any specifics. Let's just say that different drugs, different diseases, different clinical trials directed at different hypotheses will use designs that include a run-in. Sometimes the run-in is to establish that the patients are going to be compliant. Sometimes it is to set the background in the case of obesity or in the case of dyslipidemia, with regard to standard of care interventions.

DR. HIRSCH: It was posed originally, years ago, as a sort of ethical issue. I am not sure that is exactly right, the ethical issue being the following, that there may be a subset of people who just have to be put on a good diet and exercise

program and they will lose weight and they should, therefore, not be subjected to whatever hazard there is of a drug even in an experimental setting. Well, as it has turned out, even under the best of treatments with diet and exercise, and so on, long-term results are very iffy and, therefore, one might say that that ethical issue disappears because what we are testing here is the issue of even if they did lose weight by the diet and exercise, you still want to see what the efficacy of the drug would be in maintaining that new, lower weight. So, this can all be explained to the patient and then they have a choice of whether they want to enter the study or not. So, I believe there is probably no residual ethical issue for why you have to give everybody a 6-week run-in period.

But now the whole experimental issue comes up if you are going to be fooling around with categorical things. Some people are responders and some aren't. You might want to get some information before about who is who in terms of those responding and then rearrange the drug

randomization so as to randomize these factors as well. It would be a nicer intellectual study to still have the longer run-in but not for any ethical purposes. So, to some degree, there is a choice in what the investigator, company or whatever wants to do in this, it seems to me.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. S. YANOVSKI: Yes, I agree. There is really not a lot of scientific justification anymore for the run-in. I think whether you use behavioral weight loss or drug weight loss people are going to continue losing weight for the first 4-6 months regardless. People who stop losing weight after the first few weeks are probably going to be, as Jules said, poor responders to anything. So, there might be advantages in having a couple of weeks of run-in just in terms of study design and figuring out who your responders are and stratifying, or seeing who is actually going to be willing to stick with your treatment. But I don't see a scientific justification for a 6-week run-in at this point.

DR. BRAUNSTEIN: Dr. Schade?

DR. SCHADE: The biggest problem that I see with the studies that are submitted to the FDA is that the populations that are studied have very little relevance to the populations that we treat. There are so many exclusions that are included in the studies--you are too big or too little, you are too high, too wide, something--so the fact is the studies that are approved or are submitted for approval are very, very select populations.

I think this is one opportunity here to get the population that we treat as physicians closer to what is submitted to the FDA to get rid of the run-in period because no physician in the real world is going to have a 6-week run-in period. So, I am trying to get the two studies closer together so I can believe what the FDA approves is basically somewhat applicable to my patients. So, I would be strongly in favor of getting rid of a run-in period because I think in the real world it never really happens.

DR. BRAUNSTEIN: Dr. Greenway?

DR. GREENWAY: In addition, I think another disadvantage of a run-in period has to do with interpreting the data at the end. A lot of the microbiologics that we all think are so important to evaluate respond to caloric deficit. So, if you already are in caloric deficit, then you don't know where to start your baseline. Do you start your baseline before the run-in or do you start it when you randomize the drug? And, if you do it when you randomize the drug, then most of the improvement in your comorbidities has already occurred and you don't see that at the end of the trial.

DR. BRAUNSTEIN: So, are you speaking in favor of having drugs or just having behavior?

[Laughter]

Let's go around and ask if there are any specific comments that you want to make on this. Dr. Ryder?

DR. RYDER: Nothing,

DR. BRAUNSTEIN: Dr. Aronne:

DR. ARONNE: I just want to agree that the

run-in does not make sense.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: I agree that we ought to abolish the run-in but I think that there needs to be a sufficiently long baseline that we have some idea of what the stability of the values are for comorbidity, weight and things like that. So, I would want at least a few weeks, if not a few more than that, without treatment, a screening period.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: I don't see a reason to justify the current practice of a run-in period. I think some of the stratification issues that were raised by doing this--we don't even know the quality of the stratification from data obtained in run-in in this setting and perhaps it could be in some way ascertained to start with. I also think, as was mentioned earlier, that it may make a more real-world situation for the study.

DR. BRAUNSTEIN: I also agree that I think we can dispense with the 6-week run-in period.

MS. COFFIN: I am in favor of an

evaluation or a set time so you can get those initial motivators out of the studies so that you will have more completers. But I also agree with the folks that have said that most of the folk that are at the study point have tried and tried and tried and tried, and so they have already had more than 6 weeks run-in.

DR. BRAUNSTEIN: Dr. Levitsky?

DR. LEVITSKY: Well, it may just get study subjects to stay with the study if they get tested for those 6 weeks. That would be its only advantage.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. J. YANOVSKI: Just a pediatric population comment, many severely overweight children have yet to try a good diet with a good behavioral program. So, in that one instance it may be very appropriate to recommend strongly that folks carry out a good diet program and behavior modification program before having drug therapy in general. If they failed previously, then there is no reason to do it again. So, I agree, the run-in

with dropping out those who are responding well seems to be the wrong approach.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: Yes, I don't see any reason to have the current run-in design as it is currently stated. I could see a reason to have a short run-in to get rid of people who would be likely non-compliers.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: I would agree to remove it from the guidance but I would encourage the companies to have a period of observation baseline, as was suggested, and that would enhance the data at the end for their purposes.

DR. BRAUNSTEIN: Dr. Hirsch?

DR. HIRSCH: I agree.

DR. BRAUNSTEIN: The fifth question, combination drug regimens, standards of efficacy--open for general discussion. David, do you want to elaborate on this a little, the standards of efficacy for combinations?

DR. ORLOFF: Well, I just wanted to hear

some thoughts from perhaps the clinical trialists and others related to what people might suggest as the difference between mono therapy and combo therapy that should be deemed clinically meaningful.

DR. BRAUNSTEIN: To rephrase then what you said before, should it be additive, synergistic, multicative or can it just be statistically greater than one alone? Dr. Woolf?

DR. WOOLF: A point of clarification, could it be just as efficacious but with fewer side effects?

DR. ORLOFF: That is also a rationale for combination therapy obviously. Why don't we skip that one and go to weight loss efficacy? Assume that these drugs are all perfectly safe.

DR. WATTS: Well, just to follow-up on the point that Dr. Woolf made, I think the endpoint would be different if you are using lower doses of drugs in combination to get the same endpoint than if you are using two drugs and their standard dosing hoping that the combination gives you a

greater gain. It seems to me that the additional gain needs to be at least as much as the gain that you would get with one alone. So, if you are requiring a 5 percent weight loss or difference with drug A, then adding drug B, to be clinically meaningful, you would need to get at least that much more weight loss.

DR. BRAUNSTEIN: If I interpret that correctly, if you have a combination and drug A plus drug B is greater than one alone, or the combination allows you to reduce the dose of each of them and, therefore, potentially reduce the toxicity.

DR. WATTS: Right, and there the goal would be if you meet a 5 percent difference between the intervention and placebo group for a single drug, then that would be the goal for the combination drug if you use it in reduced doses.

DR. BRAUNSTEIN: Dr. Aronne?

