FOOD AND DRUG ADMINISTRATION

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DRUG ABUSE, AND ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEES JOINT MEETING

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CENTER FOR DRUG EVALUATION AND RESEARCH

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OPEN PUBLIC SESSION

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Friday, September 29, 1995

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The Committees met in Conference Rooms G, H, I & J, in the Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857, at 9:00 a.m., Richard Meisch, M.D., Ph.D., and Henry G. Bone, III, M.D., Chairmen, presiding.

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VIDEO TRANSCRIPTIONS

PRESENT:

RICHARD MEISCH, M.D., Ph.D., Chairman, Drug Abuse Advisory Committee
HENRY G. BONE, III, M.D., Chairman, Endocrinologic and Metabolic Drugs Advisory Committee
STEPHEN P. POLLITT, P.A.-C., Executive Secretary, Drug Abuse Advisory Committee
LEO LUTWAK, M.D.
GLORIA TOENDLE, M.D.
SOLOMON SOBEL, M.D.
PAUL LUISADA, M.D.
ELIZABETH KHURI, M.D.
NEMAT BORHANI, M.D., M.P.H.
ALICE YOUNG, Ph.D.
LISA MOJER-TORRES, J.D.
CATHY W. CRITCHLOW, Ph.D.
MARIA I. NEW, M.D.
MICHAEL KLEIN, Ph.D.
CURTIS WRIGHT, M.D.
DOUGLAS KRAMER, M.D.

ALSO PRESENT:

RICHARD ATKINSON, M.D.
DENISE E. BRUNER, M.D.
PIETR HITZIG, M.D.
BELINDA HAYES, Ph.D.
THEODORE J. CICERO, Ph.D.
GEORGE BRAY, M.D.
ROBERT Y. MOORE, M.D., Ph.D.
BRUCE CAMPBELL, M.D.
STANLEY LAWRENCE, Ph.D.
RICHARD GAMMANS, Ph.D.
CAROLYN McCLOSKEY, M.D., M.P.H.
JAMES WRIGHT, Ph.D.
J. JOHN MANN, M.D.
JAMES COOPER, M.D.
MARK DEITCH, M.D.
GARY WADLER, M.D.
LEWIS SEIDEN, Ph.D.
GEORGE RICAURTE, Ph.D.
CHARLES R. SCHUSTER, Ph.D.
ALEXANDER FLEMING, J.D.

A-G-E-N-D-A

AGENDA - (Continued):

P-R-O-C-E-E-D-I-N-G-S

9:11 a.m.

CO-CHAIRMAN MEISCH: Good morning, people. We are going to begin.

Steve Pollitt is going to read the Conflict of Interest statement.

EXECUTIVE SECRETARY POLLITT: Good morning. My name is Steve Pollitt, I'm the Executive Secretary for the Drug Abuse Committee and I'm going to read the Conflict of Interest statement for this meeting.

"The following announcement addresses the issue of conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208(b) Section 3, full waivers have been granted to Doctor Joanna Zawadski and Doctor Cathy Critchlow. A copy of these

waiver statements may be obtained from the agency's Freedom of Information Office from Room 12A-30 of the Parklawn Building.

We would also like to disclose for the record that Doctor George Ricaurte, through his employer, Johns Hopkins University, is involved as an investigator in a National Institute on Drug Abuse sponsored study in certain MDMA and fenfluramine. Although this involvement does not constitute a financial interest within the meaning of 18 USC 208(a), this involvement could create the appearance of impartiality. However, the agency has determined that the interest in the government in Doctor Ricaurte's participation outweighs the concern that the integrity of the agency's programs may be questioned. Therefore, Doctor Ricaurte may participate fully in all matters concerning fenfluramine and its isomers.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we

CO-CHAIRMAN MEISCH: Doctor Wright, we'll start with you.

DOCTOR WRIGHT: Thank you, Mr. Chairman.

For those of you who don't know me, my name is Curtis Wright. I'm the Senior Medical Officer for Addiction Medicine for the Pilot Drug Evaluation staff. I will be leading with some clinical comments, Doctor Klein will follow with some comments pertaining to the specific petition at hand.

Good morning, ladies and gentlemen. Today we are here to consider a petition for decontrol of the isomers of fenfluramine under the Controlled Substances Act. It is a challenging petition for us, for reasons that I hope to be able to explain.

Scheduling under the CSA invokes a system of controls that are enforced by federal authority under the Criminal Justice System. These controls, although expensive, are needed to prevent, identify, deter and punish the manufacture, importation or diversion of drugs into illicit trafficking.

The CSA should be invoked when there is

sufficient evidence of the potential for abuse of a drug substance that control under federal criminal statutes is required.

Your task is to balance the need for control against properties of the substance. Unfortunately, you must do so within the context of changing paradigms for government, popular culture and the scientific community.

For these reasons, the study of drug abuse remains an important scientific activity, for the abuse potential of a drug is ultimately confirmed on the streets of our cities and in the bodies of our citizens.

In your deliberations today, it may be of value for you to consider our own internal standards for abuse potential. In our staff deliberations, we think there are three necessary and sufficient conditions for recommending control under the CSA.

First, there must be evidence the substance is subject to self-administration due to a direct or indirect pharmacologic activity. This may be evidenced from structural relationships, receptor activity, animal testing, human abuse liability testing or evidence of actual abuse and diversion. Please do not fail to consider the possibility of

indirect reenforcement. The scheduling of the anabolic steroids by Congress was not the result of their concern about a perceived direct CNS reward mechanism, but a somatic reward mechanism based on a need to achieve a desired physical status that led to pharmacological self-mutilation by users.

Second, there must be evidence the substance is capable of producing physical or psychological harm and the dose is likely to be abused. Experience has clearly shown that our society is unwilling to consider a substance a drug of abuse unless it can be shown that there is a risk of injury to the user or to the public. We know, however, that many drugs of abuse are self-administered in doses that are far higher than the recommended dosage. For these reasons, you should consider the risk that the dose is likely to be abused.

Third, there must be evidence that there is a substantial risk of diversion of the drug into illicit trafficking on a regional, national or international scale. The Federal Controlled Substance Acts are not only national in scope, but are tied into a network of international agreements that are global in scope. Thus, the mechanisms of state control are more appropriate to outbreaks of abuse that are

limited by geography, in size or by local conditions.

These, then, are the dimensions of abuse liability, evidence of self-administration, evidence of a risk of serious harm, and evidence of a substantial risk of diversion.

I have three other comments. First, I ask you to remember that you are not here to discuss the approval of dexfenfluramine. That is the responsibility of another division, office and committee. Your deliberations should take into account the possible approval of this drug as a factor affecting its availability and its properties, but the two issues are not linked.

Second, you should know that you do not bear the responsibility for the proper use of anorectic agents in the practice of medicine. As you shall hear today, this is the responsibility of state boards of medicine and pharmacy, and I assure you they take it very seriously, indeed.

Lastly, I wish to remind you that the agency does have substantial authority over the manufacture, distribution, promotion and labeling of a drug under the Food, Drug and Cosmetic Act. If you feel that there are not sufficient grounds for continued control, but there are potential abuse risks

associated with the drug in specific circumstances, you may make suitable recommendations regarding labeling, promotion, distribution and post-marketing study to assure that the public is protected.

I ask only that since implementing such restrictions are an expense, not only to the sponsor, but to the public, and to the taxpayer as well for whom we must continue oversight, such that any possible recommendations be limited to those which we really need.

I'd like to turn over to Doctor Klein, who will talk about the petition.

DOCTOR KLEIN: There are eight factors that we must assess regarding the drug fenfluramine and its isomers in making a scheduling recommendation, whether we recommend to keep it controlled or to recommend a de-control action.

As you can see, these factors expand beyond the pharmacology. If the issue is just assessment of the drug's pharmacology, we would just consult our -- and Gilman and we wouldn't have to meet here, but we have to take into consideration the public health risks that are involved.

Now, the basis for the sponsor's petition of March 18, 1991 on the de-control of fenfluramine

and its isomers were, one, the continued schedule of fenfluramine adversely affects medical practices and the patient; two, that fenfluramine is not pharmacologically related or similar to the Schedule II controlled stimulants of which amphetamine is a prototypical example; and, three, fenfluramine is practically devoid of dependence producing physical or psychological properties or other serious adverse effects.

This slide, which is based on IMS data, shows the estimated numbers of prescriptions that totals new and refills in the United States from 1990 through the first two quarters of 1995. So, you see the projected use, which is the red bar, for fenfluramine prescriptions within the United States exceeds one million, which is certainly more than what has been prescribed at least since 1990 for the previous years.

Now, I passed around to the committee members a copy of the product package insert to support dexfenfluramine. I wish to point out to you three aspects to that insert. Number one, there's a warning of the risk of a withdrawal syndrome. There's indications that fenfluramine may give a positive reaction in drug screening that would be interpreted

as amphetamine, and that there's a warning that the drug may give rise to depression or mood disorders.

Now, the WHO database, the World Health Organization's Collaboration Center for International Drug Monitoring provided us some data relative to both fenfluramine and dexfenfluramine. These include 31 spontaneous reports of withdrawal syndrome for fenfluramine and 27 spontaneous reports of withdrawal syndrome for dexfenfluramine. In addition, there are reports of suicide attempts, three reports of abuse for fenfluramine, a few reports of dependence, and no indication of tolerance development.

I would say at this point that Doctor McCloskey, from our Division of Epidemiology, is here and she will talk in greater detail about these numbers later on. I would say at this point that I am proposing to the committee that these numbers give you a profile of the drug's effects.

So, in addition to the pharmacology of the drug which we'll look at, we are going to consider in our public health risk assessment portion of the affect or analysis looking at the following issues, primary pulmonary hypertension and neurotoxicity, which were discussed at length at yesterday's meeting considering the new drug application, and so we'll

just touch on those issues today, but in addition we'll look at the issues of some of the concerns of some of the states in the use of the anorectic drugs, for which many of them have very stringent restrictions on their use, we'll also look at the connection of the depression and suicide attempt issue, the use of what's now termed the fen-phen combination, fenfluramine and phentermine in combination, and the use of anorectics in body building or sports. In addition, representatives of the Drug Enforcement Administration are here today also to update us on any information that they may have relevant to abuse or diversion of the drug.

Thank you very much.

CO-CHAIRMAN MEISCH: We're going to proceed to the open public hearing, and Doctor Lutes is the first speaker. Is Doctor Lutes here?

The second scheduled speaker is Doctor Atkinson.

DOCTOR ATKINSON: Hello, I'm Doctor Richard Atkinson. I'm representing the American Obesity Association Lay Advocacy Group to advance the causes of obesity and obese people. I'm Professor of Medicine and Nutritional Sciences at the University of Wisconsin in Madison, and I am a researcher in obesity

with about 20 years of experience. I'm here to talk about the use of fenfluramine and dexfenfluramine.

Currently, I am the principal investigator on three separate studies that are using the combination of d/l-fenfluramine and phentermine, comprising approximately 2,400 patients with follow-up, in a few people out as long as three years. We have just submitted our data for the first 1,350 patients, of whom approximately 750 had the opportunity to complete one year of treatment.

We have entered the data on each patient, approximately once each month into a database, and thus have a very clear idea of what is happening and are able to capture the side effects and body weight, blood pressure and so forth. What we can report is that, of interest to this particular body, is that in all the patients we've followed over approximately a three-year period of time there's been no evidence whatsoever that there's been any abuse of these drugs, or attempted abuse, or attempted getting additional prescriptions or anything like that.

I have to be a little careful because if I give out all of our data the New England Journal won't publish it, but at any right suffice it to say we saw an excellent weight loss of approximately 15 to

16 kilograms in a year. We had dramatic reductions in patients with hypertension, hyperlipidemia or hyperglycemia. We saw very nice reductions, and, again, this is the combination of phentermine and fenfluramine.

Our side effects profile, the most common side effect was dry mouth. The next most common was constipation. Of concern, "memory loss occurred in 13 percent of people," however, at each visit patients fill out a checklist. And so, at any given time over the period of up to three years, if a patient checked off memory loss that was recorded. We dropped seven patients over the course of the treatment for a short-term memory loss.

We have, by the way, also used paroxetine and phentermine alone, or have treated patients who have used those drugs, and they have shown short-term memory loss.

Our position is that certainly some of the obesity drugs, such as dextroamphetamine, have an addictive potential. The fenfluramine and dexfenfluramine molecules are similar to those but do not -- are not at all adrenergic or dopaminergic. Obviously, they bind to a completely different set of receptors and are serotonin agonists, not an

adrenergic agonist, and for many of the experts on this committee, obviously, you know this, but it seems unlikely that there will be any abuse potential. Our experience suggests that there is not any abuse potential, and the position of the American Obesity Association is that this drug would not be scheduled.

Thank you.

CO-CHAIRMAN MEISCH: Thank you.

The next speaker is Doctor Bruner.

DOCTOR BRUNER: Well, I'm certainly honored to be here before the committee today and to be honored to follow Doctor Richard Atkinson.

I'm a representative from the American Society of Bariatric Physicians, and I also come to you speaking as a private practitioner in bariatric practice in Arlington, Virginia. Basically, the American Society of Bariatric Physicians is a group of physicians of over 600 members who are dedicated to the ethical treatment of obesity. Our society has developed standards of practice which I have included for your information for the committee in your handout to demonstrate our clear commitment to what we believe in. I encourage physicians who are really interested in acquiring more knowledge about the treatment of obesity and prescribing techniques for anorectic

agents to pursue our courses that we offer, and we are headquartered in Inglewood, Colorado.

But, as a private practitioner, I have really treated approximately 9,500 patients over the past 14 years. Currently, I have 428 patients who are in various stages of weight loss and maintenance, and of that group 87 percent are taking either fenfluramine and/or phentermine in combination. And, I can state with clear certainty that I have had no patients abuse these drugs.

In fact, because, of course, as you know, and I won't bore you, because of fenfluramine's serotenergic action it's really devoid of any stimulatory action and, in fact, can produce drowsiness or lethargy. And, based on these facts, I really feel myself, and according to the American Society of Bariatric Physicians, that this drug, fenfluramine, should really be descheduled.

Another reason for deregulation involves state medical societies, and I really speak as a veteran of fighting the Virginia Board of Medicine, about this same time last year. The rigidity of scheduling drugs seems to filter down to the state regulatory level, whose medical boards can actually set up barriers to the availability of therapeutic

treatment regimens. They seem to only remember the long-ago days of amphetamine use for weight reduction and consider the newer anorectic agents automatically guilty by association. They lose sight of the fact that obesity, like hypertension, is a chronic disease with multiple etiologies, and that pharmacotherapy can have a place in its treatment.

In Virginia, I wish to quote you the Board of Medicine statute that is currently in effect. It states: "It shall be unprofessional conduct for a physician to prescribe amphetamine-like drugs, Schedule III and IV, for the purpose of weight reduction or control in the treatment of obesity, except as a short-term adjunct to a therapeutic regime of weight reduction."

Well, I found out about this regulation in reading my quarterly newsletter, which the Board of Medicine happens to publish in, it's called the Richmond Times Dispatch. This paper is not available in Northern Virginia. And needless to say, after my office manager picked me up out of the floor, I immediately underwent legal processes to repeal this regulation.

But, during the course of the preliminary hearings with the legislative committee, it was

obvious that no committee member had even bothered obtaining any objective information regarding the anorectic agents. Not one member was familiar with Doctor Michael Weintraub's hallmark study in May of 1992.

Their judgment was based on several anecdotal stories which date back to the amphetamine era and not credible scientific publications. After presenting my testimony to the committee, which included a 245-page compilation of current information which included letters of support from Doctor Richard Atkinson, Doctor Sidney Schnoll and Doctor Mike Steelman, the committee agreed to rewrite this regulation, but it's going to take two years.

Now, the Board of Medicine in Florida has attempted to impose similar regulations. However, the ASBP found out about this before they were enacted, and it's a direct result of our efforts. On October 28th, Doctor Michael Weintraub, Doctor George Bray, Doctor Richard Atkinson, Doctor Theodore VanItallie will be appearing before this committee, and the State of Florida has invited all the state medical boards to that meeting. We really consider that a hallmark.

So, in summary, I wish to say that I, and the ASBP, support the deregulation of fenfluramine for

the following reasons: it has no abuse potential, and, most importantly, the FDA action would be instrumental in removing restrictions placed by boards of medicine that impede our ability to deliver the best care for a condition that affects 58 million Americans.

I thank you.

CO-CHAIRMAN MEISCH: Is Doctor Lutes here?

Doctor Hitzig will be the next speaker.

DOCTOR HITZIG: My name is Doctor Pietr Hitzig and I'm an internist in the Timonium area of Maryland.

Over the last three years I've treated more than 2,000 patients with what I call fen-phen, and have found it to be a remarkable agent. As a dopamine and serotonin agonist, that is an increase of a dopamine serotonin, these two drugs exert great effect on the entire body in many different systems.

Originally, as an anorectic, I have discovered that these two drugs have been successful in stopping the addiction to alcohol, cocaine, heroin and other addicting substances.

Excuse me, sir, I haven't taken my fen-phen yet.

Dopamine and serotonin have totally

reciprocal actions. What I mean by that is, dopamine, for instance, increases body temperature, serotonin decreases it. Dopamine increases blood pressure, heart rate and pulse, serotonin decreases it. Prolactin is increased by serotonin and decreased by dopamine.

The two parts of the immune system, which are now very much invoked, the TH-1 and the TH-2 cycles -- TH-1 and TH-2 divisions, the TH-1 type increases the cytolytic capabilities of the immune system. I mean by that that it is able to go out and take care of abnormal cells, bacteria, fungi of cells infested with viruses and cancerous cells. While dopamine increases those, serotonin decreases them.

Serotonin increases the TH-2 side, the side that is the side responsible for antibody formation and the dopamine decreases it.

I started first treating patients with alcoholism in December of 1992. Patients craving alcohol are treated with medications, fenfluramine and phentermine, and within 90 minutes, if they are having craving when they are in the office, they lose their craving. If they are having craving later at an expected hour they do not develop craving for alcohol at that time. The same is true for cocaine and

recently for heroin.

DOCTOR WRIGHT: Mr. Chairman, because of technical difficulties, can we extend Doctor Hitzig's time a little bit?

CO-CHAIRMAN MEISCH: Thank you, I will.

DOCTOR HITZIG: What did you say, sir?

DOCTOR WRIGHT: I was making sure that you were not penalized in time for the technical difficulties that we're having with the projector.

DOCTOR HITZIG: Fine, wonderful.

As I mentioned before, the relationship between dopamine and serotonin is one of converse symmetry. The blood pressure is increased by dopamine, decreased by serotonin. The blood sugar is increased by dopamine and decreased by serotonin. Prolactin vice versa, and so. In mentation, dopamine makes you more alert and serotonin, as we well know with alcoholism, makes you dumber.

The reward seeking behavior is increased with dopamine and inhibited by serotonin. In fact, dopamine is equivalent to Freud's head and serotonin is equivalent to a super ego.

As I said before, we have divisions in the immune system, and these divisions were described by Doctor Ruscetti as a yin-yang, a paired and polarized

system. I think he was very prescient when he did so.

The psychological tests we did in the alcohol study, which I'll show you shortly, measured somaticism, which is very much invoked now because that's primarily fibromyalgia, obsessive compulsive behavior and drug-seeking and alcohol-seeking behavior to the internist is exactly the same behavior as an obsessive compulsive trait.

Interpersonal sensitivity is a fancy way of saying low self-esteem, the higher the score the lower the self-esteem.

Somaticism obsessive compulsive in my viewpoint are driven by dopamine deficits, and depression is due to a dopamine deficiency. Anxiety, phobia, paranoia and hostility, in my framework, are the flight or fight responses, the acute response to stress, and those are initiated with a low serotonin.

Psychotocism, which I prefer in my patients to call muddled thinking, is clearly dopamine driven. The global severity index is a composite of all of them.

I started in the last four months of 1993 with 54 -- a total of 54 alcoholic patients. Twenty-seven of them were severely depressed and 19 of them were the cohort.

Here's the median scores. The top of the line is three standard deviations above the norm, right there, and you can see that these median scores at three standard deviation, which are the top one tenth of one percent, are extremely high. This was an extremely scaled group. Two of the men were acutely intoxicated because of the severe craving for alcohol, seven of them were cocaine -- co-addicted to cocaine, one co-addicted to three agents, heroin, cocaine and alcohol. Two of the patients also had early signs of withdrawal.

Within 19 minutes, every one of the patient's craving lost their craving, not only for alcohol, but also for cocaine and also for heroin. Two weeks later, 16 out of the 19 had psychological scores that had returned to normal, that had become normal, and the other three became normal with slight adjustment of the dopamine agonist phentermine.

You can see the remarkable differences between the median on both sides. Look at the hostility. We wouldn't be entertained by the O.J. Simpson came if he and Nicole had both been taking the medication.

Six months later there was a remarkable normalcy to this testing material. Only two patients,

we had one sub-scale score that was touching on the abnormal range. I've got a disparity between the 16 and 19 that was corrected, it is 15 patients and the numbers up there should be 78 percent.

We already have many examples of dopamine and serotonin agonists working together to treat multiple conditions, and these are just some of them. Psychiatric disorders, when treated by MAO inhibitors or antidepressants are basically being treated by dopamine and serotonin agonists.

Migraine, which responds very well to fen-phen treatment, has been treated in the past by other drugs that are dopamine and serotonin. Leprosy is being treated with thalidomide, a dopamine and serotonin agonist. And, in cardiac transplantation, bromcryptin, which is one of the classic dopamine agonists, is paired with cyclosporin, clearly an anti-inflammatory TH-2 promoting agent.

Here are some more of them. We have, obviously, fen-phen has been well documented by Doctor Michael Weintraub as a treatment of obesity, and I want to say thank you if he's in the audience, I want to say thank you for changing my life.

The rat model and the mouse model for alcohol, done both at Rutgers by Doctor Hans Fischer

and done at Princeton by the group with Bart Hobel, have shown consistently that alcohol consumption in alcohol addicted mice is successful. It stops also alcohol withdrawal seizures, a clinical finding that I've also seen in the office. In fact, one of the patients who came in for the study had such severe tremors he couldn't pick up a Dixie cup, but after 90 minutes he could pick it up with two fingers. Incidentally, it also takes care of hangovers in 15 minutes.

To continue on other treatments, xanthines are being used for asthma and even marijuana is very successful in the studies of the '70s to be effective against asthma. Immune deficiency is currently being treated with xanthines, pentoxifylline and also with thalidomide.

Here is a list of some of the diagnoses that I've had successful treatment. Psychological disorders include those difficult ones, chronic fatigue, chemical hypersensitivity, fibromyalgia. Fibromyalgia is an extremely common condition, it affects more than 25 million Americans. It is about to be studied extensively at the University of Wisconsin by Doctor Dan Malone.

SADS, currently being treated with an

antidepressant and with lights, is now 100 percent being successfully treated with fenfluramine and phentermine.

Attention deficit disorder, an epidemic of which is raging in this country, is markedly responding to the same treatment, and PMS, the symptoms of PMS, depression, irritability, hostility, menstrual cramping, and even engorgement of breasts with pain are all responsive to adjustment of dopamine and serotonin.

The addictions, as I mentioned before, alcohol, cocaine, narcotics, interestingly enough narcotics did not fall until the addition of a precursor for serotonin, 5-hydroxy-tryptophan.

PCP, the only one that totally sticks its head above the water now is nicotine, but Linda Farragut, who might be in the audience, is making strikes on that out in California.

Obsessive compulsive disorders it's 100 percent if a patient continues to have, let's say, nail biting, or hair touching, it serves nothing more than a guide is that you need more dopamine.

Bulimia, an attractable condition frequently, is now responding, 22 patients who have been treated, 22 have had a resolution of their

problem, and these are graduates of tertiary care hospitals, may be the first quadinary care center.

Immune disorders, 100 percent, or very nearly. You can take patients refractory to treatments with high dose steroids and all other appropriate medications and resolve the problem.

Hay fever is one more guide to whether you have sufficient dopamine. Anaphylaxis or allergic shock has also been remarkably resolved with this, and hives are the same.

Those are problems that are due to excess of serotonin and can be alleviated by the increase of dopamine.

On the other side, at least of the autoimmune disorders, I feel that most of the will respond to the increases of serotonin or increase in the TH-2 side of the immune system.

I've had three patients with HIV, two of them were cocaine addicted, depressed and also with HIV, of course, and they resolved their cocaine and depression as expected, and one doubled and one tripled his T-cell count. The third case, a man in his 50s, a long-time survivor of HIV, was in his terminal stage, he had a T-cell count of five, he had anxiety, depression, anorexia, wasting, thrush, yeast

infections, pneumonia, abdominal pain most likely due to inflammatory bowel, and he hadn't had a normal bowel movement for more than a year.

I told Fred that we would go first to treat his anxiety and depression, and that resolved after three days, all of his other conditions improved.

This is too busy a slide to really go into too deeply, but I believe it's the mechanism of how HIV works. The fine work of people like Raymond Brown at the University of Wisconsin, and Melvin Hayes at the NIH, has shown that the metabolic pathway of tryptophan is perverted by enough numerous agents. Instead of going down to form serotonin, it instead goes down massively to this pathway, and on to quinolinic acid. Quinolinic acid is a strong neuroexcitatory, neurotoxin for dopamine cells, and, therefore, dopamine is reduced in HIV, I believe.

Tryptophan, metabolism, the serotonin is markedly decreased and there's a loss of dopamine and serotonin as a result. It has been clearly established that patients with low dopamine and low serotonin have a markedly damaged immune system, and so, after that occurs we have a vicious cycle going on with HIV and the decrease in serotonin and dopamine.

I postulate that the marked deficiency of tryptophan, which is an essential immunoacid, it cannot be ingested, I mean, it has to be eaten, it can't be manufactured, caused by tumor necrosis factor, cytokines, tumor necrosis and interferon deplete the body of tryptophan, and as a result the body is forced to cannibalize on its own non-essential cells. I think the term is called wasting. In fact, tumor necrosis factor has another name, and that's called cachexin, because of its noted wasting characteristics.

The condition pellagra, which was endemic in the poor in England in the 19th Century, suffers from -- and that was supposedly corrected last night -- dermatitis, dementia, diarrhea and to death. As an internist that sounds awfully like AIDS.

Fen-phen also treats post-traumatic stress disorders. Vietnam, I have several cases of it, and so does Doctor Dan Malone out at the University of Wisconsin. We just submitted a grant to the Department of Defense for Persian Gulf illness, another that now the appropriate name for Desert Storm.

Nothing is new under the sun, but what the great man said, the humor is controlled, and by humors

I think we mean -- humors, I think we can say dopamine and serotonin control man's pain and health. Good health exists when the humors are duly proportional, and pain is felt when one of these humors is deficient.

Thank you very much.

Any questions?

Thank you.

CO-CHAIRMAN MEISCH: Doctor Bone, you are going to present a summary.

CO-CHAIRMAN BONE: I'm Doctor Henry Bone, I chaired the Endocrinologic and Metabolic Drugs Advisory Committee meeting yesterday, to which the registration of dexfenfluramine for long-term treatment of obesity was discussed.

As many of you are aware, the final decision of the committee, or recommendation I should say of the committee, on this subject is still pending for reasons that I will explain.

Because of this, I will, perhaps, take one or two more minutes than I otherwise might in order to give you a flavor of the discussion, so that you'll be informed as to where we left things.

The committee was really asked to address a series of questions, as is customary, and the first

question had to do with whether the evidence for efficacy was adequate to warrant approval for the indication of long-term or indefinite use.

The clinical trials for this indication were completed long before the recent formulation of guidelines for this indication, and I think this was taken into account in evaluating the information presented.

While the studies, and particularly the long-term study, did not meet the primary criterion of showing a mean weight loss of more than five percent, in comparison with placebo, that is to say five percent more than the placebo, five percent of baseline weight more than placebo, the median did, and there were significantly more responders at five and ten percent levels upon treatment than on placebo.

The committee voted that the efficacy data were adequate, although there were a number who agreed with a comment that the data on effects of treatment on obesity associated conditions was somewhat less than we would have like to have seen, especially in the long study, that the so-called co-morbidities would have liked to seen more data on that.

The major discussion centered around the safety issues. There were two main areas of concern.

First was the issue of pulmonary hypertension, which is certainly associated with the use of the drug, particularly when it is used for more than three months. This condition is usually fatal, so any prediction of reduced morbidity and mortality due to weight reduction must be balanced against the deaths which would likely be caused by the drug. Fortunately, even though the risk is increased the number is still probably in the range of tens -- say, 20 to 100 per million various estimates were provided, and I don't think we have an exact figure, but this was regarded as an infrequent event, very infrequent event.

There was more uncertainty about the question of neurotoxicity, and this is where the major part of the discussion concentrated. Invited speakers presented some information which was particularly worrisome regarding the evidence they presented for axonal degeneration and subsequent abnormal regeneration of fine fibers from the dorsal raphe.

The clinical implications of this were somewhat unclear, as the function in humans of these fibers was not really predictable.

The sponsor took issue with this or disagreed with these findings on two grounds. One was

in terms of the significance of some of the findings, as, perhaps, being more related to the desirable action of the drug, and the degeneration and regeneration issues the sponsor said had not been reproduced in their laboratories.

So, we made quite an attempt to achieve some closure on this, but it was impossible to do that in the course of the meeting, and it may that some additional studies will be necessary to achieve closure on that issue.

Furthermore, it was noted by the FDA reviewer that in the sponsor's long-term carcinogenicity studies in rats and mice calcifications were found in the brain at higher rates in the treatment groups than in placebo-injected controls -- or, placebo-dosed, I'm sorry, controls.

The medical -- as the sponsor again pointed out, the medical significance of these calcifications was not clear.

From the standpoint of clinical, you know, toxicity information, this was much less specific, although -- well, the areas of anxiety and depression were not discussed in as much detail. In the clinical trials, at the recommended dosage of 15 milligrams BID, the rate of abnormal thinking was similar between

the treatment and placebo-treated groups, but at the higher dose of 30 milligrams of BID it was a rate of about ten percent for this finding, 10.3 percent in the treated patients versus the 1.2 percent in placebo patients, and this was calculated to be significant with a p value of less than .03.

Although there was some concern expressed that in the absence of a specific set of science and symptoms such association might not be apparent, mental impairment of the type described has not emerged as a problem, we were told, in the spontaneous reports based a very extensive post-marketing experience over the last decade in Europe.

With all this in mind, the majority of the committee voted that the safety data at this point were not adequate for approval. I suspect that the absence of the additional co-morbidity data may have been a factor in weighing this on a risk/benefit basis. However, we came back to this issue later.

The third question asked of the committee had to do with what might be required in Phase IV if the drug were approved at this point, and there was discussion about a suggestion of a two-year study in which evaluation of the sequelae of obesity, the co-morbidities, would be of prominent important. This

would be looking at things like cardiovascular incidence, for instance.

Since the committee had already voted that the safety had not been sufficiently well established, the implication was that the drug would not be recommended for approval without resolution of those questions, so I asked the committee, rather than looking at this as a strictly Phase IV question, but I asked the committee members whether they favored carrying out such a study, irrespective of whether it was done in Phase III or IV. All the committee members favored doing such a study, but in the course of the discussion there appeared to be additional concern emerging about the public health and other implications of deferring approval.

In that context, the Center Director, Doctor Bilstad, asked the committee to address a further question, which was explicitly whether the drug should be recommended for approval at this time, and essentially combining the first and second questions in a more explicit way.

Since some members of the committee had actually left by that time, and it was late in the day, the voting has not been completed on that question, and I think that's the point at which things

were left, essentially, unresolved as to whether the committee specifically would recommend approval or not, weighing all these things together.

CHAIRMAN MEISCH: Thank you.

Doctor Hayes will now give the FDA report.

DOCTOR HAYES: Doctor Bone has done an excellent job of summarizing what was discussed and the outcome of yesterday, so I won't bore you again. I am just going to point out a few other things that I was going to mention.

The medical officer from Metabolic had pointed out some interesting post-marketing safety data on fenfluramine. The sponsor supplied this data with the NDA and reported some CNS effects that they classified as either serious or non-serious. With the serious CNS events, they had 162 that occurred from August, 1984 to December, 1994 with dexfenfluramine worldwide, and these were classified as strokes, 79 of these events was over dose, which ended up as suicides or hospitalization. There were 703 non-serious CNS events, of which 227 were sleep disturbance, nightmares, difficulties in sleeping, 115 events related to drug dependency, and also they mentioned about withdrawal symptoms in some of the subjects, and that actually should have been under serious CNS

events. And, some patients had amnesia, 29 events, which was basically short term.

Drug interactions was one thing that was brought up several times by some of the committee members. They also were concerned about possible drug interactions from psychiatric drugs, in particular, Prozac, and the sponsor had stated that they will mention that in the label, that you should not co-use Prozac with dexfenfluramine.

Several of the committee members was concerned about that and have requested that the sponsor do a much more expanded section on drug interaction in the label.

That's, basically, all I'm going to say, since Doctor Bone did an excellent job on summarizing yesterday's events.

CHAIRMAN MEISCH: Doctor Bone has an additional comment.

CHAIRMAN BONE: Thank you. Just to add, with respect to the need for further studies in the discussion I mentioned a few minutes ago, one of the concerns expressed by the committee had to do with the lack of extensive information on formal structured neuropsychiatric testing in clinical trials, and it was suggested as another component of further studies,

particularly, long-term studies, that this be pursued in a rigorous way.

CHAIRMAN MEISCH: We're going to defer taking a break at this point and begin with the sponsor's presentation.

DOCTOR CICERO: Thank you, Mr. Chairman. My name is Ted Cicero, with the Washington University School of Medicine. I'm also a consultant, obviously, for the sponsor, Interneuron, and it's marketing partner, Wyeth Ayerst.

Our purpose today is basically to discuss fenfluramine and dexfenfluramine, particularly with respect to their abuse potential and our specific petition that they be descheduled at this time.