DR. ARONNE: I think that both increased weight loss and reducing the doses of the drugs that are used are both valid indications. I think

that a lot of the bad luck that we have had in the past with these drugs has been because of intolerable doses, and I think not understanding how the feedback mechanisms work practitioners were overdosing people 5, 10, 20 years ago in an effort to induce more weight loss when, in fact, what was going on was that a compensating system was at work and what you wound up with was drug toxicity. If you could use tiny doses of three or four drugs that hit specific spots in the neuroendocrine mechanism, you could get a superb result. Now, we don't have those drugs yet but we certainly have seen situations clinically where we have been able to get much better weight losses than you would expect with much lower doses of the drugs that are currently available. So, I think that better efficacy but lower doses of drugs would also be a reasonable way to evaluate these.

DR. SCHAMBELAN: Could I ask for a clarification for how the agency has looked at combination therapy, let's say, for type 2 diabetes with two agents or any hypertensive combinations?

I mean, what has the bar been there to help us think about what it should be for obesity?

DR. ORLOFF: For diabetes the standard design is maximal or just submaximal doses of the two drugs in combination in patients who have failed to reach hemoglobin A1C goals on a single drug. So, it is establishment of the principle that there is some additive effect. It presumes, and in fact it is the observation in these trials that there is some effect of the first drug so that they are not completely refractory to the first drug.

I am not sure how much we need to belabor this. This one actually turns out to be quite a complicated issue because it occurs to me, listening, that there ought to be a difference between--one of the things I didn't raise as I introduced this is the possibility of a categorical win so that you could actually capture more patients into a 5 percent or 10 percent category by the addition of a second drug. But simply winning on a categorical win does not establish that you

have an additive effect. It might, in fact, indicate that you have a population that actually just doesn't respond to drug A but when you add drug B they are responders to drug B. That is not a viable combination drug product. We want both components to be contributory to the effect.

So, the question I guess I just want to leave it as is if we are looking for some sort of additive effect, so presuming an effect of drug A, how much more do you have to get with drug B? We heard an additional 5 percent as sort of a default and I just want to know if anyone else has any other thoughts.

DR. BRAUNSTEIN: With that, why don't we just go around and start with Dr. Hirsch?

DR. HIRSCH: I can't see why there is any a priori reason why it wouldn't be good to have two. I mean, consider hypertension for example. It is common clinical practice now to use a number of drugs. That is a common thing to do and that is done because it is more efficacious. What we don't know is whether any combinations are going to be

more efficacious or not.

For example, one possibility would be not to use two drugs simultaneously but to alternate them, or when the weight comes down with one just substitute another because we know that almost inevitable failure comes in. So, it just seems to me there has to be some experimentation with some very carefully thought out studies of possibilities for efficacy, but until we know that there is no sense even talking further about it because we have no idea whether two would work, or three, or alternating, or whatever.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: I find it hard to come up with a number to answer the question. I do agree with your principle that you want to have both of the two drugs be effective to some degree before you use them together. You don't want to just add a drug in a drug failure situation and then continue the other drug. But I don't know how to come up with a number. I struggled enough to be comfortable with 5 percent in the first place.

DR. ORLOFF: Okay, we will put that in the guidance!

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: I don't have any great thoughts on how to change the standards of efficacy for combination drugs, but I think it is more exciting to think about sequential therapy, maybe interrupted therapy, if we are going to consider more elaborate drug regiments than just straight two drugs for a long period of time or short period of time.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. J. YANOVSKI: To amplify on what I think Dr. Hirsch said, since we believe obesity is caused by so many different etiologies, each individual drug might help a small subsegment. Together, you might see a population effect from combination therapy because you have now treated successfully many people and so it is not necessary to treat with multiple drugs simultaneously but, rather, you know, to make the punishment fit the crime, if you will. And, the problem is we don't

yet have good nosology so we are stuck with the issue at hand. What would be considered a good combination drug benefit, I am struck that it would be hard to argue--why should we be more strict about this than we are for diabetes is based on the fact that we know what we want to get for hemoglobin A1C. We know, you know, that that is where we want to be.

Whereas, for obesity, since none of our drugs yet are efficacious enough to get us where we want to be, we are figure out how lower, how much closer to the goal we should be. If 5 percent change is considered efficacy for a single drug it is certainly not going to over-classify effective combination therapy. It might miss some drugs which together might still give some clinical benefit. And, the idea of a clinical win might capture those combinations which were at least of greater benefit to the population than the single drug alone. But, you are right, it is hard to know. You wish you knew better how to treat the disease properly.

DR. ORLOFF: Combination drugs are really a complicated area but it is also important for people to know that we have combination drugs that are indicated and labeled as first-line therapy for a target disease. But I believe probably the majority of first-line drugs, at least for metabolic illness like hypertension and diabetes and dyslipidemia are sort of sequential therapies. Avandamet is recommended for patients who have been on metformin or Avandia but are inadequately controlled who are then now going to go on double therapy.

Frankly, the indications for those uses are directed by the designs of the trials and by their results. I am listening to this and it has occurred to me that as a first step combination drug trials for obesity should employ that sequential model, again, to ensure--to use the aphorism that Dr. Yanovski should not have used, the punishment fits the crime. That will be quoted all over the place. But, no, just to assure that you are not seeing an increase in the mean weight

loss not related to a true additive effect but, again, related to a spurious effect of treating with the second drug non-responders to the first drug.

DR. BRAUNSTEIN: Ms. Coffin, any comments?

MS. COFFIN: Just that, like Dr. Atkinson said, if one drug will get us 5 percent and if you put it in combination with something that gets you a little bit more, great; we love it if it works better. Whether there is a number, I go back to the statistical significance.

DR. BRAUNSTEIN: I think that I am fine with combination drugs. I would use as the endpoint a statistically significant increase of the combination over either one alone. But it needs to be carried out in a trial that has a head-to-head comparison, a contemporaneous head-to-head comparison with each of the agents plus the combination in order to not rely upon historical data from which the original agents were approved since we do know there is a lot of variability between results of trials.

DR. GREENWAY: I think that most of the discussion is sort of centered around two approved obesity drugs in combination. I think that there are other types of combination drugs that have minimal effects on their own and when combined may do something special. That kind of synergism I think should be another indication for a combination drug.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. S. YANOVSKI: Again, I just think that I don't see a particular cut-off. I certainly wouldn't hold it to a standard of having to double the weight loss but if it adds something or reduces side effects and gets you at least that 5 percent, I would think that would be of benefit.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: I think that establishing a guideline for percent delta with the second drug would be premature. I think it is going to be very interesting to see what studies come out of that but is an exploratory outcome at present and that, as well as other permutations such as alternating

months, such as some therapy we saw earlier today versus sequential therapy versus combinations all should be part of the experimental designs to come but a standard for them--we are not able to do that yet.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: I guess the full answer to my question is it depends. There are drugs--and I can't remember which one it is, where drug A is no longer effective. By adding drug B the effect is now greater than B alone. I think it is some of the oral agents. So, just because a drug is not effective anymore--excuse me?

DR. J. YANOVSKI: Augmentin.

DR. WOOLF: Okay. So, there are examples where that works and so I wouldn't exclude that possibility. Adding two drugs that are known to work, where each alone creates a 5 percent weight loss, and having the two together statistically different, while that may be satisfying the statisticians it may not be clinically useful. So, if each drug is 5 percent but the combination is

statistically significant at 5.5 percent, I don't think that is worthwhile. I can't tell you what percent above would be clinically worthwhile but it has to be something meaningful that a group of reasonable clinicians can at least agree about.

Finally, I would go back and say that if the safety profiles of the two drugs are not really terrific at maximal doses, then adding submaximal doses to get a cumulative effect of 5 percent at a reduced adverse event rate would be very satisfactory to me.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: Just to follow-up on what Dr. Woolf said about statistical significance, the amount of difference that you can say is statistically significant depends on the sample size. If you have a large enough sample size a tenth of a pound could be statistically significant, and I think there really needs to be a minimal level of additional weight loss that also is statistically significant.

DR. BRAUNSTEIN: Dr. Schade?

DR. SCHADE: I just wanted to follow up on something Dr. Greenway said and many other member of the committee, which is to point out that synergistic weight loss has been shown by several groups in animal studies of combination therapies. To my knowledge, it hasn't been shown in humans but it has been shown in animal studies. So, maybe it is at least theoretically possible that some type of much more effective therapy can be achieved through combination of drugs.

DR. BRAUNSTEIN: Dr. Ryder?

DR. RYDER: I would only comment that we may be at a different place in terms of our learning, but I do think that we should tool up and make sure that the principles that have led us to have successful combination drugs for antihypertensives, diabetics, hyperlipidemics--I mean, this is not the first time that this committee or the agency has been presented with this. We should make sure that we have that learning and use innovative designs as best as we can, but I do think it is probably in the end going

to be a challenge worth facing up to.

DR. BRAUNSTEIN: We will go on to the next question, endpoints. Define obesity prevention, weight maintenance, prevention of weight gain. Are these distinct clinical effects? Are these distinct pharmacological effects? Are studies needed to document efficacy and safety in each? I will open this up for general discussion.

DR. ORLOFF: And we do need definitions if people think it is relevant to distinguish all these effects.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: I think there may be a difference between prevention of weight regain and obesity prevention/weight maintenance. That is, the mechanisms may well be different to stop someone from gaining weight who has never been more overweight than in someone who has had significant loss and preventing them from regaining. But I think the first two, to me, sound pretty much the same, prevention of obesity or weight maintenance.

DR. BRAUNSTEIN: Ms. Coffin?

MS. COFFIN: I would actually disagree. I think that obesity prevention and weight maintenance are different but the prevention of weight regain--of course, I am coming from the perspective of folks to whom weight maintenance means that they have already lost some weight and are maintaining it is different. That would be different than the prevention of the regain so I think they are the same.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: I think the only difference in these really is sort of the group that you randomize to obesity prevention being, I guess, people who are at risk of becoming obese. Prevention of weight regain would be those who had successfully lost weight and now are worried about gaining weight again. So, the populations could, in principle, be different but I think you would still want to use the same endpoints, which is, you know, does the drug compared to placebo show a significant and 5 percent difference between the two groups. So, to me, that is a minor distinction

from means and so I would just say, you know, you can use the same designs and endpoints that we have talked about all along. Maybe you would want to just look at different patient populations that you are randomizing.

DR. BRAUNSTEIN: Dr. Greenway?

DR. GREENWAY: I think that there is a difference between weight loss and prevention of weight regain. At least with the drugs that we have now, if you cause weight loss with diet and then randomize people to orlistat or placebo you get a weight regain that is less in the orlistat group than in the placebo group. But if you get weight loss through dietary means and randomize people to sibutramine versus placebo you get an additional 7 percent weight loss. So, it appears that there are some drugs, presumably the ones that act centrally if that observation is correct, that may do better at working after weight loss has already been induced than starting from the beginning.

DR. BRAUNSTEIN: Any other general

comments? Yes?

DR. HIRSCH: Except that there are special challenge situations, like I mentioned before, like smoking cessation or perhaps pregnancy or menopause--there are periods in which weight gain so frequently occurs. I am not answering the question as to the definition of what would be the suitable thing. I presume that just comparison with a placebo group under these circumstances would be a very helpful thing.

DR. BRAUNSTEIN: Dr. Flegal?

DR. FLEGAL: Maybe I am thinking about this a little too literally, but I see very different issues arising from these three terms. For example, weight maintenance--what BMI level would that go down to appropriately if someone had a BMI of 23 and wanted to maintain weight? Would that be an issue?

There is also the issue of the weight gain that occurs with age, which is extremely common. Would that be something where there would be an indication for weight maintenance?

Also, obesity I interpret perhaps more literally as not meaning overweight but as a BMI over 30. So, preventing obesity would be basically maintaining your BMI below that.

So, I see those as definitional issues about what BMI levels these would all apply to that would be very confusing.

DR. BRAUNSTEIN: Let's go around and ask if anybody has specific comments. Oh, Dr. Schade?

DR. SCHADE: I have one other comment. I think these are different, and they are different in the sense that prevention of obesity can occur in a normal weight individual where the other ones tend to be maybe already starting with a treatment. For example, if you treat somebody with steroids for Graves eye disease for a 3-month period they are all going to gain weight--a well-known effect of steroids. We are now treating their bone disease to prevent them from getting osteoporosis. In that situation I can well see we will need one of these drugs to prevent the obesity that occurs. So, I think these are certainly different at least

in different populations and I think there will be individual studies addressing these. These are not the same thing.

DR. ARONNE: I think as far as the issue of are these distinct pharmacological effects, in some cases it is going to be yes and in others no. An example would be in the case of leptin, for example. I think it would not prevent weight gain but in someone who has lost weight it might prevent weight regain. That would be an example, but that might not be true for other drugs and other situations so I think that there may be distinct pharmacological effects that differentiate these two situations.

DR. BRAUNSTEIN: Dr. Ryder, do you want to add anything?

DR. RYDER: No.

DR. BRAUNSTEIN: Dr. Aronne, any other comments?

DR. ARONNE: I don't think that you need studies to document separate safety but I think that efficacy is the next question obviously.

DR. BRAUNSTEIN: Dr. Wierman?

DR. WIERMAN: I would just say that it seems that we know so little about the maintenance of peak body mass and these different perturbations in all the different systems, both centrally and peripherally, that until we understand the physiology better it is very hard for us to predict if the pathophysiologic states or these different states along the time line are the same or different, or are going to respond similarly or differently to different interventions. So, I think we will just have to stratify in patient recruitment and different types of studies and look at that very carefully.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: I think clear distinctions between these terms will emerge in a clinical context when people start to design studies and they will require, I think, specific applications to the clinical context. If the harbinger is to begin a course of steroids, to begin an antipsychotic medication, etc., those will imply

perhaps prevention. Changes with age may all imply maintenance issues in the context of the study will I think result in emergence of more specific definitions for these terms and we will see that as time moves on.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. S. YANOVSKI: Yes, I think there are at the very least differences between a primary prevention of weight gain, as in the case of smoking cessation, and prevention of weight regain where I think some of the underlying physiology is going to end up being different, and you are clearly going to find weight regain in that second year regardless of what the drug modalities are, at least the ones we have now. I get a little bit concerned about having arbitrarily a 5 percent difference required for that weight regain indication. But I can't pull out of thin air what I would like to see there.