I think in 1973 they were scheduled, for reasons which will become clear as we give our presentation, but there's been a substantial amount of preclinical, clinical and epidemiologic data which strongly indicate that these compounds are simply not abused. And, therefore, we really believe it's in the interest of public health, and the obesity indication is the main point I want to get to, that these compounds should be descheduled and made more widely available to people desperately in need of them.

A word before we begin about defining

abuse and mis-abuse, I've heard that term today, and I think we, perhaps, saw a few examples of misuse. Abuse is going to be very clearly defined by the Controlled Substance Act and I think we need to very carefully consider abuse in terms of what the Controlled Substance Act tells us.

Doctor Wright did a very good job of explaining what that is, self-administration, withdrawal behavior that leads to drug-seeking behavior, these are what's on the Controlled Substance Act, that is what we need to be discussing today. Misuse is any off-label use of a compound. There is nothing a sponsor can do to control off-label use of their compounds.

If we begin to expand the Controlled Substance Act to control off-label uses of compounds we are in for a big amount of trouble. I dare say 80 percent of every drug used by a pediatrician is off label, and I would prepare to control it. I think we need to bear this in mind as we go along, really distinguishing misuse and abuse, they are not equivalent terms, and I think we must take this into account when considering the Controlled Substance Act.

Although the primary focus of what I'm going to be discussing about is, in fact, the abuse

liability of dexfenfluramine and fenfluramine, I think it's also very useful for us to spend a brief period of time on the clinical indication for the drugs, specifically, obesity management. I think it's very important that when you assess the overall picture of what decision you are going to make today that you have a context of risk benefits. We always have to assume that, and if there is a low level abuse, which we do not believe there is, if there are some other factors potentially that might be of some concern, what are the potential benefits of this as well, and the issue to deschedule.

I have assumed the major responsibility today for walking you through the abuse liability data, just so we don't have a bunch of popping people up and down throughout the day, and try to get some coherent flow to the presentation, but if I need help I have a whole crew of people surrounding me that can answer the questions. I'll give the brief introductory remarks, Doctor George Bray will discuss obesity as need for treatment, I'll then move into a discussion of the mechanism of action of this particular compound, Doctor Moore and I will jointly address this issue of, let's call it what it is, neurotoxicity, that has been raised as an issue

certainly yesterday and it's certainly in your packet, is a very heavy emphasis of the FDA so we ought to deal with that head on. Finally, I think Doctor Schuster would like to give some perspectives on fenfluramine and the Controlled Substance Act. I will then discuss the descheduling decision, which is basically a lack of abuse potential. Doctor David Smith, from Haight Ashbury, will also discuss some data that he carried out on behalf of the FDA, actually, to survey treatment centers to get some idea of the scope of the current abuse of dexfenfluramine.

I will then summarize the abuse potential and have a few concluding remarks.

Okay, what is the current status of dexfenfluramine and fenfluramine. In 1973, and I'll be slipping back and forth saying fenfluramine and dexfenfluramine, you all understand, and I may be a little simplified today because we do have non-Drug Abuse Committee members present, and while I think many of you are very familiar with the guidelines and what's required, perhaps, some of the people on the Endocrinologic and Metabolism may be as familiar, so I will tend to walk through this a little more slowly and explain, I think, again what are the criteria for control under the Controlled Substance Act, and,

really, what are the criteria for abuse, so that we can really deal with this issue.

In 1973, fenfluramine was scheduled in this country on a preliminary basis, and I want to stress that, as a Schedule IV substance by the Bureau of Narcotics and Dangerous Drugs. It was done so because it structurally looked remarkably similar to amphetamine, and even though there was no evidence of abuse at that time, and, in fact, the decision was that it was felt that we will temporarily schedule this for 18 to 24 months, until data could be produced that would document that this compound, although it bears structural similarities to amphetamine, in fact, shares no pharmacological properties with that drug.

I think now 22 years later we can come back to state that, in fact, substantial epidemiological, clinical and pre-clinical data collected since 1973 indicate a clear lack of either past, current, or the potential for abuse. On this basis, I think the Controlled Substance Act would mandate that we recommend fenfluramine as an isomer should, in fact, be descheduled.

Before reviewing any of the data with respect to the abuse potential, I do again want to put it in context what we are going to be using these

drugs for and the clinical indication for the drug, and again, both fenfluramine and dexfenfluramine will be used in the management of obesity.

In connection, I want to stress this, this is going to be in connection with a physician-directed weight loss program, this is not a magic bullet, this is not going to cure this terrible problem facing this country, but as an adjunct, and people have to adjust lifestyle, diet, et cetera to go along with it, the sponsor is absolutely committed to marketing this in a responsible fashion.

Before we begin that discussion, though, I don't know, the Endocrine and Metabolism people are very aware of this, but when you talk about obesity and try to define it I get very confused. They talk about a BMI, and I had all kinds of illusions of what that meant in the beginning, I won't go through what that is, it's a body mass index which is defined as kilograms per meter squared. You'll see numbers throughout the remainder of the slides that refer to BMIs of 22, 27 or 30. I wanted to put this in terms of, at least I can understand what that means, a five foot ten male weighing about 150 pounds would have a BMI of about 22. A five ten male of 190 pounds would be about a BMI of about 27, and you can see the

remainder.

Obesity has been defined by the NIH and other consensus committees as a BMI exceeding 27. In part, this cut off has been established on the basis of well-established morbidity and mortality data, which would suggest that 27 is a threshold, but I think you've got to realize, for the most part this is quite an arbitrary number. And, it's arbitrary in the sense -- I think it's reasonable, but it's arbitrary in the sense that one could argue that given the fact that it's been amply documented that any weight gain over an ideal level is detrimental, one could argue that 24 or 25 is just as reasonable as 27, 28 or 29, but you will, in fact, hear and I want to define for you, in fact, what obesity is. Pleasantly plump falls somewhere in there, but I can't figure out where that might be.

Okay, let's deal with -- move then to a discussion of obesity and it's need for treatment. Just a couple of bullet points, and then I want to turn it over to someone who can really more effectively deal with this, obesity is associated with excess morbidity and mortality. There is really absolutely no question about that, and you'll hear some, I think, very compelling data to that effect in

a few moments.

Weight reduction of any amount, as little as five percent or less, can, in fact, decrease risk. Fenfluramine and dexfenfluramine, in combination with a physician-directed weight management program, have been shown to be a useful tool for obese patients as an aid to successful weight loss and reduction of risk.

Doctor George Bray will now discuss these data. Doctor Bray?

DOCTOR BRAY: Thank you, Doctor Cicero.

Good morning, ladies and gentlemen. It's a pleasure to be here to talk about a subject on which I've spent the last 30 years or so of my professional career.

The issues that I want to talk about this morning are the need for treatment and to talk about one of the barriers to this appropriate treatment which I wrote about in the Annals of Internal Medicine some years ago, and which we are dealing with this morning.

The six points that I will go over are listed here on the outline for this talk on my first slide, and this will take me a few minutes. I have presented some of this material with my colleagues

yesterday, the Endocrine and Metabolic Section as well in more detail last fall, in order to give them the background and hopefully the conviction that this is a serious problem for which we need a growing armamentarium of drugs which can be used in the long term.

First, obesity is a chronic disease which is increasing in prevalence. The most compelling data are those of Kuczmarski, which I have plotted here, published last fall using the National Center for Health Statistics, showing for all subjects, for men and for women, that the prevalence of obesity has risen from about 25 percent of our population in the last ten years to nearly 33 percent or some 60 million Americans. So, it is a problem which has increased dramatically into epidemic proportions in a matter of less than a decade in this country. It is the only goal in the Year 2000 Report which is going in the opposite direction from the Surgeon General's proposals.

The second point is that it increases the risks for mortality and morbidity. I will show you a figure from the recent paper by Manson in the New England Journal of Medicine, but there could be a substantial number of additional data from men, from

women, from life insurance sources, from prospective trials. This is the Nurses' Health Trial, and over this range of body mass indexes, which Doctor Cicero kindly defined for you, which is essentially the normal range of weights between 20 and 25, covers the life insurance lowest weight for small frames for highest weight for large frames. And, as you get above that in the Nurses' Health Trial and in all other trials, there is a progressive increase in the risk of death from heart disease, particularly of diabetes, of osteoporosis -- osteoarthritis, sorry, and a variety of other conditions, so it is a major health risk which is increasing in prevalence.

My third point is that it not only increases risk to health, but the costs that we pay for the health of treating America. I've taken this data from Colditz's paper from the Harvard School of Public Health in 1992, in which he estimated that costs attributable to obesity in billions of dollars per year for a variety of diseases for which obesity plays an important role, the highest, because it is the most prevalent, is heart disease with 22.2 billion, musculoskeletal diseases, primarily, osteoarthritis, at 17 billion, diabetes at 11 billion, and a variety of others at somewhat less cost, but a

total figure that approaches 56.2 billion or 7.8 percent of our total health care budget, a major contribution from obesity.

That obesity increases risks is countered by the, I think, important observation for this group that weight reduction lowers that risk and that a five to ten percent reduction can play a significant role in reducing risk, and I will show you three slides to illustrate this point. This is data from Scott Grundy at Southwestern Medical School and his estimate of the impact on cardiovascular disease of a 20 pound weight loss, roughly, ten percent of body weight for someone weighing 200 pounds, of the impact of this loss on cholesterol, ten milligrams per deciliter decrease, which translates into a ten percent reduction in the risk of heart disease, a three milligram per deciliter increase in HDL cholesterol, which translates into a six percent reduction in cardiovascular disease risk and a five millimeter fall in diastolic blood pressure, which translates into a reduction of approximately 15 percent in cardiovascular disease risk. That is a 20 pound or ten percent over average reduction for an over weight population group that many of us see would reduce cardiovascular disease risks by some 30 percent or more.

Two studies, two parts of a study using the American Cancer Society's database by Williamson earlier this year show the effect of weight loss on mortality risk in never smoking women who had no pre-existing illnesses, there were 28,000 women in this group who with an intentional loss of 20 pounds or more there was a 25 percent reduction in all cause cardiovascular and cancer mortality, that's very close to the 30 percent that Scott Grundy estimated from his estimates of the changes in cardiovascular risk factors and their impact on heart disease.

In this same group, there were another subset of women who had comorbid conditions, including all of these, there were 15,000 women in this group and in the intentional weight loss here of any amount, five percent, ten percent or more, there was a 20 percent reduction in all cause mortality, a 30 to 40 percent reduction in diabetes associated mortality, and a 40 to 50 percent reduction in mortality from obesity-related cancers. So, these are major changes that can be produced by relatively small reductions in weight, which you can achieve with chronic treatment.

Obesity has many causes and many treatments. This is a list slanted from an endocrinologist's perspective, which I am, showing a

variety of diseases, most of which are rare and, indeed, in most cases we can't identify the specific cause for the obesity, and, thus, our ability to cure it is rare, long-term palliative treatment is what we are about.

Because there are many causes, there are also many treatments. These are a variety of them, including several ways in which you can use pharmacologic agents to reduce weight. One of the problems that exists for physicians in this country in using drugs is the scheduling, particularly of the fenfluramine group, where the risk of abuse from our perspective, that is, those who deal with it, is vanishingly small, but the barrier to use of these agents appropriately for treatment of a serious problem is made very difficult by this barrier, and I would urge that you deschedule this drug for the benefit of the country and the physicians who deal with this serious problem.

Treatments don't work when not used, when drugs are stopped, as they often are, because physicians feel compelled by their agencies to stop in three months or so, weight is regained, and you would expect it to be. You do not expect anti-hypertensive drugs to lower blood pressure when the drug is

stopped, you do not expect anti-high cholesterolemic drugs to lower cholesterol when the drug is stopped, and you don't expect anti-obesity agents to lower weight when the drug is stopped. So, weight regain is to be expected, and recidivism is thus a common problem which would be alleviated for many patients if they were allowed to continue treatment beyond barriers erected by most state regulatory agencies and by the Drug Enforcement Agency.

Recidivism, and this is from the NIH Health Consensus Conference, suggests that somewhere between 20 and 80 percent of patients drop out of trials or treatment, that something like a third of patients will regain their weight in a year after stopping treatment, another third in the second year, and almost all by the end of three years after treatment, as you would expect when drug treatment has been discontinued.

Well, in the last few minutes I've tried to put the need for treatment into perspective, but let me do that from a personal point of view. We have a group of men, and now women, in Baton Rouge that we treat using a program very similar to the one that Doctor Atkinson described, and we have a protocol under which we do this, because the state regulatory

barriers are severe in Louisiana. And, under that protocol we now have men treated for a year with, essentially, no drop out because they pay for the program, where we have a 25 percent overall weight loss, that is a 25 kilogram loss, these men were 125 kilograms when they started, from their perspective health benefits had been substantially improved. The barriers for us to provide this treatment would be greatly facilitated if the drugs which we are considering today were descheduled.

Doctor Cicero, let me turn the program back over to you.

DOCTOR CICERO: Thank you, Doctor Bray.

Let me give you a brief review of the history of these compounds. Dexfenfluramine and fenfluramine, fenfluramine is a racemate. It's approved in the United States for the treatment of obesity, and it has been approved since 1973. Worldwide, there have been an estimated 30 million patients that have utilized this drug. Dexfenfluramine is the d-isomer of fenfluramine, again, worldwide ten million patients have been treated with this worldwide and it is currently under review, as you heard Doctor Bone mention for its approval by the Endocrine and Metabolism Advisory

Group of the FDA.

Fenfluramine and dexfenfluramine are going to be positioned and marketed as pharmacological tools to help weight management in obese people, involving a physician-directed weight loss program. The specific indications are shown on the next slide.

Fenfluramine and dexfenfluramine should be used only in conjunction with a physician-directed weight loss program. They will be recommended for obese patients with a BMI greater than 30, that's a 5 foot ten inch male, 107 pounds, or a BMI of 27 with co-morbid conditions.

I very briefly want to move on and discuss the pharmacology of dexfenfluramine and fenfluramine. Basically, it's shown on the next slide. Dexfenfluramine and fenfluramine share, obviously, the same -- many of the same properties. Dexfenfluramine is the serotonin re-uptake inhibitor. It's isomer dexnorfenfluramine is the serotonin releaser, which also acts as a serotonegic agonist. Fenfluramine looks very much the same, with one exception, the l-isomer, in fact, has slight dopamine antagonistic properties.

What I want to contrast it to is sympathomimetics like amphetamines, the compounds,

remember, which I said it bears structural similarities to, it has a very different neurochemical profile. Sympathomimetics are norepinephrine releasers, they are dopamine releases and adrenergic agonists.

The take-home message from here, the only purpose for me discussing it, and that's the last you'll hear of mechanisms of action, is, although fenfluramine and dexfenfluramine has structural similarities to amphetamine, they bear no similar pharmacology.

As we will walk through the data later today, you are going to see that that distinction has been amply documented in all the pre-clinical, clinical and epidemiological evidence, these drugs don't look like amphetamines.

Okay. I'm not going to discuss the efficacy of fenfluramine and dexfenfluramine, because I think they are both well established. I think you heard from Doctor Bone yesterday that the FDA Advisory Committee actually agreed that the efficacy for dexfenfluramine was there. Fenfluramine, again, has been approved since 1973, and has a well-established efficacy profile.

What I would like to do is briefly discuss

a few safety concerns, which I think you've heard a bit of a discussion earlier today, and certainly Doctor Bone reviewed those that occurred yesterday as well.

This is a general statement, and I'm not going to review any of this data for you, both with respect to fenfluramine and dexfenfluramine, they appear to be in clinical trials and in 40 million patient exposures worldwide. I think we have to keep that figure in mind. They are well tolerated. The common adverse events are mild and self-limiting. In the post-marketing experience, your serious events are very rare. The figures that Doctor Hayes showed earlier, put those in context, they showed a few examples of CNS events, we are talking about 40 million patient exposures. When you look at serious adverse over a ten-year period and a conductor rate, these are minuscule. These are extraordinarily safe compounds.

Although I believe the safety of fenfluramine and dexfenfluramine are quite clear, I was a bit disturbed reading the FDA packet that a large number of tables were included that dealt specifically with intentional over doses with dexfenfluramine in France, but there was no attempt to

interpret these data.

I must make an assumption that the inclusion of these data suggests that the FDA reviewers are very concerned about excess suicide in patients exposed to dexfenfluramine.

I would like to take this opportunity to discuss this issue with you directly, and I think to correct what I believe is a misinterpretation.

In your insert, in your background packet that you received, the FDA report of 41 intentional over doses from dexfenfluramine, in the period of 1987 or 1993, or an incidence rate of 5.8 per year, 6.6 million people were exposed during that period of time. If you assume that the incidence of reported over doses is only one tenth that which occurred, I think a very conservative estimate, then we would estimate there would be 58.6 cases per year, or a rate, assuming the denominator here, of 6.2 intentional over doses per 100,000.

Let's look at France as a whole, and this data, by the way, are based primarily in women, there are 28 million French women, the rate of suicides was 350, by drug now, drug over doses in France, was 350 per year. Again, we made an assumption that suicides are one tenth the actual number of over doses, so

we've multiplied this by ten just to try to give us some assumption.