DR. BRAUNSTEIN: Dr. Greenway?

DR. GREENWAY: I think weight regain is different from the other two, and Dr. Hirsch has

spoken very elegantly about the fact that when people lose weight their body is just really trying to get back to their original weight that they started at. So, I think you do have a different pathophysiologic process going on there, and it may very well be a duration effect. After you get over a certain period of time of maintaining somebody at a certain weight they will sort of reset all their homeostatic mechanisms that are trying to make them regain weight and keep the weight off. So, I do think that is a little bit different than prevention or maintenance.

In regards to prevention, my only issue would be, again, a safety issue. If we define a large group of the population who are likely to gain weight because they are sedentary or they only eat Big Macs or they have a strong family history of obesity and we want to prevent that from occurring in that group, the risk of the drugs has to be very, very minimal because otherwise we are going to be doing more harm than good I think in that setting.

MS. COFFIN: The only indicator that I have come across for long-term maintenance of weight is long-term lifestyle changes. So, drugs are going to be a way to get started and at this point we are not showing a weight maintenance so, as I said before, I am not seeing much of a difference there.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. J. YANOVSKI: As I was thinking about the categories here, obesity prevention and weight maintenance could both be terms applicable to individuals who are of normal body weight, BMI 20-25. It could also be applicable to individuals who have lost weight to that point and now want to prevent regain. So, all three terms could potentially be applied to that population. For 25-30, again, all three terms could be applied. In fact, weight maintenance is what we are recommending for the overweight population right now by the NHLBI guidelines. Then, for over 30 it is conceivable that one might consider a drug for weight maintenance or prevention of regain even in

those people who haven't gotten below 30 BMI because, as we know, the folks over BMI 30 are clearly at risk for continued weight gain.

I think that you might conceivably wind up studying these issues, other than obesity prevention, in all three weight categories that we are sort of thinking about. The changes from placebo obviously are going to have to be defined at some level and clinically significant weight change of 5 percent has been proposed so that is perfectly reasonable. Clearly, indications can be sought that are different for prevention of weight regain and maintaining weight. But I think there would have to be sufficient size populations to study these different subgroups and then document safety and efficacy in each of those subgroups. But I do think they are reasonable targets for drugs to seek indications within each of these categories.

DR. HIRSCH: These matters are so complex, it just came to my mind that there is some evidence that smokers in general weigh less than

non-smokers. That is probably one reason for the J-shaped curve of BMI versus mortality, and so on. On the other hand, people who stop smoking seem t have gained weight back to those who never smoked. So, you almost have to ask yourself the question is smoking is being used by smokers to not become obese, then would you be concerned about trying to prevent the obesity that occurs when you have had a successful treatment and you stop the treatment, and you are going to look for another drug because of the possibility of becoming obese? Do you see what I mean? So, the complexity of these things is enormous and this sort of underscores the necessity for trying to figure out how some of these agents work on the complicated system of weight maintenance.

DR. BRAUNSTEIN: I wonder if Dr. Greenway can tell is if that is the reason why bupropion which is used for smoking cessation works, that the patients on placebo gained weight and the patients on bupropion didn't change.

DR. GREENWAY: The lack of weight gain

with smoking cessation is certainly one of the advantages of using that drug and the other drugs that are used to treat that condition.

DR. WOOLF: Dr. Hirsch just reminded me there is another group that fits in the same category, and that is the hyperthyroid patient who, when he becomes euthyroid, gains about 10 percent of their body weight. Could you use a drug to keep them from regaining their weight? I have some patients who are 180 lbs, went to 120 and are destined to go back to 180. Could you use a drug like that?

DR. BRAUNSTEIN: Well, that is a good segway into number seven, which is requirements for approval of treatment or prevention of drug-induced obesity; data on risk for and associated drug-induced obesity by drug; issues of interactions impacting safety and efficacy; criteria for efficacy. Dr. Schade mentioned glucocorticoids as one type of drug associated with weight gain and there are certainly other types. Should a weight-loss drug be indicated for

prevention of that type of weight gain? We will open this up for general discussion. Yes, Dr. Levitsky?

DR. LEVITSKY: The rather remarkable and severe weight gain sometimes associated with type 2 diabetes that we see with some of the psychopharmacologic agents certainly would be an indication for these agents. The question of what your criteria of efficacy would be, I am inclined, because these drugs don't work that well, to look to the Europeans and suggest that in a controlled study you would have to have a 10 percent difference between your control group and your group that is treated with one of these drugs, but that is just an intuitive inclination and there is nothing to back it up.

DR. ARONNE: I think that this is a very complex area, this is an area that we deal with clinically all the time because of the amount of weight that can be gained and the complications. I think using similar criteria to the ones already established would probably be what makes the most

sense but, in general, you would probably design studies like this for when someone gains weight. In other words, you wouldn't start everybody who starts a drug on a preventative therapy but you would set a limit and at that point the preventative drug would be started, and from that point on if the difference was either statistically significant or 5 percent or 10 percent difference evolved, then I think you could say that the drug was effective. Our experience is that we use drugs, other than the drugs that are approved for obesity treatment, so the main drugs that we use are not drugs that are used for obesity treatment; they are drugs for diabetes and for other indications. So, I think that the criteria for efficacy--you know, I just think that we don't have enough data to say what that number is. I think the 5 percent is what I would argue for or statistical significance.

I think the issues of interactions--you know, in many cases they are not very material because you are talking about, in some cases,

psychiatric drugs versus metabolic drugs so but in other cases you are talking about other psychiatric drugs or other epilepsy drugs for the same indication and there those issues need to be addressed. So, I think if the drug is in the same category, then the interactions need to be addressed. But if drug is in a completely different category there may be no reason to be concerned about these potential interactions.

DR. BRAUNSTEIN: Dr. Watts, any comments?

DR. WATTS: No.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. S. YANOVSKI: I just want to agree with Dr. Aronne, particularly for using these medications for weight gain prevention, I think that having a 10 percent difference from placebo would be a very difficult standard to meet because you are really starting out at a lower BMI.

DR. BRAUNSTEIN: Dr. Greenway?

DR. GREENWAY: I would tend to think that there are certain situations, like Dr. Schade suggested, when you start people on steroids and

you are almost sure they are going to gain weight I think that you wouldn't wait for them to do so. I think you would start them on the drug if you had a drug that could potentially help them.

DR. BRAUNSTEIN: I agree. I think the example of using bisphosphonates for glucocorticoid therapy is an excellent example of how you could prevent one condition while you are treating another. But I do think that for each drug for which this would be a labeled indication there needs to be a study that is adequately powered, with a placebo control, to look for drug-drug interaction as well as to show that it does prevent the weight gain greater than placebo alone. Dr. Yanovski?

DR. J. YANOVSKI: I agree with the Chair.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: Just to agree with you too.

DR. BRAUNSTEIN: Dr. Hirsch? Dr. Schade, any comments? No? We will move on to number nine. We have actually covered number eight previously. Number of patients in phase 2 and phase 3 studies;

rationale based on magnitude and nature of efficacy; rationale based on size of target population; rationale based on expectations regarding safety. Open for general discussion.

DR. WATTS: I think the change in weight could probably be demonstrated with a fairly small sample size. I think a number of people have talked about safety issues, and I think that expectations regarding safety should be the primary determinant of sample size and that part of that issue relates to the size of the target population to be treated and the vulnerability of the target population to be treated. So pediatric/adolescents are perhaps more vulnerable to safety issues and older patients with established coronary disease may be more susceptible to certain types of safety issues. There the sample size needs to be adequate--you are not going to have a large enough sample to detect something that occurs 1/10,000 people but you should certainly have a sample size adequate to detect something that occurs more commonly, 1/100 people.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: I would sort of broadly agree I guess on the sample size to show the magnitude of efficacy is going to be relatively small; the size required to show some level of comfort for the safety of the compound. I think we do have to keep in mind the size of the target population when we are worried about safety. So, for a BMI of 25-27, 27-30, which would be a much larger population I think we are more properly concerned about safety. The final point, just I guess depending on the mechanism of action for the drug, we would be more or less concerned about safety based on what you know about it, maybe its history. I actually did some calculations before I came here, speaking about the safety issue. I guess I get some comfort to the idea of having the larger sample size, maybe 1500 so that if the true probability of an adverse event were, say, 1/1000 and we had 600 in each group we would have about a 50 percent chance of detecting an adverse event and about a 25 percent chance of detecting it if we had

half as many, 300 per group. So, you know, more is better and it is based partly on what you think the underlying adverse event rate would be.

DR. BRAUNSTEIN: Dr. Schade, you are next.

DR. SCHADE: I would like to argue for a larger sample size for efficacy because with a small sample size you cannot look within the population that you are studying for subgroups. I think, for example, age and sex are two very important subgroups, and I think the difference between men and women ought to be able to be evaluated within the population, and I think the first tertile and maybe the last tertile, or something like that, in age ought to be evaluated because we have seen a difference in drug efficacy in those two parameters and those are very common parameters, and that doesn't even get to ethnicity issues. So, I think a population of 1500, which would let you look at those very straightforward, simple questions of male versus female and young versus old are very important in drugs that we are going to use in all these populations. So, I

would argue that a larger, rather than a smaller, efficacy population would be advantageous.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: Just to look at the converse, I can't see a compelling reason to try to make all possible efforts to keep the sample size small.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: I agree with Dave Schade for all those reasons, but I would even go above 1500. We are talking about a patient population who has excess morbidity and mortality but it is over a very prolonged period of time, and I think I would like to get a very good handle on safety in this population and in order to do that I need a bigger N. So, 1500 to me still strikes me as very small, particularly since certain trials are in several thousands and that seems to be the bar. I think 1500 is below the bar. The size for phase 2 I think is sufficient to do a dose-ranging trial and to pick up gross toxicities.

DR. BRAUNSTEIN: Dr. Greenway?

DR. GREENWAY: I don't have a particular

number that I am trying to promote but I would like to see it sort of driven on some sort of rationale. If you want to detect something that occurs 1/100 or 1/1000, or whatever that might be, then kind of figure back on your sample sizes and find out how many you really need and what sort of degree of safety you require to feel comfortable. What I am getting here is sort of a feeling that more is better, and maybe it is but I think this ought to be driven by something other than that. With regards to age, I think there is a real argument that could be made that weight loss in the elderly is not an appropriate thing, that it may well do more harm than good.

DR. BRAUNSTEIN: Dr. Aronne, did you have any comments on this?

DR. ARONNE? No.

DR. BRAUNSTEIN: Dr. Yanovski? Dr. Carpenter?

DR. CARPENTER: I was just trying to locate something I read in the handout regarding the sample size calculation to detect a phen-fen

problem, and the numbers that are reported were actually less than the requirement for the sample size at the time that study was done. I think it was used by one of the industry respondents to reduce the sample size requirement. I think the arguments for expanding the efficacy data that one can cull from these studies is a good argument for the 1500 figure. I have not heard or seen an argument that would convince me to extend that beyond 1500 for a phase 3 study for the efficacy component. If Dr. Follmann's calculations are right I would think 1500 would be about in the ball park to detect reasonable safety incidence. For phase 2, I would think this would actually be a much smaller number but I would defer to statistical help for determining that.

DR. BRAUNSTEIN: I don't think the set number should be indicated on the magnitude or nature of efficacy. I think that should be figured out from a phase 2 trial and extrapolated to phase 3.

In regards to the size of the target

population, I am less concerned about that than I am about the safety issues. So, I really think the numbers need to be driven by safety concerns and, rather than have a set number, I would advocate setting a minimal side effect profile for picking up serious side effects, let's say at a level of 1/100, in some populations. In a pediatric population I may want to go even higher than that, depending on the population. But certainly a minimum of 1/100--a sample size large enough to pick up a side effect that occurs with a frequency of 1/100.

DR. ORLOFF: I just want to clarify the way we think about these numbers. A 1/500 adverse event in 1500 patients exposed, assuming that there is no time factor, if you don't see a case you have a 95 percent confidence that you have excluded the 1/500. I guess the other way of looking at it is if it does occur in 1/500, you have a 95 percent chance of seeing one case in 1500 patients. If you see one case and it is sudden death, it doesn't get you anywhere.

So, this is the problem we face over and over and over again. That is really where we stand. As I said in my introduction to this, we do rely heavily on preclinical signals. We do rely heavily on, obviously, pharmacologic mechanism. We do rely heavily on surrogate markers, laboratory markers, as well as on--well, I guess those are the big ones.

DR. BRAUNSTEIN: I think the point is though that although the harmonization document and several of the written comments from industry suggested that we should lower the number to a total of 100 at one year for safety/ efficacy, I think that is much, much too low, and I can't imagine that we will find a side effect that occurs with a frequency of 1/100 and be pretty sure that that is related to the drug at a level of that. So, my gut reaction is, going back to the original meeting where the guidance was formulated, the statisticians at the time had figured out around 1500 in order to pick up, as I recall, a side effect profile of 1/100 with a certain degree of

statistical assurance. So, that number probably is pretty good. I would use that as a rationale rather than just picking a number out of thin air.

DR. WOOLF: If we are talking about a drug that is potentially going to be available to millions of people, and if we have a severe drug reaction of 1/1000 and we have 5 million people being treated, that is 5000 people, which is far in excess of what it took to get troglitazone off the market. We are talking about a drug that is meant to treat morbidity and mortality over the very long haul, not for the short term. So, I would argue vociferously that we ought to exclude the likelihood of a severe problem with 1/1000 and do the statistics to find out what the number would have to be to exclude that, and it is going to be a few thousand.

DR. BRAUNSTEIN: I think one has to weigh the practicality with what is reasonable and protective of the population, which is one of the reasons why I would strongly advocate for second-year safety data, as well as sort of

long-term follow-up information, which is how the troglitazone problems were picked up. They weren't picked up in the original trial.