If you do this and do these calculations, they actual -- and most epidemiologists who have looked at this data will confer will agree these are conservative estimate, the actual rate of drug over dose is actually 125 per 100,000, indeed, fenfluramine appears to be -- or dexfenfluramine in this case -- appears to be highly protective in this situation.

That is not probably very surprising. This is a drug which has powerful serotonergic, it looks very much like some of the other antidepressants currently in use.

One additional safety concern that has been raised about fenfluramine, and particularly dexfenfluramine, is the claim that these agents may be neurotoxic, and once again I note in the FDA packet that there was a very large number of articles that contained documentation that, in fact, this was the case, but I was a little disappointed at the arguments of the opposite side and the number of papers that failed to show such effects were not included.

We'd like to take the opportunity today to address this issue, and we've actually expanded it a bit in view of the extensive discussion that occurred

yesterday with respect to neurotoxicity.

At the outset, I just want to make a couple of general comments. I'm certainly not an expert in this field. My perception is that we have a bunch of preclinical observations, and we have some superb scientists who happen to be very good friends of mine, I think good scientists can have reasonable differences of opinions. I think Lou Seiden, without question, passionately believes in what he's shown, he's done it in a highly rigorous fashion. George Ricaurte, impeccable credentials once again, Bob Moore, again, I think everyone dealing with the pre-clinical model is doing exquisite work in this area.

I think we have a distinction. I think we have a problem. We are going to have a little bit of discussion of that, but I think, again, the focus ought to be, we are dealing with a pre-clinical situation, and its relevance to the human is the big unanswered question. And, while I sort of jokingly refer to this, we could have the dueling neurobiologists present an hour and a half or so of talk, the real crucial issue to me is, does this have clinical relevance?

Why I don't think this is going to get resolved, I'm mindful of the fact, one of my dear

colleagues was involved in the MSG controversy back in the late '60s, there is still a dispute 25 years later about whether that compound is neurotoxic, based upon mouse and rat studies. I don't know whether it is, and I certainly don't know whether in humans it is. I don't know that we can resolve the situation. The acid test is, is there a problem in humans. That's the unanswered question.

There are numerous animal studies that have shown that have shown that high dose dexfenfluramine administration may produce decreases in forebrain serotonin content. No dispute on that. I think everybody would agree with that. There is a reliable relationship across species between dexfenfluramine concentration and reduction in brain serotonin. The brain dexfenfluramine, the metabolite concentration of these patients receiving dexfenfluramine is substantially below those that produce significant prolonged decrease in the serotonin content.

Let me give you an example. You'll see when Doctor Moore presents data at a normal therapeutic level, 15 milligrams twice a day of dexfenfluramine, you get brain levels of four micromolar in all these situations. Let's not worry

about doses and milligrams per kilogram, although I will point out the human dose is .3 milligrams per kilogram. All of these studies involving rats, mice and primates have used doses that are at least 20 to 100 times that level.

But the acid test is what are the brain levels. The brain levels are four micromolar after human administration. We are reaching levels between 50 and 150 micromolar in all of the animal studies. So, the brain concentration in these studies, there is a huge margin of difference between the brain levels generated in these studies and what one sees in a human. So, we need to bear that in mind as we look at the human significance.

Even with the very high doses that decrease brain serotonin content in animals, we are going to show you today that using the same identical doses that reported caused brain lesions, the animals have completely normal neuropsychological function. So, even if a rat has reportedly what appears to be a destroyed brain, they have normal function as assessed by a battery of tests.

With human therapeutic dose there is no evidence of significant changes in neurological function shown by neuropsychological testing in

clinical trials or by post-marketing experience. Let me expand on that. There have been four or five studies that have indeed examined neuropsychological status in patients that have been maintained long-term on dexfenfluramine. In addition, I do want to remind you that there have been 40 million patients exposed to this compound worldwide since 1973. There has been no indication. We can pick up primary hyper -- what is it? Pulmonary. We can pick that up. It's a very, very rare event. No one has been able to detect any evidence of any neuropsychological impairment.

I think we have to bear these in mind as we approach the significance of what I believe to be solid pre-clinical findings. I believe that Lou Seiden, George Ricaurte and Bob Moore are finding similar sorts of things. I think there are other explanations for it. I think we have to rise above that and ask, "Is it clinically relevant?" I think the issues that I've just raised to you would argue that, no, I don't think it's clinically relevant.

Is the question addressed finally? No, it isn't. What we need to do now is do more systematic studies as this compound is approved and marketed in this country to, in fact, demonstrate in a fashion that would satisfy everyone that, in fact, there is no

neuropsychological deficits here. Certainly this sponsor doesn't want to produce a drug and certainly this committee doesn't want to get involved in anything that's going to hurt people. Again, we're talking about risk benefit. We have to realize what that risk benefit is. You've heard the enormous toll of obesity and how we could help that. We've got to balance off some risk associated with that. But certainly no one wants to promote a drug that's going to cause gross neurotoxicity.

I think you'll hear later that the company is actually committed to making sure when this compound is, in fact, marketed that this issue is more rigorously examined. But I think in contrast, Doctor Bone accurately reflected what occurred yesterday. That frankly was the sponsor's problem. The sponsor did not present this case clearly to you to indicate this has no clinical relevance. I think had that been done, it would have been a very different tone of the discussion. I'm here to present that to you and I think we needed to get that data in front of you.

I'm not going to turn this over to Doctor Moore who will, in fact, discuss some of the preclinical data and then we have two or three speakers which I promise are only going to mention a

[redacted]

We are talking about serotonin neurons. In the top panel is the primary nucleus of serotonin neurons in the brain stem that projects to the forebrain. This is the dorsal rafe nucleus. The small brown dots that you see are the serotonin neurons shown with an antibody to serotonin. On the bottom panel you can, at least if you're close, see a very fine lacy network of fibers which is the axon terminals and terminal plexus of those serotonin neurons in cerebral cortex.

It is clear that the administration of high doses of dexfenfluramine will produce decreases in brain serotonin content. Here is an example of

this. This is in an ongoing, long-term study in which the drug is given over a 21 day period in oral doses with pair-fed controls. The values are shown as either percent of pair-fed control or percent of control and the doses are two, four, eight and 16 milligrams per kilogram. When one gets to doses in the range of eight and 16 milligrams per kilogram, there are quite large decreases in serotonin content that over at one week after discontinuation of the drug at 13 weeks there is recovery at the eight milligram per kilogram dose. This is not in my view regeneration. When I look at the histochemistry with this, this is simply a reappearance of serotonin in the fiber plexic and all of the dose levels are back to the level of pair-fed controls by six months after the termination of dosing.

Another example was brought up yesterday, but I think is an important one and this is a long-term mouse study which was part of the carcinogenicity trials. In this, mice were given 27 milligrams per kilogram per day of dexfenfluramine in feed for 106 weeks. At the immediate end of this two years of treatment, the serotonin content in the brains of these animals was normal. Paroxetine binding, which is an independent measure of the integrity of the

serotonin neurons, it is a measure of the serotonin transporter. This is also normal. Then, two months later, after the cessation of treatment, it is also normal.

There was a question raised yesterday as to whether the animals were actually receiving it in the feed. I think if you look at what the brain concentrations of the drug and metabolite were at the end of the two years of treatment, it's clear that the animals were receiving it. That is the concentrations were quite high, 51 micromolar.

The issue of calcification was also brought up. Let me try to put that into context. It appears that there was more calcification in the thalamus of the brain of the animals receiving the dexfenfluramine. Calcification by itself, in my view, is not a meaningful thing. Most of the people in this room will have some calcification of their pineal gland, but in that context the pineal gland still functions perfectly normally.

In addition, there is a condition which has been discovered since modern imaging techniques and that's calcification of the basal ganglia. By looking at basal ganglia with CT or MRI, you see marked calcification in individuals who otherwise are

absolutely asymptomatic. It's a finding that came up with the techniques. So, calcification by itself really doesn't mean anything.

I think it's necessary to deal with the issue of what doses mean and whether one can extrapolate from animals to man. We tend to think that perhaps a monkey would be a better experimental animal than a rat or a mouse, but in this context I don't think that that's the case. There are data that suggest that the acute effects of dexfenfluramine on brain 5-HT levels are related to brain drug and metabolite concentration and that this is similar in rats, mice and primates and that any species differences are pharmacokinetic.

This is shown in this graph where brain serotonin content is plotted against the concentration of the drugs and you can see that the brain serotonin content is a function of concentration of drugs along this curve regardless of whether we're looking at mouse, rat, rhesus monkey, cynomolagous monkey or squirrel monkey. All of these behave exactly the same.

Consequently, we think it is reasonable to extrapolate from measured human levels and to compare then humans and animals. This is data obtained from

a magnetic resonance spectroscopy study in the human with obese subjects given dexfenfluramine in a dose of 15 milligrams twice a day for 90 days and their concentrations of drug and metabolite were obtained at the beginning of the study, at 10, 60 and 90 days. As you can see, there is a rapid rise of the drug and metabolite in brain as measured by MRS spectroscopy at ten days and that this is maintained and there is no accumulation of drug metabolite with continued treatment.

If we then take these values and put them on the curve that I just showed you from the animals, you can see this is all of the patients from the study and all of these fall well below the part of the curve where one begins to see significant or large changes in brain serotonin as were shown in the study that I showed you, the first study of the rats, the long-term study. The 50 percent level is over here and this is substantially higher. It would require substantially higher brain concentrations than are obtained in the human with therapeutic doses. These are levels in the range of 2, 4 micromolar.

I should have said that with the prior human study that I showed you, that that was not corrected for concentrations as shown in the monkey

study in which the MRS was done and then brain concentrations were obtained directly.

I will now turn it over to Doctor Bruce Campbell who was going to tell you about the English conclusions regarding neurotoxicity.

DOCTOR CAMPBELL: Mr. Chairman, ladies and gentlemen, I'm Doctor Bruce Campbell, Director of International Scientific Affairs for Servier in the U.K. I've just been asked to say a few words because clearly the experience that we have in English and in Europe is obviously very much larger than you have with this drug, because the drug is not on the market. It was clear from yesterday's discussions that it really wasn't apparent that we do have an enormous of experience in Europe and clearly we can't forget that.

We obviously as a company have been very concerned with the possibility of these so-called neurotoxic effects. Together with the various regulatory agencies, we've been looking at all the adverse reactions. We saw some of these already today and I would also like to comment. The fact that relatively low levels with 10 million to me is surprising and also surprising to the agency because these are very little.

This we have recently received from the

MCA, which is the medicine control agency in the U.K. who commissioned an independent report by an expert in neurotoxicity, Professor Atterwill, and also together with all the spontaneous reports that they have English, together with the adverse reactions which we have to give from all over the world. You note the date is the 5th of September. So, it's as much up to date. There is no different information that they have that the FDA have. Based on this, you will see that they have reviewed the spontaneous reports and the neurological adverse drug reactions associated with dexfenfluramine and fenfluramine received to date. We conclude that no action is required in relation to this aspect of the drug safety profile at present. Clearly, like yourselves and ourselves, we must continue to evaluate it. But based on this very large experience that we have for more than ten years in the U.K., the MCA feel that this is of no clinical importance.

Thank you.

Now I'd like to introduce Professor Stan Lawrence, Professor of Pharmacology and Neuropharmacology at Chicago University who specifically looked at the meaning of these very high doses in animals in terms of their potential changes

in behavior.

Professor Lawrence?

PROFESSOR LAWRENCE: Good morning, ladies and gentlemen. The introduction is not quite correct. I'm not at the University of Chicago, although like Doctor Seiden I was trained there by an eminent group of serotonin pharmacologists, neuroscientists, including Doctor John Harvey, who happened to direct my dissertation. I might add that Doctor Moore played a vital part in my dissertation research as well because he was on the committee. I had learned greatly from that experience.

My laboratory since that time, over 20 years, has been concerned with the functional properties of serotonin neurotransmission, and more in particular the functional effects of CNS serotonin depletion. Our efforts have been greatly disappointing from the standpoint that central nervous system serotonin depletion, and by that I mean falls in 5-HT and its metabolites content of greater than 80 percent, do not result in major functional or neurological deficits.

Now, let me just, to be brief, review studies that were conducted beginning in the 1970s with 5,7 dihydroxytryptamine and continued up through

1989. I'd like to emphasize that none of this work was supported in whole or part by either Interneuron or Servier. We're funded, in fact, in part by funds from the National Institute on Drug Abuse, university funds and others.

Now, what we have done is to compare the effects of intraventricular bilateral administration of 5,7 dihydroxytryptamine, which is a classical serotonin and neurotoxin. The administration of 100 micrograms bilaterally intraventricularly results in serotonin depletion in various regions of the brain which measure in the magnitude of 85 to 96 percent. In comparing the effects of d/l fenfluramine to those of 5,7 dihydroxytryptamine, we have measured brain levels after these two different treatments at two and eight weeks in separate groups of animals, two and eight weeks post-treatment.

Now, you'll note that the doses of d/l fenfluramine that were used here fall into the so-called neurotoxic range. Five or 20 milligrams per kilogram were administered subcutaneously twice a day on four consecutive days and a variety of behavioral tests were then used to look for functional alterations between two and eight weeks post-administration.

Now, the neurochemical evidence indicated that these doses will produce falls throughout the central nervous system in serotonin which maximally reach, in our experience, about 70 percent, 70 percent reductions. By eight weeks post-administration, these falls have been normalized in the sense that the falls have been overcome and measure in our experience about 35 percent. So, you have recovery of the effects on at least fenfluramine on serotonin content.

In contrast, 5,7, DHT produces a prolonged, I would say probably permanent reduction in, CNS 5-HT consistent with its true neurotoxic effects. So, at eight weeks post-administration 5,7 DHT administration will result in 95 percent reductions, continued reductions in the hippocampal 5-HT, 5-HI AA levels.

Now, we have looked at the effects of fenfluramine using a variety of behavioral tests, including exploratory behavior, motor coordination and stamina and that's in the Loyola University Medical Center swimming pool. That's a joke. In fact, the only swimming pool at the medical center is in this testing facility.

Defensive behavior toward an intruder in the home case is a measure of hypergrasivity and I'd

like to mention that perhaps one of the most commonly reported or certainly the research evidence from Linoila's lab from Finland, from other groups, is that CNS serotonin depletion or major reductions leads to violent combative behavior. You will note that these doses on fenfluramine do not in any way affect this aggressive behavior of treated animals toward an intruder.

We've also looked at one and two way -- this is a place conditioning two way discriminated condition avoidance, acquisition retention, spacial memory formation using an eight arm radial maze for food reinforcement, thermal pain sensitivity, morphine-induced analgesia. We have found no adverse effects of these treatments with fenfluramine on any of these functional measures.

In contrast, 5,7 dihydroxytryptamine will produce deficits in exploratory behavior, can produce dysfunctions in motor coordination and stamina. Clearly, this effect, the 5,7 DHT has been reported by several laboratories, major reductions in CNS serotonin result in hyperaggressive, combative behavior. In addition, 5,7 DHT can affect thermal pain sensitivity using a hot plate method and morphine analgesia. None of these treatments effect learning

capability or cognition using these preclinical tests. It's overwhelming evidence that serotonin depletion induced by this toxin do not lead to learning and memory deficits using classical tests.

Thank you.

Oh, excuse me. I'd like now to introduce Doctor Richard Gammons from Interneuron.

DOCTOR GAMMONS: Thank you.

I am, again, Doctor Richard Gammons. I'm the Vice President of Clinical Research at Interneuron. As Doctor Bone correctly and succinctly pointed out, there was a burning interest first expressed yesterday in neuropsychological tests that might be available and I'd like to at least briefly and succinctly review that, which I have at hand.

In the interest of both clarity for those that are not familiar with the test and explaining abbreviations that are on the final slide, I'd just like to explain what the tests were. First, the profile of mood states which uses 65 descriptors rated on a five point scale by patients and addressed the dimensions of mood listed, depressions, anxiety, hostility, fatigue, vigor, confusion or bewilderment. There was a reaction time test employed in one study which is a test designed to test vigilance,

integration of reaction to that stimulus and ability to respond to it and the Stanford sleepiness scale, which is a widely used scale to look at sleep disturbances both directly and self-rated by the patient as regards their sleep and their daytime sequelae, if there were lack of sleep or other loss of alertness from other sources.

In one study, two studies actually, there was a Center for Epidemiologic Studies depression scale, again a self-report questionnaire, 21 items, a wide variety of symptoms that are associated with depressive illness, not just the word "depression" as it might be commonly used in adverse experience reporting on in a lay sense and the Mini-Mental Status Scale, which is a widely used, relatively simple and straightforward test of orientation as to location, attention, registration, recall, language skill.

There were three studies that we share with you today, all of them small and carefully conducted to assure consistency with respect to administrations of the instruments. Two of the studies were MIT studies identified as 291 and 296. 291 was, in fact, a smoking cessation study, not an obesity study. It was five weeks of treatment duration. The dose was 30 milligrams per day. The

ends are shown, 15 and 16. Palms and the reaction time test were employed in that and there were no significant differences at weeks baseline or weekly during the course of that study.

The second study was, in fact, the weight loss study and employed the ends as shown at doses of either 30 or 60 milligrams per day, 12 week treatment duration and two weeks post-treatment cessation. Follow-up, profile of mood states and the CESD were used. Again, there were no significant difference noted on the items tested.

These two studies are published and included as such in various submissions we have made. In fairness, the remaining study is -- these data from the remaining study were not analyzed until just very recently and have not been submitted to the agency. It is the study which we refer to as the Noble study. Again, the dose was typical of the 30 milligrams per day. The treatment duration was six months and then there was a 12 month post-treatment follow-up assessment. The ends again are small.

The data that we have available with us that has been analyzed are the Stanford sleep questionnaire and the Mini-Mental Status. Again, no significant difference either during the treatment

phase or at the end of it there at six months or during the follow-up period.

Also, I'd like to mention one remaining psychometric assessment that was, in fact, included in two of the weight loss studies, the Hamilton Depression Scale and it was included at the suggestion of the Neuropharmacologic Drug Division to address the issue of either treatment emergent or post-treatment withdrawal, depression, illness. For those of you not familiar with it, it's a 17 item scale. It assesses the whole dimension of symptoms typical of depressive illness. Each are rated on various scales, usually zero to four and some zero to two. Typically when employed in depressed patients, an entry score for moderately depressed patients would be 18. These again were included not because the patients were depressed but because of an interest in assessing the emergence of a depressive syndrome similar to that of major depression.

At entry into the study, the scales in both studies average something below four which is not depressed. At the end of 12 weeks of treatment, either on 30 milligrams per day, which was included as one group in the dose response study and was the only treatment group in the remaining weight loss study,

both studies combined at that dose approach 150. The ends at 10 milligrams per day are 50 and end at 60 milligrams per day are 50.

I'll just try to speak globally rather than the specific value for each group. At baseline those values average under four. At the end of 12 weeks treatment they were unchanged. At the end of the four week post-treatment follow-up they remain no change.

To provide further reassurance and to assure we weren't obscuring something in the total score, although it's very difficult to imagine with a mean of four, the data I just described to you are included in the regular study report. In addition, in the recent days, I went back and looked at the individual scores on each of the key items, for the central symptoms of depression, such as depressed mood, suicidal ideation, guilt, somatic or psychic anxiety, psychic retardation, loss in work and interest, and identified those patients who at entry in the study, which was the vast majority, did not have those symptoms and assured that at either the 12 week treatment point nor at the four week post-treatment follow-up point were those patients exhibiting signs of moderate symptoms that were not

present at baseline. Again, those were uniformly convincing that there were no emergence of either the depressive syndrome or a suggestion, a hypothesis that I could generate that would suggest that that were true.

In addition, it is customary in those two studies in particular to include a structured neurological assessment of those were again negative.

Thank you for the opportunity to speak to you about this.

DOCTOR CICERO: I'll just wrap it up. This is the very first slide I began with, but I'm not going to bore you by going over it.

I think what you have heard is that I think without question there's some indication at preclinical model that you had some reduction of serotonin and I believe there's a debate about how long that does persist. I think what we try to do is put into perspective that at least in the animals treated with similar doses, there don't appear to be any neuropsychological substrates or correlates of this behavior. To the extent we have systematic data in the 50 or 60 patients that they've just reviewed, there don't appear to be any neuropsychological deficits once again.

I guess I still have to keep reminding us that we've had 10 million people worldwide exposed to dexfenfluramine and 30 million people exposed to fenfluramine and no agency, the WHO, anyone has been able to -- including the company, has found anything indicative neuropsychological deficits.

Now, I want to stress it doesn't mean that there's something very subtle and we've been hearing that yesterday. I don't know how one measures it if it's so subtle we can't see it, but clearly the company is committed to doing a careful, careful, neuropsychological screening in a systematic, large data set once the compound is available. At the current time there is just no evidence to suggest that this compound had any neurotoxicity.

Mr. Chairman, we have about 20, 25 minutes left. I noticed we skipped our break. This would be a wonderful opportunity to break in our presentation, if you so desire.

CHAIRMAN MEISCH: Exactly my idea. We'll take a 15 minute break.

(Whereupon, at 11:08 a.m., off the record until 11:36 a.m.)

CHAIRMAN MEISCH: Doctor Cicero, please go ahead.

DOCTOR CICERO: Thank you, Doctor Meisch.

Why am I so mechanically inept?

I'll bring us back. We've had an extended discussion of the safety issues and the indications for the compound and I think the need for this compound in treating obesity. I hope that point has been driven home.

Just to remind you again, the compounds were scheduled in '73 on a preliminary basis because of structural similarities.

I think, going to a second point, I'm not going to present these data and I've talked to Doctor Meisch and I think we can all generally, I believe, concede at this point that the epidemiological, clinical and preclinical data collected since 1973 indicate that there really is either a lack of past, current or potential abuse of these compounds. Again, abuse being defined by the three factors.

I'd like to read Doctor Wright's three comments, introductory comments he made at the beginning of the meeting.

A substance should only be controlled if it meets all of the three following criteria. One, evidence of self-administration because of pharmacologic activity. We will all concede there is

no evidence that point to this effect.

Two, evidence that the substance is capable of producing physical or psychological dependence at high doses. I think again the data is compelling to indicate that that is not the case.

Three, evidences of a substantial risk of diversion of illicit traffic at the local, state, national or international levels. Once again, we submit there are no data to support this position.

On this basis, the sponsor would like to recommend that fenfluramine and its isomers should be descheduled. We will not present any further data relevant to that point today.

The issue of misuse is an important one, as is toxicity. I think there are a number of concerns that one could raise about any compound. However, this is not the format, I believe, for us to be discussing toxicity issues. It is not the forum for us to be discussing efficacy issues. This is the Controlled Substance Act. We are dealing with the abuse liability of this compound and that is what our discussion has to focus on.

So, the remainder of the discussion of neurotoxicity and/or efficacy or lack of efficacy to me is not a suitable topic for this discussion. It

may be informative, but I don't think it's germane certainly to the Controlled Substance Act, because remember, we're talking about public health interest if there is a substantial abuse problem. That is factor 6. Clearly, there is no substantial abuse problem. So, we do not have to address the public health interest.

That's not to say that we're not all interested in public health decisions. I do want to clarify my previous statement about misuse which my dear friend Curt Wright pointed out I overstated the case. I said basically that a sponsor or a pharmaceutical company has no control over misuse of the compound. That clearly is an overstatement. There are a number of recent examples of companies that have taken a position to take strong post-marketing surveillance programs which will tend to identify pockets of misuse and take corrective actions should those things come up.

You'll find the sponsor -- and that will be presented at some later point. I'll ask the Chairman's discretion on when he wants that presented -- is committed, in fact, to the responsible marketing of this compound and indeed will investigate should there be pockets of misuse and attempt to educate and

correct that problem. So, thank you, Doctor Wright, for correcting that perception.

Mr. Chairman, the sponsor is willing to not discuss any of the data further, of course pending if there's any additional comments that should question that conclusion. But our recommendation to this Committee is to deschedule at long last fenfluramine and its isomers.

CHAIRMAN MEISCH: Doctor Cicero, we're going to have, I guess, a couple of people from the FDA give some information. If you want to add some qualifications at that point, fine. Otherwise, I'm going to poll the Committee after the FDA presentations.

DOCTOR CICERO: Thank you.

CHAIRMAN MEISCH: Doctor Wright, who are the people now that want to talk?

DOCTOR WRIGHT: Well, during the break, Mr. Chairman, you asked me if any of the agency personnel had specific information with respect to self-administration.

CHAIRMAN MEISCH: Yes.

DOCTOR WRIGHT: And I will honor your request. I will ask two of our speakers and I will call for any of our other speakers that have

information that I don't know about to specifically talk about the data that they hold that is related to the potential for self-administration of this drug. Will that acceptable to you?

CHAIRMAN MEISCH: Yes, sir.

DOCTOR WRIGHT: Thank you.

Doctor Kramer, will you address that issue?

DOCTOR KRAMER: Yes, I will.

The basic clinical data relating to the abuse liability of fenfluramine includes case reports,, a survey of addiction medicine specialists and recent popular press coverage relating to fenfluramine and phentermine. The reports of dependence and abuse of fenfluramine date from the 1970s. Three case reports and one case series comprise the body of this data.

The first case was reported by Harding and is of a woman being treated for post-partem depression and weight loss with amitriptyline and fenfluramine. She became depressed, sleepless, anorexic, agitated and suicidal when she discontinued her fenfluramine. She was successfully treated with reintroduction of fenfluramine and taper of her antidepressant followed by fenfluramine over four months.

Rosenvinge reported the second case of

fenfluramine abuse in 1975. The patient was a woman who had successfully lost weight on the drug and continued to use it for four years at doses up to 240 milligrams per day. She experienced euphoria, excess energy, little need for sleep and increased libido. When she came to treatment she had forged three or four prescriptions.

The third case was reported by Dare from Australia in 1976. At that time fenfluramine was available without prescription. He reported a man and a woman who presented together with acute symptoms of fenfluramine abuse. The man, aged 29, had a ten year history of drug abuse, including amphetamine and LSD. He had been using 200 to 300 milligrams of fenfluramine two times a week for a month.

His companion, an 18 year old woman with anxiety, hallucinations and depersonalization following 200 milligrams of fenfluramine and alcohol. She gave a one month history of twice weekly use.

Of note, the man in question reported sadness as a mild withdrawal symptom, which he readily treated with additional fenfluramine.

Levin reports on what appears to be an accumulated case series of fenfluramine abuse among young drug dependent South African servicemen. He

reported treating 60 drug dependent young men who claim to have used fenfluramine as a drug of abuse and reported euphoria, derealization and hallucinations after ingesting 80 to 400 milligrams. Increasing quantities of the drug were required to achieve the same initial high, suggesting tolerance development.

In 1971, fenfluramine abuse was identified in 7.4 percent of patients screened. In 1972, that proportion rose to 22 percent. Since then, it was seen in 13 percent of those screened. The author notes that this increase occurred around the time that amphetamines were withdrawn from the South African market in December of 1971. He reports that the source of abuse fenfluramine was regularly illicit with no fenfluramine abuser using fenfluramine for weight control.

In addition, that's the body of the case series data. Some of the other data that we have relevant to human self-administration include a survey of addiction medicine specialists affiliated with ASAM reported by the sponsor. This specifically included the ASAM Board of Directors and ASAM Chapter Presidents. None of those interviewed had heard of a case of fenfluramine abuse or addiction. None of the eight treatment facilities interviewed reported having

treated such a patient. Pharmacists at the institutions surveyed were not aware of problems with falsified prescriptions or persons going to multiple doctors to obtain medication.

Finally, I would raise the question again of recent reports of combination of fenfluramine and phentermine being used in the treatment of a wide variety of addictive disorders in addition to obesity. You have heard some about this today. While there may be reason to rigorously investigate the possible therapeutic use of fenfluramine and/or phentermine in the treatment of addictions, there is concern about the possible increasing use of fenfluramine and phentermine in a population of patients particularly vulnerable to drug addiction.

I would summarize this data in addition to some other laboratory type studies that I included and summarized in your packets by saying that the available reports are sporadic, that high doses of fenfluramine greater than 80 milligrams a single dose seem to be the most common subject of abuse. These doses appear to be capable of producing euphoria, hallucinations and other psychotropic effects. Although reports are few, abuse of fenfluramine originally perspective for weight control may be

associated with stimulant effects and euphoria, while primary abusers may be more likely to report hallucinations in addition to stimulatory effect.

The largest case series suggests that the emergence of fenfluramine abuse occurred at a time when access to amphetamine became relatively more restricted to a population with a substantial drug abuse problem. Other reports of abuse are potentially consistent with these observations. Reports suggest that abusers of fenfluramine may experience tolerance dependence and a withdrawal-induced depression in addition to euphoria and hallucination. It has been suggested that dependence on fenfluramine may result in order to maintain a normal mood.

The report of the ASAM survey suggests that the problem of fenfluramine abuse, however, is not likely to be widespread at the current level of control and with no changes in the availability of other more attractive stimulants.

I would add one more note to this, which is that the analytical toxicology of amphetamines and anorectic drugs is of some concern here. While fenfluramine will produce a causative result in screening for drugs of abuse, it does not appear likely that fenfluramine would be identified as the

cause of such a reaction in the absence of a specific program screening for its possible abuse.

CHAIRMAN MEISCH: Doctor Kramer, I think that some of the information presented suggests that within the last eight years or so there have been no systematic series of cases of fenfluramine abuse. Is that something you would agree with or disagree or comment on?

DOCTOR KRAMER: I would agree with that and I would just add the concern about the analytical toxicology of amphetamine is not resolved in the extent to which one might see fenfluramine as a potential drug of abuse resulting from routine drug abuse screening is not clear to me.

DOCTOR WRIGHT: May I ask you to clarify that for me, Doug? If I understand you, what you're saying is that since a common method for detecting drug abuse in America is toxicologic screening, there exists a possibility that cases of fenfluramine have not been identified because of deficiencies in the way in which laboratories screen for stimulant compound.

DOCTOR KRAMER: That is correct.

DOCTOR WRIGHT: Thank you.

CHAIRMAN MEISCH: Doctor Cicero?

DOCTOR CICERO: I apologize for the

spontaneous outburst by that group down there. They're not to be doing that. I think I just have a couple observations and we'll directly address Curt's point.

Doug, I don't have any difference of opinion with you whatsoever on the data that you presented. I would remind you, as the Chairman did, that the period covered 1971 to 1975. Since 1975 there has been nothing, not even a case report. I think that's important for us to remember.

There is an issue with respect to the measurement of fenfluramine in urine which prompted the outburst. I'll ask Doctor Campbell to address it.

DOCTOR CAMPBELL: I originated the first methods for measuring amphetamines and fenfluramine in blood in the world, so I have a little bit of expertise in this area.

Could I just ask what the screening method is for these drugs in urine?

DOCTOR WRIGHT: There's no simple answer to that. The difficulty is that in American practice over the last 20 years the standard for screening has been very, very variable, has gone all the way from very rudimentary TLC screening in some locales through antibody testing by a variety of different kits and

methods in others, sometimes with confirmation, sometimes without. I do not think the implication is that there has been a widespread complete failure to recognize fenfluramine.

The concern which I believe is legitimate and must be raised, that given the wide variety of testing methods that have been used in drug abuse treatment, that it is clear that fenfluramine is likely to show up positive on many forms of antibody screening, but unless it was looked for on confirmatory GC mass spec it might not be identified by all facilities or it might not be identified by facilities that did not routinely use GCMS confirmation of positives.

DOCTOR CAMPBELL: As far as I know, the sort of methods which I use, TLC, GC, HPLC, and even ELISA methods, they would all pick up fenfluramine and its metabolite. In fact, I know of none which probably won't.

The problem that you might have is false positives in comparison with, let's say, amphetamines, and therefore you might pick up fenfluramine thinking that it was an amphetamine. But clearly, if that was the case, your techniques would do GCMS and you would be able to separate those out. So I must admit, I --

even though you --

DOCTOR WRIGHT: Let me try to clarify again. I'm sorry to interrupt you, but our concern was that it was only in the very recent years that routine GCMS confirmation of positives became a standard of practice. Our concern was that fenfluramine would be identified as amphetamine if only antibody testing was done.

DOCTOR CICERO: Absolutely a valid point.

DOCTOR CAMPBELL: But I think now things have changed.

Coming back to the original point, would you now say that even with the methods which are now in routine practice the majority, except if they're very bad, even though you're denigrating those, would pick up fenfluramine?

DOCTOR WRIGHT: My perception is that at this point in time with many programs adhering to the federal standards which require confirmation and certification of the laboratories that fenfluramine would be identified perhaps within studies done within the last five years, ten years, five years certainly, ten years possibly.

CHAIRMAN MEISCH: Doctor Kramer?

DOCTOR CICERO: I think Doctor Wright was

referring to, again, the Controlled Substance Act which we're discussing, which refers to past as well, and I think Doctor Wright was trying to make some very perceptive comments on that point. They're well taken.

CHAIRMAN MEISCH: Doctor Kramer?

DOCTOR KRAMER: I would bring to your attention the fact that, for example, under NIDA drug testing regulations it is not required that fenfluramine be identified as the cause of, for example, a false positive screening for amphetamine, and that is part of my concern in talking about this particular issue. I don't know the extent to which clinical screening laboratories that have adopted a screening program based on that type of philosophy will go on to identify the positive or false positive screening for amphetamine.

DOCTOR CICERO: Well, if that is true, I think there probably are steps that could be taken to correct that. In fact, the educational material -- what you're really talking about is if somebody is using it in an inappropriate method some form of education should take place, but I'm not aware of what you're speaking in terms of NIDA.

Jim Cooper is sitting there. I don't know

if he can comment.

DOCTOR WRIGHT: I made a promise to the Chairman that I would try to keep our attention focused to those issues that deal with self-administration in the interests of serving the Committee.

I think there is a legitimate point that when a new drug enters into increasingly common use that acknowledging that and dealing with it in the routine toxicologic testing that's done is there.

I think Doug's point that there is a possibility of under-recognition is there as well.