MS. COFFIN: The justification that I saw for 1500 made sense to me. Also, a population of that size means that you are going to get more of a cross-section and you are going to be less likely to have excluded all of the people who aren't going to show well. So, that seems to make sense, the 1500 at a minimum.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: I agree that safety is driving this and we should make our determination about numbers based on calculations of what we want to be able to detect. I think the 1/100 number maybe a little too common for me. I think I would prefer something like maybe 1/500, something between 1/100 and 1/500.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: I think I would agree with the principle that the safety is the issue that we should be using to do these calculations,

and I also agree with Dr. Woolf's comment that we are talking about drugs that might go out into millions of individuals so that our bar has to be very high for making sure we are not going to ultimately do harm. So, certainly not reducing the number below 1500 and then using things about the pharmacology of the drug that might predict toxicity as a way of driving the number up. I am curious, for example, why we ended up, Dr. Orloff, with thousands of patients in the statin trials. How did you get to that figure as opposed to 1500 here?

DR. ORLOFF: We were just asking ourselves that, as a matter of fact. This is not pertaining to statins but clinical trial programs are designed around demonstration of efficacy primarily. That is how trials are powered. And, the requirements with regard to safety are ultimately arbitrary. So, we don't really have a reason. I think it is striking and I am glad it has been emphasized here--it is striking how relatively small the exposure requirements have been for obesity drugs.

I can't speak to the actual numbers of patients who were exposed but the requirements that are cited in the comments to our guidance are actually small compared to diabetes, lipids, osteoporosis. So, we will take that back for consideration.

DR. BRAUNSTEIN: Dr. Hirsch?

DR. HIRSCH: We are not dealing with drugs that we have talked about that are going to eradicate obesity so, you know, they have fairly low efficacy under the best of circumstances and in an enormous potential target population. So, I can't see any good rationale for reducing the number of people studied. I would like to keep that as high as we reasonably can.

DR. BRAUNSTEIN: Let me ask the committee members again to try to, you know, take into account sort of the clinical experience here, what frequency of side effects, what sample size or what should we be aiming at as far as being able to pick up side effects, 1/100, 1/500, 1/000, just to give a sense to the FDA as to what we think would be reasonable with this group of drugs, is that fair?

DR. ORLOFF: Let me just say someone made mention of the troglitazone issue, 61 cases and I believe something over a million prescriptions, at least from IMS. I think 31 deaths were reported, and one never really knows what the true numerator is from spontaneous reports--31 deaths, I believe 2 million prescriptions, although I could be wrong.

DR. WOOLF: Glenn, define serious side effects. Define side effects. Are we talking about life-threatening side effects?

DR. BRAUNSTEIN: What I would call clinically significant side effects. I don't mean, you know, hemoglobin going from 40 to 39.5. I mean significant three times elevation of liver function tests, creatinine that goes up, rhabdomyolysis, something like that. That is what I consider to be clinically significant side effects.

DR. ORLOFF: Let me also say that in our approach to adverse effects of drugs, obviously, we worry most about the irreversible ones. When it comes to other kinds of side effects, even if serious, we make a judgment in our overall risk

management for a drug as to how effective we believe the labeling will be, whether the side effect is monitorable under standard or at least readily available clinical care situations. So, again, something like a little drop in blood count that might merit stopping the drug, if that is something that can be monitored and it doesn't occur in a huge proportion of patients--I mean, I think that is one question you are asking.

The other question is perhaps the one that we tend--not tend to but the one that we have nightmares about is the big unknown. You know, 1500 patients so you are pretty sure that you are not seeing anything horrible at a rate greater than 1/500 but 1/10,000 is still pretty bad.

DR. J. YANOVSKI: Is there any thought of developing postmarketing programs, similar to what we do for growth hormone in kids, for obesity agents? Given the tremendous exposure to the population, is there a role for that sort of thing?

DR. ORLOFF: Yes, and these are cumbersome undertakings. We actually have one in place now

for Forteo, which is human recombinant PTH for osteoporosis, and based upon the preclinical finding of osteosarcoma in rats with that drug, really the consensus that this could not be excluded as a potential risk to humans there are limitations not only on the eligible treatment population but the marketing, detailing of the product, and then there is actually a system of surveillance in place that involves capturing all the incident osteosarcoma cases occurring around the country and essentially, if a signal arises, working towards a possible formal case controlled study. So, those are possible.

Again, case control studies for cardiovascular disease death in a population that is taking all manner of drugs is a pretty complicated, maybe fruitless, undertaking, from the little I understand of it.

DR. WOOLF: As I recall, David, with Crestor the committee recommended surveillance for proteinuria and hematuria post approval. The drug has been on the market for about a year. Do we

have any information?

DR. ORLOFF: It is always one step forward and two steps back with this committee--no, I am kidding! To update you, I will just say, without going into the details, that we actually have ongoing surveillance of the incident spontaneous reports. There is no formal postmarketing safety study but we are looking at those reports both from the standpoint of their numbers relative to prescriptions compared to other statins, but also with regard to the clinical nature of the reports just in the event that even given the inadequacy of that system something peculiar and remarkable comes out about the kinds of cases that you see with Crestor as opposed to with other statins.

So, we do have methods. None of them is perfect. But let me just say again that I think Dr. Braunstein's question is a good one and it is worth just hearing some thoughts about it. We are never going to have 100,000 patient pre-approval exposures for every drug in the pharmacopeia. And, I am a believer that the answer doesn't necessarily

lie in a total mortality trial either. The example I always raise is that BeCalm in patients with hypercholesterolemia and cardiovascular risk would have won against placebo in an endpoint trial, even as Zocor, Lipitor, and so on, do.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: I think there are just a number of issues about possible side effects that make it hard to come up with the right number--severity, the timing, some may occur without a lag time some may have a lag time--you may get some idea from preclinical work, certain body systems that might be more likely to be affected; others may come out of the blue. You have to be reasonable in the study design but also have some type of additional--the next question is the need for an open-label study so if you had a year- or 6-month even placebo-controlled study you would have another year where potentially twice as many subjects are on drug to being to look for safety issues that might delay approval or put in place a phase 4 monitoring program. DR.

BRAUNSTEIN: Let me just try to rephrase the question so I can get off this and go to the next one. We have had three estimates out for what people would be comfortable with for an initial one-year safety trial to figure out the number needed to treat with the drug in order to pick up side effect incidence at different rates. So, I said 1/100. Dr. Woolf said 1/1000. Dr. Follmann I think said 1/500. So, we have three numbers out there and we sort of want everybody else to sort of weigh in with what they would be comfortable with, and we are just defining it as a significant clinical side effect. Dr. Aronne?

DR. ORLOFF: You know, it occurs to me we really need somebody from Las Vegas on this committee!

[Laughter]

DR. ARONNE: I would say 1/100. It is interesting because in talking to the kind of patients we see, BMI greater than 40, they have 1/100 or 2/100 chance of dying and, yet, they are still willing to go for surgery they are so

desperate for treatment. So, in my mind, a 1/100 chance of a significant side effect would be a reasonable one.

DR. BRAUNSTEIN: Dr. Schade?