Mr. Chairman, I'd like to call upon Doctor Hayes to give some of the parts of her talk that pertain to self-administration at this time.

DOCTOR HAYES: Well, look like you all are going to be spared from a long preclinical presentation on fenfluramine.

I have to agree with Doctor Cicero that the preclinical and the clinical studies that has been conducted with fenfluramine and dexfenfluramine have shown that is lacking in reinforcing efficacy. The discriminant stimulus properties of the compound, in other words the subjective effects of it, have shown that it is -- first slide -- it is not amphetamine-

like in a variety of species that has been used in the various types of drug discrimination paradigms. Rats, monkeys do not call it amphetamine-like, but there is some overlaps with the subjective profile of fenfluramine with cocaine.

Next slide.

Consistent with its mechanism of action, drug discrimination studies have shown that apparently there's a serotenergic component to its subjective profile such that varieties of 5-HT1 and 2 direct agonists were generalized to fenfluramine and vice versa. Serotonin antagonists will attenuate the stimulus effects of fenfluramine. Consistent with this mechanism there is some overlaps in the subjective profiles with LSD, mescaline, MDA and MDMA. I won't go into details with this studies.

Next one.

Self-administration paradigm is routinely used to look at the reinforcing efficacy or, in other words, this positive reinforcing effects in a variety of laboratory animals. Looking at rats, primates and dogs, the results are very consistent. Fenfluramine is not self-administered in these animals that are trained to self-administer cocaine or the amphetamine or the one study, methohexital by Woods and

colleagues.

In a study on the progressive ratio, I want to point these two studies out. They are used to measure the strength, the reinforcing efficacy strength of a compound such that an animal in this study done by Roland Griffin and colleagues, the animals, baboons in particular, started off at FR 160. These animals are allowed to -- I mean with each session the FR values increase until the animals reach what we call a breaking point. A breaking point is how high can you push the FR value and the animal will still self-administer drugs.

Well, when fenfluramine was tested in animals trained to self-administer cocaine, it would not maintain self-administration and no breaking point value was attained. Similar results was attained with dogs, which again support the lack of reinforcing efficacy of fenfluramine.

Next slide.

Now, very few clinical studies have been done with humans, but on the few studies that's been done either using something similar to the drug discrimination paradigm that is used in animals or used in a standard double blind clinical trials have shown that within therapeutic dose ranges fenfluramine

is not amphetamine-like. But when you start pushing the doses up and what you will see in some of the cases that Doctor Kramer was discussing where people were abusing fenfluramine, when you start getting into these high dose ranges you do get an LSD-like subjective effect which is consistent with what you see in drug discrimination paradigms. When you get to 80 to 400 milligrams, some of the patients describe it as being euphoric-like, hallucinations and derealization.

But in a study done by Johanson looking at five and 20 milligrams of fenfluramine in comparison to d-amphetamine, when the subjects had a choice in whether they wanted to take d-amphetamine or fenfluramine, they chose amphetamine, 5 milligrams over 20 milligrams of fenfluramine.

Next slide.

So, in conclusion, the racemic fenfluramine and dexfenfluramine subjective effects are dissimilar to those of d-amphetamine. Apparently the subjective effects appear to consist of a non-hallucinogenic serotenergic component and a hallucinogenic serotenergic component and fenfluramine does not possess reinforcing efficacies at doses that are comparable to those used at therapeutic levels.

CHAIRMAN MEISCH: Okay. Thank you.

DOCTOR WRIGHT: If it is acceptable to you, Mr. Chairman, I would ask Doctor McCloskey to talk a little bit about some of the suicide data.

CHAIRMAN MEISCH: That's acceptable.

DOCTOR WRIGHT: The reason is that our current divisional experience with drug addicts suggests that the fatalities among drug dependent individuals run about one-third trauma, one-third overdose/suicide and one-third medical complications.

CHAIRMAN MEISCH: All right.

DOCTOR McCLOSKEY: Good morning. I'm Carolyn McCloskey from the Epidemiology Branch and I've been asked to present the drug use data and the adverse event report information for certain events associated with the abuse potential of fenfluramine.

Next slide.

Fenfluramine has been available in the U.S. since 1977. It was approved and controlled in 1973. The U.S. FDA Adverse Drug Event database called the Spontaneous Reporting System or the SRS contains reports which are voluntarily submitted from U.S. and from foreign cases. This table shows the numbers of reports from both U.S. and foreign cases for each of the specified COSTARTs or coding symbols for adverse

reaction terms in the SRS database. Under reporting of adverse drug events is well known and duplicate reporting of cases is not unusual. Each case my have more than one COSTART term to describe the event. So, the numbers in the charts are the numbers of reports, not necessarily cases which were obtained by computer line listings. So, the next to the last column should really be reports total.

I reviewed the hard copies of fenfluramine reports and found that the two suicide attempt cases were also COSTARTed as a type of overdose. There are four additional intentional overdoses and five additional overdose reports. Therefore, withdrawal syndrome cases, but no drug dependence, addiction or increased tolerance cases. The two deaths were an overdose and an attempted suicide case. The other anorectic agents in the SRS are listed in this table. However, these numbers reflect on the computerized data and not a hard copy review. Thus, these numbers may include the duplicate reports.

Of the fenfluramine cases, the two suicide attempt cases were both reported from France and neither had much information, but both had elevated blood levels of fenfluramine. One also had an elevated blood alcohol level and died with

bronchopneumonia. The other case also took chlorodimethyl diazepam in a suicide attempt and was hospitalized in a coma with seizures and hypotension.

As mentioned, two of the 14 overdose cases are also costarted as suicide. So, I'll just cover the remaining 12 overdose cases of four intention overdose, five unspecified overdose, and three accidental overdose cases.

Of the four intentional overdose cases, two were U.S. cases, a 36 year old female with hypotension, and a 13 year old male with mydriasis. There's little additional information. The other two were reported from France. A 36 year-old woman who was found dead in her home with an elevated fenfluramine blood level and evidence of chronic fenfluramine use and a 12 year old girl who was admitted with hallucinations and nystagmus.

There are five unspecified overdose cases, all from the U.S. Two may be intentional overdose cases. Both were female. One had no additional information and the other was a 12 year old who had tachycardia and mydriasis but there was little additional information. The other two cases were female. One had AV block. The other reportedly also took diethylproprion which has been alleged to be the

cause of her acute psychosis with hallucinations, depression, schizophrenia and brain damage. The fifth case, a 51 year old male, developed a personality change with assertiveness and forgetfulness after starting what his wife believed was a higher than prescribed dose of phentermine and fenfluramine.

The three accidental overdose cases were all in children.

There were four withdrawal syndrome cases associated with fenfluramine in the SRS. Two were from the U.S., one from the Netherlands and a 13 year old female from France. In all of these cases, the onset of symptoms occurred one to three days after decreasing or stopping the fenfluramine. The two hospitalizations were the 13 year old female who developed seizures and a 49 year old female without a prior psychiatric history who developed an acute psychosis. The other two cases had insomnia which resolved on restarting fenfluramine. These withdrawal syndrome reports indicate that patients on fenfluramine can develop a dependence to the drug.

Next slide.

Since dexfenfluramine is not available currently in the U.S., the World Health Organization's database of worldwide reports of adverse drug events

was searched for reports of potential abuse with various anorectic agents. The under reporting to this database makes it unreliable but we used it to find the dexfenfluramine reports. This table is of WHOART counts from the WHO database. WHOART stands for WHO Adverse Report Term. As you can see, there were five reports of suicide attempt for dexfenfluramine and three for fenfluramine.

For drug dependence and drug abuse, dexfenfluramine had two dependence reports and fenfluramine had one. There were three abuse reports for fenfluramine and none for dexfenfluramine. There were 31 withdrawal syndrome reports for fenfluramine and 27 for dexfenfluramine. There were no reports of increased tolerance for fenfluramine or dexfenfluramine. All but one of the reports were non-U.S. reports and the one U.S. withdrawal syndrome was for fenfluramine. We received these WHO counts but not line listings or case reports.

Next slide.

The Drug Abuse Warning Network, or DAWN, is handled by the U.S. Substance Abuse and Mental Health Services Administration. They collect data from about 500 to 600 emergency departments around the U.S. Available data is from 1988 to 1993.

Fenfluramine is implicated in six cases of attempted suicide and two cases of using the drug for a psychic effect. Two of the suicide cases also reportedly took phentermine as well.

The following Pondimin drug use data is from the National Prescription Audit Plus, or NPA Plus, computerized records of IMS America. Since 1992, NPA Plus collects data from 20,000 computerized retail pharmacies and 600 manual data pharmacies in the U.S. These are independent chain and food store pharmacies. The estimated new dispensed prescriptions, not refills, of fenfluramine has been increasing, 39,000 in 1991, 64,000 in '92, 155,000 in '93, 282,000 in '94 and 547,000 as of July of 1995.

The demographic data for fenfluramine drug use is from the National Disease Therapeutic Index, or NDTI, also of IMS America. This information is based on patient and treatment data collected from 980 randomly selected office-based physicians each month which includes new and refill prescribed or office-dispensed fenfluramine. Information is available starting in 1994 because the previous years had too few numbers. Of the office visits where fenfluramine was dispensed, 89 percent were women, all of them in the 20 to 59 year old age range.

Of the males, the remaining 11 percent, 64 percent of them were in the 40 to 59 year old age range. For all patients, obesity was diagnosed in 97 percent of them and obsessive compulsive disease in three percent. Phentermine was the concomitant drug in 66 percent of these visits.

The reporting rate for fenfluramine suicide attempts in 1993 is two per 100,000 new prescriptions calculated from the DAWN cases and the NPA Plus prescription data. This is only a rough estimate due to the wide confidence limits for such small numbers and certainly is not a valid incidence rate. There was only one case reported in any particular year for the other event categories.

Last slide.

There are several limitations of voluntarily reported data and the SRS database. These should be identified clearly before interpreting this data. Due to the voluntary reporting of cases, there is no consistent quality of data. There may be duplicate reports and under reporting of a particular adverse event. In discussing the tables, I have already mentioned that one case may have more than one COSTART term to describe it and therefore may be counted under more than one COSTART term in the table.

The drug use data presented as new prescriptions is our best estimate of the number of persons exposed to the drug or who used the drug, but these are only estimates of the denominator. These COSTART counts and drug use data can be used to calculate a reporting rate but incidence rates and estimates of drug risk cannot be assessed based on this data alone due to the duplicate reporting and under reporting.

It is not recommended to make comparisons of the number of reports between different drugs because of a number of factors. One, the length of time a drug has been on the market. Two, the type of use the drug has. Three, the population in which it is used. Four, the advertising. These factors affect the type of reports, the number of reports, and the periodicity of reporting. Therefore, it is not recommended to compare reporting rates, the number of reports per year or other types of comparison. Once again, because voluntary reports do not reflect the actual numbers of an outcome, it is impossible to determine incidence rates.

In conclusion, we cannot determine incidence rates for these events and these reports should not be used as a predictor of events,

especially if there are different drug use circumstances. However, the numbers of dispensed prescriptions of fenfluramine, although low, are continuing to increase, thus increasing the probability of more reports of suicide, overdose or withdrawal.

The anorectic agents, fenfluramine, phentermine, amphetamine and benzphetamine, do have several spontaneous reports of attempted suicide and intentional overdose associated with the drug. These and other reports, such as unspecified overdose and withdrawal syndrome, do lend credence to the possibility of drug dependence and of drug abuse for the anorectics, including fenfluramine.

Just before I leave the microphone, I felt that somebody should address Doctor Cicero's statement earlier in his presentation that dexfenfluramine has a protective effect on overdose as compared to the whole population of all women in France.

First, I just wanted to point out that it appears there are two populations being compared here. One was the population of dexfenfluramine users and the other population was of all women in France. I suggest that since these are different populations, comparing the different drugs is questionable. To say

that dexfenfluramine is protective is really not a valid statement unless we know more about it.

CHAIRMAN MEISCH: Thank you.

DOCTOR WRIGHT: I have talked with Doctor Lutwak and he does not have any information that pertains to the self-administration of the drug. I would ask the guest speakers, Doctor Wadler, Doctor Wright, and Doctor Seiden, if they have any information that pertains to the likelihood of self-administration in man.

CHAIRMAN MEISCH: Doctor Seiden says no.

DOCTOR WRIGHT: All right. I think there is some information held by these speakers that we should go through, but I understand your desire to press the main question at this time, Mr. Chairman.

Is Mr. Tolliver here?

DOCTOR J. WRIGHT: Good morning. My name is Jim Wright. I'm a physiologist retired from the military and presently am serving as the editor of Muscle and Fitness magazine, one of these bodybuilding publications.

Obviously, bodybuilders and other strength power athletes do use drugs and other legal substances with anorectic properties. However, their primary intent in using these substances is not appetite

suppression, but rather a search for the stimulatory effects of the sympathomimetic type effects that they might offer.

The most common stimulating/anorectic substances currently used by the bodybuilding community are ephedrine, caffeine, often accompanied by aspirin.

The use of fenfluramine in physical culture came to my attention last year. As a result of a talk I was asked to give to the Department of Justice, I surveyed 18 top level athletes, coaches and gym owners around the country. In the course of those surveys and subsequent interviews, I was able to identify six individuals, all males, all in their mid-30s, all at or about at some point in the past a national level status in bodybuilding or the strength power sports. These six individuals had indicated that they had used fenfluramine in dosages ranging from 15 to 60 milligrams. All used fenfluramine to induce drowsiness, not for the stimulating effects. All were also simultaneously using anabolic steroids and a variety of stimulants, mostly over-the-counter substances like ephedrine. All were heavy ephedrine users.

A follow-up approximately a month ago on

five of these six individuals indicated all five had terminated use. The longest period of use of any of these individuals was approximately ten weeks. The rationale for cessation of use was that there was sort of -- not a depressive state. I didn't attempt to pursue any definitive psychological thing, a diagnosis, but there was a sense of fatigue that even though these individuals were continuing to take, self-administer these stimulatory substances, they felt that they were unable to train at the requisite volume and intensity that they desired.

So, essentially, my conclusion from a rather limited survey is that there is essentially no misuse and no diversion in the bodybuilding and strength training community at this time. However, if a PR and marketing campaign gears up, any time the public becomes education, and if in fact any thermogenic or antilipogenic effects of these drugs are made available to the public, this type of information in the popular press, particular the bodybuilding press, then I would see certainly the potential for some increase in use of these substances.

CHAIRMAN MEISCH: Thank you.

DOCTOR WRIGHT: Doctor Wadler has spoken

to me and he does not have specific information with respect to fenfluramine and would like to speak later.

Doctor Mann?

DOCTOR MANN: Well, I was actually expecting to present after lunch and I had some slides. But very briefly, let me give you some background.

The data that we have, having used fenfluramine as an acute challenge agent to look at the responses of serotonin in normal controls in patients over approximately a 12 year period doesn't, pertain directly to the question of its abuse potential, but does address a number of sort of related issues, like the question of the relationship of dose to CNS effects, specificity for the serotenergic system and the effect of test, retest in animals, non-psychiatric subjects and in psychiatric subjects. So, all of this to some degree addresses in a way the potential, I suppose, for adverse CNS effects.

First, just sort of an obvious thing. I can see a fingerprint on this transparency. But anyway, the dose of the drug that's administered to individuals is of some considerable relevance. We've tended to use approximately one milligram per kilogram

and here an important divergence begins to emerge between normal subjects in patients with various kinds of conditions.

Briefly, what you can see from this slide is that there is somewhat of a correlation between the plasma level of the drug achieve and the weight-related dose.

If I could have the next transparency, the relevance of this will become clearer. I'm sorry for those of you who are at the back. I didn't realize this was such a large room.

These data come from a study that my colleagues Matthew Muldoon and Steve Medig and I have been performing at the University of Pittsburgh where I was until about a year and a half ago. It's a study that's being done in non-psychiatric individuals who are presenting with mildly elevated cholesterol for cholesterol reduction. All of these have received a very detailed psychometric battery before they begin a course of cholesterol lowering.

From this study, looking at the baseline data, you can see that body weight does correlate with plasma concentration. In other words, the heavier the individual the lower the concentration that's achieved in the blood. I think the most important issues here

really relate to the symptoms that are generated by administering the drug. It's clear I think from this slide that plasma concentration does bear some relationship to the symptom severity. The level of prolactin which is serotoninly mediated in its release bears a still stronger relationship.

Now, if I could have the next slide, please.

The types of symptoms that are generated on acute administration are listed as follows. You can see that actually fatigue is at the top. That covers a large range of types of symptoms. In fact, 83 percent of the subjects reported that 43 percent reported headache, 41 percent lightheadedness, 34 percent cold and 18 percent difficulty concentrating.

Now, the significance of these data are that, in fact, if you asked the question how many patients reported on the first day after receiving fenfluramine symptoms that interfered with normal activities, the answer is approximately 50 percent. If you ask how many people still had symptoms on the second day, the answer is about 30 percent. So, the appearance of symptomatology in response to the drug that involved what we would regard as CNS effects are really very prevalent.