DR. SCHADE: Yes, 1/100 sounds reasonable if that equals 1500 people in the study.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: That sounds good to me.

DR. BRAUNSTEIN: Still 1/1000?

DR. WOOLF: I will hold.

DR. CARPENTER: I am in the 1/500 camp. I think we have to be a little tighter with it.

DR. S. YANOVSKI: One in 500.

DR. FLEGAL: I would say 1/500.

DR. GREENWAY: I would say 1/100 if that is what is being used now. We have had bad experience with obesity drugs but it hasn't been due to not picking it up in these early stages.

MS. COFFIN: I will go with the 1/500 only because it will be extrapolated so much.

DR. LEVITSKY: Yes, 1/100 if your BMI is 40; 1/1000 if your BMI is 27. That is the problem

with these decisions.

DR. J. YANOVSKI? I would to with 1/500 for adults and maybe a lower number for children.

DR. SCHAMBELAN: I will see 1/500 and I will nominate Jimmy-the-Greek to serve on this committee the next time.

DR. HIRSCH: One in 500.

DR. BRAUNSTEIN: Question number ten, need for second year of open label study, rationale based on nature of drug, toxicity acute versus cumulative. Open for general discussion.

DR. ORLOFF: This question relates, as I think I said before, to what is the utility of that second year. It is open-label. You don't have concurrent control. Does anybody have any sense based on experience with other drugs in the pharmacopeia as to how we should think about this?

DR. J. YANOVSKI: I think the main reason we, in the obesity community, want to see longer treatment studies is because of the return to baseline phenomenon that occurs. We see plateau at 6 months, maybe maintenance over the next 6 months

but then there is an inexorable decline the question is how bad is it. You know, if we are going to recommend that a drug be used for 50 years in some individuals we would like to know that it lasts longer than a year. So, I don't think it is really the toxicity issue per se that makes us want to see the two-year data. It is really knowing whether there is any remaining efficacy.

DR. BRAUNSTEIN: I am also interested in looking at toxicity over a period of time. The issue with phen-fen, as was pointed out, may very well have been a chronicity issue and how long the drug was used, not just being picked up in short-term trials--

DR. J. YANOVSKI: I didn't mention this but almost certainly these trials are going to be with limited number of subjects. If we are talking about detecting a 1/500 chance, there is no chance of that with a few hundred that we are going to be able to study for a second year.

DR. ARONNE: I think it is also valuable having the second year to keep people in the trial

for the first year by dangling the hope of getting the active compound in the second year because most of the people that come to the trial do want the drug.

But one of the questions I have is why can't the drug be submitted after one year when the data is accumulated after one year? If we are doing this primarily for toxicity, why can't the drug be submitted sooner than having to wait until the end of the second year?

DR. BRAUNSTEIN: I think from a practical standpoint--correct me if I am wrong, David, if there is a one-year efficacy and safety trial before the data can be submitted to the FDA the last patient in that trial has to finish the trial before the blind is broken, the data is analyzed by the company, written up for submission to the FDA, goes to the FDA, there is about a 90-day evaluation period--so, in all practicality, by the time it comes before the FDA there is probably going to be close to two years worth of data accumulated anyway if there is a requirement for an ongoing safety

study.

DR. ORLOFF: This is actually an issue that comes up quite frequently as well. We have a policy that we increasingly try to enforce that an application should be complete at the time it is submitted to the agency. So, even if there are ongoing trials, the extent of the efficacy and safety data that are included in the initial report to the FDA should be what is deemed, on the part of both the agency--presumptively deemed--and on the part of the sponsor, based upon the sponsor's analysis, sufficient to support safe and effective use according to the proposed labeling.

So, yes, we do have lots of trials that are ongoing. There are regulatory requirements for safety updates 4 months after submission and then 120 days in advance of the user-feel determined action date, should the application go past that date in review. Anyway, the point being that we get what we ask for and we have to ask for what we want, and we increasingly are discouraged from saying, well, send us one year's worth of data on

day 1 but, given the fact that you have a rolling enrollment, given the fact that trial closure and data analyses cleaning and reporting takes a certain amount of time, we realize that just a few months into the application review we will be able to get the report of the next 6 months worth of data. If we believe we need that, we are going to ask for it up front.

DR. BRAUNSTEIN: I guess my question was if you have a trial that is designed for one year of efficacy and one year of safety for approval--and I assume the approval would only be for a year's period of time if that is all the data you have available for use of the drug--but you have also requested a second year open-label extension, but not for approval but for review by the agency and presumably for presentation for the advisory committee, or what data is available, since it is open-label, that data should be available at the time of the committee. Isn't that what sort of practically happens? There have been a number of drugs where we have had safety updates

that were not submitted in the original application.

DR. ORLOFF: Increasingly we don't like to proceed along those lines. Our principles are around putting our own eyes on the information. For example, we do not want to come to an advisory committee and have information presented at the advisory committee by the sponsor that we have not been privy to in advance.

DR. BRAUNSTEIN: Dr. Greenway?

DR. GREENWAY: It is my impression that the toxicity that has been identified with the drugs that we have studied so far has been identified during the first year. I am not sure that that second year really serves very much purpose except to hold things up for another year. I personally would sort of okay not including that. I don't think it adds much in the way of safety and doesn't even have the control group that you would like to have to compare with.

DR. FOLLMANN: I think if the issue is an issue of safety the benefit of the second year is

not that great. I think if you are concerned about safety you would want to have more patients followed initially for the first year and base your safety decisions on that more pristine cohort rather than what happens in the second year with the dropouts, and so forth. So, I don't see a strong rationale for that.

DR. CARPENTER: Just a question about the nature of what happens in practice when these longer studies break the blind and an open-label component goes on, in practice does the degree of monitoring change? Would we feel less comfortable with the data obtained during the open-label phase of the study in terms of its quality than during the initial year, in this case, where the real meat of the comparison with the placebo group is going on?

DR. BRAUNSTEIN: Certainly you lose the placebo control so any placebo effect, either positive or negative, on the side effect profile is going to be gone. Dave?

DR. ORLOFF: Well, just to wrap this up,

the message that I have heard is that we ought to give consideration possibly to increasing exposure in the first year--collectively, all this discussion about sample size and exposures, increasing the exposure and experience in the first year while foregoing the extension into the second year because of the minimal utility with regard to certainly safety, and there is some disagreement about its utility with regard to durability of efficacy.

DR. BRAUNSTEIN: If it is one-year safety data then I would like to go to 1/500 instead of 1/100. Dr. Hirsch?

DR. HIRSCH: I am very much for having the second year because I am much more interested in the dropout rate and monitoring that than the safety issue. I think we obesity this is particularly important. If we look at the data we have on other drugs that have been used for more than one year, you can see that the dropout rate and the efficacy wanders off, and you can't even get an idea of what the trajectory of that is going

to be if you don't have the second year. So, I think that is essential.

DR. ORLOFF: So, that becomes an issue, as both Dr. Yanovski and Dr. Hirsch have said, that relates to sort of full labeling of the drug with regard to expected effects in the broad population that doctors are going to see. One consideration that we might give in this unique instance would be not requiring that small number of patients extended into the second year for the initial approval because it is not truly necessary, perhaps, to deem the drug safe and effective for the proposed use but certainly relevant ultimately to completing the information in the label so that people can understand what they can expect with the drug. That is something we will take back.

DR. SCHADE: I want to make the same comment I kind of made before. The second year I think is valuable because all of a sudden the patients know they are on the drug. Remember, during the first year they don't know if they are on the drug and their behavior may be significantly

different--and we have seen this in the trials I have done, they really know and they tend to have different dropout rates, and they also have different side effect rates. I am not talking about serious side effects. I am just talking about abdominal pain. When they know they are on a drug you will see a whole different profile than if they don't know they are on the drug. We saw that with metformin.

So, I think the second year provides some valuable insight into what the real world is because when we treat a patient they know they are on a drug. You don't give the patient a placebo. The second year gives you that information. The first year doesn't give you that information at all. So, I would strongly support a second year because, again, it gives you different types of information that is much more real world.

MS. COFFIN: From a patient point of view, I think that a second year provides a lot of good information because--I have sort of lost my train of thought at this point. What you were saying

about real world makes a difference, but if we are talking keeping patients, if this is a chronic illness and we are going to treat it as a chronic illness and we are going to use drugs to do that, we are going to need to know what it does past the first 6 months. We know people can lose weight. People have lost weight doing a whole bunch of things, but can they keep it off, and the second year would give us more of that without the requirement that drug companies have no incentive to study it.

DR. COLMAN: Can I ask something? The comments related to the second year, are people suggesting that the ultimate efficacy determination should be made at the end of the study, in other words, at the end of the second year? When do you make the cut for the efficacy of the drug?

DR. SCHAMBELAN: I think the discussion has been around that being at one year but gathering additional data in the second year, including in essence an intent-to-treat assessment of what happens to people over the long haul.

DR. COLMAN: And still under double-blind conditions?

DR. SCHAMBELAN: No, I think you would have to break the blind at the end of the first year, unless you rolled everybody over to active therapy. You know, as your point was earlier to have an incentive to patients who got placebo in the first year of therapy, but I am not recommending that. I think we really ought to do it on the basis of the years.

DR. GREENWAY: Well, from an efficacy point of view, the efficacy takes place in the first 6 months, with the exception of fluoxetine and that was within a year. So, I can't see that one really needs more than a year to determine efficacy of these drugs.

DR. BRAUNSTEIN: Let's go around and query the panel members about how long the trial should be and whether you think there should be a second year of open-label study. Now, our understanding is that if there is a requirement for a second year of open-label study, that study must be completed

before it can be submitted to the FDA. Is that correct? Yes. Dr. Aronne?

DR. ARONNE: This is too difficult. I would say that one year based on what you are saying because, you know, it is just taking so long to get drugs out that I would have to say one year. But they should send you the data on the second year but it shouldn't be part of the requirement for approval. How does that sound?

DR. SCHADE: I again vote for two years because I think these drugs are going to be used for the lifetime of the patient. We are not just talking about one year. And, I think the second year in which that curves in some drugs goes up and sometimes stays flat is very important to see. I think the second year would greatly influence me, as a physician. If all the weight returned to the base of weight by the end of the second year, I could at least show that to the patient and say, you know, you can use this for short term but not for long-term kind of treatment. I think from a physician point of view that extra year is very

important.

DR. WATTS: I agree that a second year would be valuable.

DR. WOOLF: I would give up the second year if I could get the first year to a bigger trial in the first year.

DR. CARPENTER: I think important information comes from the second year. I would be in favor of keeping it. I would ask the question though if the information related to dropout, real-world issues, etc., that second year open-label is intended for, if that data might be answered in a briefer period of time than an entire year.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. S. YANOVSKI: Yes, I think that probably the first year would give adequate data about the safety and efficacy, but I would be in favor of encouraging a second year and perhaps requiring it for the weight maintenance indication that the companies want.

DR. FLEGAL: Yes, I would say that the

data from the second year would be fascinating and very important but I can't see that it would be a requirement for approval. I think that first year would be enough for that.

DR. BRAUNSTEIN: Dr. Greenway?

DR. GREENWAY: Yes, I think that one year is adequate for safety and efficacy and I can't recall that other chronic diseases have requirements for two years. I don't see any reason why obesity should be different.

DR. BRAUNSTEIN: I would vote for one year of efficacy and certainly a year of safety data. I would prefer a second year of safety data but I would not want to see a drug held up from approval if it was successful at the end of one year. Therefore, I would want to see a large N for that one year to try to pick up some of the safety issues.

I would also want to see that the labeling be restricted to just one year for use if it is efficacious over one year, and to be extended beyond that, and if the manufacturer of the agent

wants it extended, they have to do the studies for a longer period of time to show that it remains efficacious. Ultimately, I think the patients will vote with their feet; if they regain the weight they will go off the drug.

MS. COFFIN: One year for efficacy and safety. I would like the second year data so perhaps you could start the application--if it takes an additional 120 days you could start the application 120 days before the second year's end.

DR. LEVITSKY: As I recall the osteoporosis decision, since the measurement was not so accurate two years would be required. Is that not correct, in order to really see whether there was an effect? I think we have some of the same thing here. We need to know the second year outcome for several reasons, not the least of which is that if most of these drugs to tail off after one year we need to know that so that we can then try other drugs at that tailing off period, and if we don't encourage the manufacturers to do the second year we will not have those data in order to

develop those sort of stacked continuous therapies.

DR. BRAUNSTEIN: Dr. Yanovski?

DR. J. YANOVSKI: One year for safety and efficacy, and then a second year open-label.

DR. BRAUNSTEIN: Dr. Follmann?

DR. FOLLMANN: I go for one year safety and efficacy. The second year of an open-label study gives I think sort of weak evidence and maybe, as you suggest, ten years from now we will be doing randomized studies where we get long-term and more global information but to try to get that now within the context of an open-label study I think is not doable. So, I don't have much appetite for it.

DR. BRAUNSTEIN: Dr. Schambelan?

DR. SCHAMBELAN: I would agree also with one year for safety and efficacy and, although I think the data from the second year might be of interest, in the studies that I have done that have included an extended open-label period I have been struck by the absence of a control group and the variable dropout rates so it has been hard to

interpret those data scientifically. So, I think one year would be what I would want to see.

DR. BRAUNSTEIN: I have been informed by Dr. Orloff that the last question that he had for us we have pretty much covered in one aspect or another. So, this completes all the questions.

I certainly would like to thank all the members of the panel and all the presenters for a fascinating day, a very informative day, and ask Dr. Orloff to make final comments.

DR. ORLOFF: I too want to thank all the panelists. I want to thank Dr. Atkinson for agreeing to come to talk to us even though, as matter of the rules, he wasn't able to sit at the table. It was an interesting discussion. We found it very useful. We will take your comments and advice back, review the transcript carefully, and we will take it from here. So, again, thanks to all. Thanks yet again to Drs. Braunstein and Levitsky, and we will see everybody soon. Thank you.

[Whereupon, at 4:08 p.m., the proceedings

were adjourned.]

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