Now, what's interesting is that when we set up the study and the dose that averaged out to a little just over .7 milligrams per kilogram, we had assumed that there would be relatively few symptoms. In fact, the symptoms were far more common than in our patients. The reason for that, we assume, is related to the prolactin response as a guide.

The prolactin response in these individuals tends to be far more robust than in many patient groups. People who are suffering from major depression, people who have certain types of personality disorders characterized by impulsivity and aggressivity, people who have a lifetime history of a serious suicide attempt, all of these types of psychopathologies are associated with a blunted prolactin response to fenfluramine. And interestingly, relatively little symptomatic response to acute challenge.

So, there's an apparent difference in the severity of responses behaviorally and in the brain neuroendocrine wise in normal subjects compared to people with psychopathology. Another way of putting it is that effects on the brain in psychiatric patients tends to be in those diagnostic categories or with those behavioral characteristics tends to be less

than in normal subjects. I think that may be relevant for the Committee's deliberations.

The second point that I'd like to make in relation to this -- in fact, we actually reduced the dose subsequently in normal subjects because we were having trouble with people tolerating the acute challenge.

The second I'd like to make is that when you rechallenge subjects two weeks later, and these are not our data, these have been reported elsewhere, the neuroendocrine responses are blunted. But if you rechallenge subjects four weeks later, and we have data on this in monkeys, in healthy individuals to a very limited degree and also in patients to a significant degree, the degree of response, at least from the neuroendocrire standpoint and the symptomological standpoint, appears to be the same. So, there isn't really much evidence that the first dose, which had been 60 milligrams for an average individual, produced an effect that was diminished when retesting subjects four weeks later. I think that speaks to the question of some sort of enduring CNS effect.

The final point that I think I'd like to make before closing relates to methodology of --

actually, if you could go to the very last transparency, I think this shows you actually.

If you use the prolactin response, and I've referred to that sometimes as an index of effect on the CNS, you can see that it's actually not a bad index because the symptom severity shows quite a strong relationship to the prolactin response. You can see that more clearly in this slide, this transparency.

The final point that I wanted to make is that we've been using very crude measures. We now use far more sophisticated measures to look at CNS. We're developing cognitive batteries that we think would be more sensitive to the effects of drugs like fenfluramine that cause an increase in serotonin release. There are really very minuscule data on this subject. I see the Committee is struggling to find relevant information.

What I had in the slides was a series of pet studies showing the effects on the brain directly, the regional brain effects of giving acute challenges of d/l fenfluramine to normal controls and to patients. When you do that, what you see is that although there's very little difference between the groups in terms of prolactin response, a mild blunting

in patients compared to controls, and the blood levels achieved by the patients are comparable to the controls, the effects on the brain are dramatically different. There are substantial robust increases and decreases in different brain regions as measured by regional glucose metabolism on PET scanning in normal individuals receiving fenfluramine. They are substantially greater than as seen in patients.

So, this represents functional brain imaging data to support the notion that for some reason patients, particularly with the major depression on which you have the most data show a blunted behavioral, biochemical, neuroendocrine response to this agent.

Thank you.

CHAIRMAN MEISCH: Thank you.

I want to keep the Committee focused on the question of abuse. Actually, I'd like to know at this point where we stand.

Doctor Wright, was there any additional speakers at this point?

DOCTOR WRIGHT: I just simply want to ask the speakers.

The Chairman has called for any information we hold on the self-administration of this

drug. Doctor Fleming, do you have any information in that regard? Okay.

Doctor Tolliver?

DOCTOR TOLLIVER: No, I don't have any information on self-administration.

DOCTOR WRIGHT: Okay. Do any of the liaison members have any additional information on self-administration that has not been presented at this point?

DOCTOR COOPER: I have information --

DOCTOR WRIGHT: Of what type of abuse?

DOCTOR COOPER: Well, what we've actually done is gone through and looked at some of the other surveys data on actual abuse and looked to see whether or not any reports have been actually reviewed.

DOCTOR WRIGHT: I think that would be very germane.

DOCTOR COOPER: That's not self-administration.

My name is Doctor Cooper and I'm the liaison from the National Institute on Drug Abuse.

Maybe what I'll do is I'll also hand out something that we've prepared. We were going to speak this afternoon, but I can tell you what I've actually been able to find so far.

CHAIRMAN MEISCH: Good. Please.

DOCTOR COOPER: I would ask that the handouts that I've presented or am handing out, I'd ask you not to look at that information at the moment because it needs to be put in the context of the other information we have.

From the discussions you've heard this morning so far, we face the same kinds of questions ourselves. Here's a drug that's not self-administered. From the case reports, it's relatively rare and abuse and consequences. So, we went back and looked at it. For those of you who are not aware, there are two different surveys, the Household Survey and the High School Senior Survey, which NIDA has had some part in for a long time. The Household Survey has been moved to SAMSA, but its origin started in NIDA. We have frequent communication, liaison with those folks.

So, we went back and looked at the data from those over the last ten years in both of those surveys and found absolutely nothing as far as the abuse of fenfluramine in either the Household or the High School Senior Survey.

We looked at the DAWN data, the DEA report, which those of you who have this in your

packet have seen and also found results similar to what Doctor McCloskey showed this morning, that indeed since 1988 when they've been collecting from this particular panel that there's been eight reports and total mentions.

So, what I had prepared this afternoon and what I have handed out here for the Committee is trying to put it in some perspective. In thinking this thing through, clearly how would we compare it with what and whether it would be stimulant or a depressant or LSD type drug. We chose, because of its indication, it's most often associated as an anorectic, to compare it with other stimulants. That's what I'd like to move to and that's what I handed out.

If you'll go to the last page first, you'll get a sense. What I tried to do was to put in perspective for the Committee the relative -- DAWN data is obviously a consequence, potentially a consequence of abuse. What I tried to do is compare other stimulants, both scheduled drugs as well as uncontrolled drugs and just take a look at the aggregate mentions of these various drugs, keeping in mind during the same time there were eight mentions of fenfluramine. I think it becomes fairly obvious when

we talk about the fact of the consequences at least. And it also put into context the fact that over the last few years the actual number of fenfluramine prescriptions is going up.

Okay. Now, just to help you understand the first chart, the second page actually talks in terms of percent of total ER mentions. Again, you have to keep in mind fenfluramine doesn't appear on here because, again, the data only talks about -- there's no data on anything under the 200 mentions. The chart actually gives you again some perspective, which I would leave you with and, in fact, it is far and above. The drugs that are primarily abused in the stimulant category are amphetamine and methamphetamine and according to DEA those drugs are primarily clandestinely manufactured.

CHAIRMAN MEISCH: Okay. Doctor Cooper, just to summarize, you've mentioned that it was not self-administered, that the abuse is rare, and then what you've stated, that it's rarely or never mentioned in some of the surveys. Is that correct?

DOCTOR COOPER: That's correct, in comparison to these other drugs, both controlled and uncontrolled, and two of these compounds we chose to

mention in this draft are actually over-the-counter, or three of them, actually, ephedrine, caffeine, and pseudoephedrine are over-the-counter products.

CHAIRMAN MEISCH: All right.

Doctor Wright, I want to proceed ahead unless you have some additional people that want to speak.

DOCTOR WRIGHT: I know of no additional speakers that we have that have information relating to the likelihood of self-abuse, of self-administration and abuse of this agent. Am I mistaken in this? Does anyone hold any additional information at this time?

Mr. Chairman, it is your meeting.

CHAIRMAN MEISCH: I want, to state again, to focus on abuse at this point, not on efficacy and not on toxicity.

DOCTOR BONE: I just have a question on the distinction between abuse and misuse. I understand that misuse would be considered, for example, off-label or inappropriate prescribing, and abuse, as we've heard about it, would be, for example, self-administration in order to get high or have some experience like that. What would be the classifications for the persons for whom the drug had

not been prescribed taking it for weight loss? For example, adolescents that did not receive prescriptions from their doctors but were wanting to obtain it from others.

DOCTOR MEISCH: I don't know if there is a technical term or phrase for that. Doctor Wright?

DOCTOR WRIGHT: Generally, failing to use a drug in accordance with the recommended labeling is considered to be off-label use or misuse. Obtaining a drug through illicit means for purposes of abuse is considered to be abuse. Traditionally, someone obtaining a drug for its psychoactive effects or to get high would be abuse. Someone illicitly obtaining a drug for purposes of weight loss would be misuse.

DOCTOR MEISCH: All right. Doctor Cicero, did you want to say something?

DOCTOR CICERO: As usual, Doctor Wright summarized it beautifully. I don't have to make any comment.

DOCTOR MEISCH: All right. I want to poll the committee at this point to see where people stand. The question is, is there evidence for self-administration/abuse? I would like the question considered without regard to whether it is effective or not and without regard to whether the drug is toxic

or not. Who wants to start that? Doctor Young?

DOCTOR YOUNG: Mr. Chairman, in view of the presentation by both the FDA sponsor and by Doctor Cooper from the National Council on Drug Abuse, I would

-- if you are asking us to answer the first question, do we recommend decontrol -- is that the question?

DOCTOR MEISCH: Well, the question is very specific, which is about abuse.

DOCTOR YOUNG: I saw no evidence to suggest that this compound supports self-administration abuse.

DOCTOR MEISCH: All right. You, sir?

DOCTOR BORHANI: I agree with her.

DOCTOR KHURI: You've focused us so well, Mr. Chairman. I certainly agree.

DOCTOR MEISCH: Okay. Doctor Luisada?

DOCTOR LUISADA: I agree with Doctor Young.

DOCTOR MEISCH: Okay. The next person, please?

UNIDENTIFIED SPEAKER: Agency.

DOCTOR MEISCH: Okay. Doctor Bone?

DOCTOR BONE: I agree that the information we've heard does not indicate that there is a

significant problem with abuse.

DOCTOR MEISCH: Ms. Torres?

MS. TORRES: No, I agree.

DOCTOR MEISCH: Okay.

DOCTOR CRITCHLOW: I also agree. But I would also like to state that -- I guess I would like to state that I am not sure that all -- that we can say based on this data that incidences that are out there would be picked up. I don't know to what extent--

DOCTOR MEISCH: Well, I think you have to make that judgment, again, based on the data.

DOCTOR CRITCHLOW: I mean, based on what we heard. What I don't know is what else might be out there that -- I mean, this has not been systematically looked for in my opinion. But at least based on what I hear today, I would have to agree that the evidence is not there.

DOCTOR KHURI: I would just like to make the comment that with increased use -- vastly increased used and increased marketing, abuse might occur. But we can't get a handle on that now.

DOCTOR MEISCH: Well, all we can do is take the existing information and make some statement. Doctor Wright, the general thought of the committee is

that these substances are not abused and do not seem to have potential for abuse. This statement is made, once again, independently of presence or absence of efficacy and independent of presence or absence of toxicity.

DOCTOR WRIGHT: It is necessary for you to address the questions. Those are what we did ask you to address. It appears, if it is the uniform opinion of the committee that there is no or vanishing small evidence of abuse of this substance at this time, that you may properly address question 1. The rest of the presentations, I think, do bear on question 3. So, from my perspective, you may, if you choose, using the powers of autonomy that have been granted to you, address question 1 at this time. I would ask that you hear the remainder of the presentations before you address question 3 in any way.

DOCTOR MEISCH: How about question 2?

DOCTOR WRIGHT: Question 2 will depend on the answer to question 1.

DOCTOR MEISCH: Okay. Can I have a motion to decontrol?

DOCTOR BORHANI: So moved.

DOCTOR MEISCH: A second?

DOCTOR YOUNG: Second.

DOCTOR MEISCH: Okay. Any more discussion at this point?

DOCTOR WRIGHT: You need to specify what you plan to decontrol.

DOCTOR MEISCH: Yes. The statement is to decontrol fenfluramine and all its isomers, including dexfenfluramine.

DOCTOR WRIGHT: Fenfluramine and all its isomers?

DOCTOR MEISCH: Yes.

DOCTOR WRIGHT: Mike, I need a chemists opinion. Does that cover both of them?

DOCTOR MEISCH: Yes. That is it. All in favor, please raise their hand for decontrol. Opposed? Abstain? Two abstentions.

DOCTOR WRIGHT: Steve, will you give me the totals now?

MR. POLLITT: That is 6, 4, and 2 abstain.

DOCTOR WRIGHT: Mr. Chairman, I am receiving mixed messages here. Could we call for that vote again just to make sure that we've got the numbers right?

DOCTOR MEISCH: Sure. All those in favor of decontrol of fenfluramine and all its isomers, please raise your hand. Opposed? Abstain? All

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

1:49 p.m.

DOCTOR MEISCH: People, please sit down. We are about to start. Doctor Cicero?

DOCTOR CICERO: Thank you, Doctor Meisch. I want to thank the committee for their favorable reaction to the petition by the sponsors to deschedule fenfluramine and its isomers. I think it was not only a wise decision based upon the scientific evidence available to us and in conformity with the Controlled Substance Act, but I think most importantly there has been a major step taken toward developing and getting appropriate medications to the millions of obese people in this country who need it.

Although that actually completes our portion of the presentation, and I think we have hopefully convincingly demonstrated that there is a lack of abuse potential with this product. Wyeth Ayerst and Interneuron, the co-sponsors of the petition, are committed to insure that their products are used appropriately and safely. To that end, Mark Deitch, Vice President of Medical Affairs and the Medical Director of Wyeth Ayerst would like to address the committee briefly.

DOCTOR DEITCH: Thank you, Ted. Mr.

right. We can --

UNIDENTIFIED SPEAKER: Could you announce those numbers?

DOCTOR MEISCH: Yes, I'm sorry. 5 individuals were in favor of decontrol and 3 abstained. By the positive answer to 1, we can bypass question 2 and start considering question 3. And Doctor Wright, does the FDA want to comment on number 3?

DOCTOR WRIGHT: Well, I believe that it is necessary to hear the presentations.

DOCTOR MEISCH: Yes. We will take an hour break at this point and come back and begin to hear those presentations. Thank you.

(Whereupon, at 12:45 p.m. off the record until 1:49 p.m.)

Chairman and members of the committee, thank you for the opportunity of appearing before you today. Let me first apologize if my voice goes. I am suffering from about the third day of a first grader's cold. Fortunately, mine is worse than his. He is in school and I am here.

Let me first tell you a little bit about Wyeth Ayerst and sort of how we got here and what our relationship is with Pondimin and, of course, with dexfenfluramine. Many of you know Wyeth Ayerst is a substantially large pharmaceutical company in the United States. We are number one in total prescriptions in the United States for our products. We are quite well known, I think, to the endocrine and metabolism division as a leader in women's health care.

We also have what we consider to be one of the most highly trained and professional territory representative staffs marketing our products throughout the United States, and they are very much accustomed to educating physicians and health care providers on the proper use of products.

Let me give you an example that may be relevant to the drug abuse advisory committee. You may not know it, but Wyeth Ayerst, through one of its

divisions, the Elkins-Sinn Pharmaceutical Division, does, in fact, market many controlled substances such as morphine and demerol and has for many years, and developed the TAMP-R-Tel system to show tampering. It has manufactured the TUBEX System and one of the main educational programs that they have participated in for years is in helping pharmacies in small hospitals, as well as large hospitals, set up inventory control systems to be in accordance with DEA regulations.

So with that as a background, Wyeth Ayerst acquired A. H. Robbins and thereby acquired Pondimin in 1989. Of course, together, this product has been marketed in the United States for a considerable period of time as you hears this morning, well over 30 million exposures worldwide since its introduction.

Some of you in looking at the slide that was shown this morning may question why the increase in prescriptions in the past couple of years, and I think I need to explain that to you and give you a little bit of perspective. It was mentioned, I believe, earlier this morning that there was a publication in 1992 by Doctor Michael Weintraub, who, as many of you know, is currently head of the OTC Division here at FDA. At that time, at the University of Rochester, he had published what was considered

then a fairly landmark study demonstrating the effectiveness of Pondimin when used with phentermine and also when used alone in a very well-managed program of diet and behavior modification.

The time was probably ripe at that moment for many of the lay press and the magazines, women's magazines especially, to have picked this up, and what occurred was that patients, as they often do, brought those articles in to their physicians, and we have, of course, experienced an increase in prescriptions at that time.

Against that background of increased prescribing, you certainly have noticed that there has not been any kind of concomitant increase or spike in adverse event reports of anything very unusual.

What I am going to go through with you today is what our plans are, what we would offer up, and maybe put into context the types and kinds of things that are available to us in the pharmaceutical industry for managing the use of our products, for tracking the use of our products, and for assurances that they are, in fact, used appropriately.

Let me put into context what we consider what we are calling here initiatives for proper use. Interneuron and Wyeth, as co-marketing partners, as

Wyeth Ayerst expects to market the product in the United States, that being dexfenfluramine, but currently is the marketer of Pondimin or fenfluramine, as with any of our products are committed to the appropriate and proper use of these products.

First and foremost, as we do with all of our products, we will be marketing them in accordance with the FDA-approved labeling -- the currently approved labeling for Pondimin and what we expect to be the approved labeling for dexfenfluramine in the future.

As with any product, since we have not been promoting Pondimin, but of course when the decision is rendered to deschedule, as has been today, that possibility does exist and with increased usage, we will be training our sales force once again in the proper use of this product, as we would with dexfenfluramine. Our sale force will be trained exquisitely well. They are trained generally by the physicians who are in my medical affairs department as well as very well trained trainers as well as outside individuals. Especially in this case, we will certainly be putting it in the proper context.

What we also do is review very carefully any communications that go from our sales department

either directly to physicians and health care providers or to our sales force. They are under not only control for medical accuracy, which my people look at, but also to make sure that they are in concordance with the regulations, that they are in adherence to the labeling, and they also have legal review. We do that with all of our products and will be especially careful here.

Initiating medical education programs for health professionals and patients to stress proper utilization. There are many ways we can do this through professional communications, professional education, pharmacy education, and patient education. We have developed quite a bit of expertise in this. There are many newer technologies that are available to us today that were not available before such as interactive video, which is often used at conventions and medical meetings and is often even brought in to smaller medical meetings, even at the hospital level.

There is computer assisted learning and program learning. But in this area, as we have done in other areas such as the in the area of contraception in trying to educate health care providers on the proper ways to avoid unintended pregnancy, in the area of menopause management, and so

on, we will put together equally exquisite programs for education.

More importantly, let me tell you about the methods by which we currently do and will continue to do, and we will even upgrade systems if necessary, so that both Interneuron and Wyeth Ayerst can conduct surveillance programs to detect any potential abuse or any misuse of Pondimin, fenfluramine, and dexfenfluramine.

Now the components can include, will include, and may include some of the things that we can do. We do have the intention of establishing an independent expert review panel. This would consist of individuals who are, in fact, experts in areas not only of obesity and obesity management, but in fact of abuse and drug abuse. We would have these people meet with us on a regular basis. Our adverse event reporting system is such that it can be looked at on a daily basis. It can be queried on a daily basis. We can see any signal that comes up, and we would utilize these experts to give us feedback on what is it that we are seeing so that, in fact, if there are subtle signs or subtle signals of any potential misuse or abuse, it would not just be the medical people at Wyeth Ayerst and Interneuron who would be seeing

these, but we would have independent review.

We will be able to, and we certainly would, conduct surveys in specific settings to identify abuse and misuse. And since, as was noted this morning by Doctor McCloskey, I believe, from the NDTI information on prescription use for Pondimin in the past year or so, we are looking at a baseline as we start out of approximately 97 percent use for the indication of obesity. That NDTI data base can be used on a regular basis. If we see slippage there or if we see other mentions coming up, we can certainly take educational action to try and correct that.

There are, as you know, many eating disorder clinics. There are substance abuse treatment programs which we've heard about and national sports federations. We will provide them with educational materials and provide them with a line to us, not only our 800 number but other methods of contacting us, and contact people so that we will have an early warning system should there be any indication of misuse or abuse.

Now something that is something new in pharmaceutical medicine and in health care in the United States is the existence and the ability to link and cross-link data bases on not only prescription use

but on, in fact, the indication for use, the length of a prescription, the number of tablets prescribed. That is very sophisticated and, I guess, it really is as a result of managed care and of pharmacy benefit management companies. The so-called PBMs, the pharmacy benefit management companies, didn't exist several years ago, but I am sure if we polled everyone in this room and asked them to hold up a little plastic card in their pocket that was their health care provider card, many of them would have a pharmacy benefit card.

Those records are kept and they are shared with insurance carriers and there are several data bases. In fact, we have exclusive access rights to several of these, where not only can we link the actual patient's usage and prescription usage, but we can link the diagnostic criteria, and in fact we can look at outcomes. This is a tool that many of us use to determine whether or not the proper outcomes have been achieved. Through this, we can also work with the pharmacy benefit managers in a drug utilization program to provide them with educational programs. And to take it one step further, we have full intentions of instituting what some people call disease management programs. We prefer to be less

pejorative and call them health management programs for obesity and weight control. Elements of that certainly would be, among others, proper use of the products with attention to the fact that the labeling, as we've proposed, should include at least a marker of efficacy at four weeks of a pound a week over that 4-week period of time or 4 pounds in 4 weeks.

So through this, we can establish baseline utilization, even though we do have a handle right now on baseline utilization as was shown this morning. That can be refined. We can certainly identify unusual usage. We can easily identify unusual purchase patterns. We do that now under the Controlled Substances Act, and we can continue to do that.

We can look at total exposures and so on. And should misuse or abuse be detected, both Interneuron and Wyeth Ayerst will intervene appropriately. So that pretty much puts into context what we have put together as a plan. This would be the plan that we would initiated immediately or be ready to initiate immediately and certainly be very happy to discuss with Food and Drug Administration other elements that they might suggest or certainly any of the suggestions the committee may have. Thank

you.

DOCTOR MEISCH: Thank you. Doctor Wright, the third question that was here for us to discuss relates to decontrol. If it is recommended, does the committee recommend the sponsor implement a risk management plan to detect, evaluate, and intervene in cases of abuse. I, therefore, ask the committee to turn their attention to this for a few minutes. Comments from committee members?

DOCTOR WRIGHT: Mr. Chairman?

DOCTOR MEISCH: Yes.

DOCTOR WRIGHT: I think there is more information to be heard. I think there are other speakers to be heard before we address question 3.

DOCTOR MEISCH: I didn't mean this is the last question. I mean that the sponsor had --

DOCTOR WRIGHT: I understand. I am sorry, sir.

DOCTOR MEISCH: We will hear additional people speak.

DOCTOR WRIGHT: I believe, if I've kept track properly -- we did jump around quite a bit here -- the next speaker on the program was Doctor Lutwak.

DOCTOR LUTWAK: In a way, what I'm going to say is background to try to help the panel come to

a decision or partial decisions as to what constitutes overall benefit/risk in the use of a medication, and in particular, dexfenfluramine and its closely related parent, fenfluramine.

This is the sort of process that we go through on a regular basis. Many of you heard me say this yesterday. Much of what I am going to say has been touched on earlier this morning. But I think it bears repetition.

When we deal with any drug that has any potential for risks or harm, we are concerned with two aspects, the benefits and the risks. Obviously, nothing is totally risk free and, therefore, we have to accept a certain amount of risk depending on the amount of benefit one expects.

We have heard yesterday and today about the horrendous nature of the growing problem of obesity in this country. The large impact it has in the development of other conditions. We have heard that weight loss may be related to improvement in some of the co-morbidities that produce huge expense to the medical system and tremendous impact on the health of the patient. The epidemiologic studies suggest that voluntary weight loss can improve many of these problems.

What we have not heard yet and what we have not seen in the agency are any solid control data indicating that drug-induced weight loss is the same as the weight loss that has been used and demonstrated to have beneficial effect on heart disease, diabetes, hypolipidemia, et cetera, with weight loss instituted by hygienic methods and by dietary control and improvement in exercise and so forth. As a matter of fact, we know that change in diet and institution of exercise, even without weight loss, does have very definite benefits, particularly in Type II diabetes.

Now where does the drug under consideration today fit into this. The weight loss that has been produced by administration of dexfenfluramine in well-controlled studies shows a statistically significant benefit as compared with placebo. It is borderline from a clinical point of view but it is statistically significant, which falls within the agency's older guidelines.

Decreased co-morbidity has been suggested in various studies that have been carried out on populations that were under control, but these are not quite as clear cut and really have not been defined. Obviously, prolongation of life is not something that we can expect to be demonstrated to us before the drug

is considered. But this is to be hoped for if there can be any clear cut demonstration of improvement to co-morbidities.

That is the one side. So we know what the potential benefits are of wide use of these drugs. And as we heard this morning, if these drugs are decontrolled, they are going to be used extremely widely. We know that even with controls in effect right now with the scheduling of the drug, the drugs are being used quite widely in off-label uses and for off-label periods of time, which are considerations, that the FDA has no control over, of course. But control does seem to have some aspect of control over the misuse of the drug.

Now what are the potential risks that we, as clinicians, have to consider. The neurotoxicity is obviously one of considerable importance to this panel and to this consideration today, and I have to admit that as a clinician I am still confused by the data that have been presented on both sides of the issue. We know that there are histologic tissue changes that occur in a wide species of animals. We do not know what the clinical correlates of these changes may be. We do not know whether these clinical correlates are of any significance. And to me, this remains a wide

open question.

Many drugs in this category have effects on blood pressure, and there have been reports of hypertension reported in certain types of patients when drugs of this type are given and also hypotension with certain anergic drugs. Stroke has been reported in the spontaneous reporting of adverse events. And the one that we are most concerned with is the adverse event of pulmonary hypertension.

As Doctor McCloskey pointed out this morning, most of the data we have concerning adverse events come from spontaneous reporting. And spontaneous reporting is a very poor way of getting a handle, with both over-reporting and under-reporting being possible, depending on the publicity associated with an adverse event. And the true significance is hard to determine without adequate control studies.

But we have to remember something. When we talk about benefit, we want clear cut evidence of benefit. We want good solid data. When we talk about risks, we have to accept much softer type of data. We accept epidemiologic surveys. We accept epidemiologic evidence of potential risks because if we error, we have to error on the side of the patient on protection of the patient.

Now fenfluramine has been widely used, as we've heard, since it was approved on June 23, 1973 by the agency. It has been widely distributed in other countries. Dexfenfluramine has not been available in this country as an approved drug, and we have to combine our experiences or our knowledge by using data from both fenfluramine and dexfenfluramine. As was pointed out, fenfluramine was a drug that was not widely used. Probably it was not promoted widely. It was controlled, but so are all of the other anti-obesity agents, which were used much more widely. And it isn't until we come down to 1993 and 1994 that we start seeing a rise in the use of fenfluramine in this country with a projected use as was pointed out this morning of about 1,100,000 prescriptions this year.

Now the serious adverse events that have been reported with fenfluramine thus far are also rather small in worldwide reporting. Nothing really stands out, but we notice that these data end about 1994. The neuropsychiatric aspects that have been discussed here up until now are effects that one may expect to see soon after the patient starts taking the medication.

Primary pulmonary hypertension and renal failure are conditions that have prodromata that are

very often overlooked and may not be diagnosed until the conditions are full-blow, which may occur sometime after increased use of the drug becomes apparent. So we may expect to start finding, if there is a relationship -- if there is a relationship -- between fenfluramine and dexfenfluramine and primary pulmonary hypertension and possible renal failure, we may expect to start seeing a rise in reports sometime this year, and the data, of course, are not here.

Now we have some other information that we can use to substantiate these hypotheses. The sponsor for dexfenfluramine submitted post-marketing safety data in the past few weeks of all of the data that had been summarized from August 1984 to December 1994, 10 years of experience with this drug. Again, these spontaneous reports, the majority of these, have been reported to various vigilant agencies worldwide and they have been categorized using coaster terminology as serious events or non-serious events. I have listed them here in parallel fashion. CNS events, as was pointed out this morning, includes many that would be considered serious such as stroke, which may or may not be related to the drug use. They also include psychiatric disorders such as severe depression, but these include disorders that led to discontinuation of

the use of the drug or hospitalization of the patient.

Non-serious events are categorized as those that did not lead to discontinuation of the drug and that may have been evanescent and that may have disappeared on discontinuation and the patient did not require hospitalization and never was followed up. So these are rather crude numbers.

But of interest is the fact that of the 703 events that have been reported in these 10 years, a large number of them were listed as some type of sleep disturbance generally characterized as nightmares or daytime somnolence. Dependency was listed -- and of course, many of these occurred in the same patient. So dependency may be the same patient that also showed withdrawal symptoms. But dependency was reported in 115 instances.

Memory loss, specifically listed as memory loss, was reported in 39 cases. There were others that were included as miscellaneous in my breakdown of this because I couldn't determine what the event really was from reading the brief description -- such items as confusional thinking, disordered thinking, aggression, hostility, and so forth.

What I am particularly concerned with is primary pulmonary hypertension. There have been 101

defined cases of primary pulmonary hypertension. Primary pulmonary hypertension is generally an extraordinarily rare disorder. Most of us who have been in practice for any length of time have never seen a case. In 40 years, I have seen one case of primary pulmonary hypertension. So this is a rare condition. Yet, 101 cases have been characterized as primary pulmonary hypertension by the sponsor with full case reports including cardiac catheterization, profusion scans of the lung, with deaths and lung transplants as the consequence.

There were 27 other cases that had pulmonary symptoms. Pulmonary symptoms are very common, of course, in a general population, and extremely common in a population of obese patients. But many of these may be prodromata of primary pulmonary hypertension and at least raise a slight suspicion.

Well going through these 101 cases that have been characterized in the reports from the sponsor as primary pulmonary hypertension seen with dexfenfluramine, we come up with some interesting demographics that lead to a strong suspicion of risk. In the approximately 100 cases that were reported, the female to male ratio was 93 to 7, which is

characteristic both of obesity and thus the population that uses drugs for treatment of obesity, and for primary pulmonary hypertension, which is primarily seen in women.

There were 14 deaths that occurred or that were reported. Because in many cases, follow-up was not possible. Lung transplants were carried out in 6 of the reported cases. Doctor Stuart Rich discussed primary pulmonary hypertension yesterday, and he had two or three points that I think are extremely relevant to our discussion here.

One, primary pulmonary hypertension is almost invariably lethal. The treatment to date prolongs life anywhere from 6 months to 5 years. The treatment consists -- at present, the major treatment is the use of calcium channel blockers, which is relatively unsuccessful, lung transplantation, which is extremely expensive and requires continuing expensive medications thereafter, and recently the use of prostacyclin, which Doctor Rich estimates will cost the patient approximately $5,000.00 to $20,000.00 per month, with the added risks of infection due to indwelling catheters, et cetera.

The patients with primary pulmonary hypertension associated with the use of

dexfenfluramine had an average age of 49 years, plus or minus 13, with an age spread of 18 to 78, in other words, the general population seen with obesity. BMI was average, 31.0 plus or minus 5.8. But of interest is the fact that one third of the patients taking dexfenfluramine who developed pulmonary hypertension had BMI values well below the range for which dexfenfluramine has been advertised. One fifth of the patients had BMIs in excess, in the high range, where drugs to assist weight loss may be of some value. But approximately 20 percent, 1 out of 5 patients, who go on to die within 6 months of diagnosis or go on to live for 4 or 5 years at extreme cost to society and to themselves, were well below the range of weight where the drug logically should be used or where the drug has been used and probably will be used.

Of interest also, and of extreme importance and consideration here, is that many of the cases with primary pulmonary hypertension used additional medications. Again, this is not unexpected since obese patients generally are on many medications and have tried many medications -- antihypertensives, antidepressants, antianxiety drugs, and hypoglycemics, surprisingly, in a very small population. In other words, the patients who may have Type II diabetes are

generally not those that go on to use this drug to the extent that it produces death, and similarly with dyslipidemic drugs.

The drug of most concern is the concomitant use of other anorectics. For various reasons, dexfenfluramine has been used in conjunction with other drugs. Frequently other drugs that have been prescribed for that specific patient's condition and also equally frequently patients obtaining these drugs on their own by doctor shopping and obtaining multiple prescriptions. And of interest are the drugs that were used in conjunction with dexfenfluramine. Fenfluramine has been frequently prescribed in addition to dexfenfluramine. If an education program is to be instituted, physicians have to be educated that the two drugs are almost identical.

Diethylpropion, which is sold in Europe as amfepramone, an amphetamine derivative, has been used in conjunction with this and has been responsible for a large proportion of the primary pulmonary hypertension. Phentermine, another potent amphetamine derivative which we heard much about earlier this morning, is frequently used in conjunction with fenfluramine because of the push/pull effect on obvious side effects, and is also responsible for the

high risk of primary pulmonary hypertension. Other amphetamines, many of which are not available in this country, have also been reported as part of the primary pulmonary hypertension picture.

Now to put this into perspective, even if it can be shown, and even as it probably will be shown, that weight loss induced by the use of fenfluramine or dexfenfluramine does have some protective effect in hypertension and diabetes, this is a long-term protective effect. It may, in a certain proportion of the patients, protect against long-term complications of these serious diseases. One case of primary pulmonary hypertension that will occur through the use of this drug will lead to death in every patient who develops it and will lead to an increased cost of medical care.

Now what is the true incidence in the population that will be taking the drug. We have heard all kinds of numbers that this is a rare disease that occurs in 1 in a million. Yes, it occurs in 1 in a million in the general population. But it is much more prevalent in obese patients. It is much more prevalent in obese patients who take medication for their obesity. And if we use that as our denominator rather than the 40 million patients who have received

[redacted]

pattern which demonstrates dramatic increased usage. And we know that once a drug is decontrolled, the usage will increase even further. But if we use that as a rough estimate, 1 in 1.1 million, which means approximately 1 in 500,000 patients per year, and we expect 1 in 10,000 to develop the disease, we are talking about 50 new cases that are going to die of primary pulmonary hypertension every year through the use of this family of drugs. Now this is a projection that should be taken into account in the consideration of making this drug widely available, and secondly, in consideration of what type of controls should be used to monitor the proper usage of the drug. At present,

fenfluramine is approved by the FDA for no more than 3 months continuous use, and yet we heard here today widely discussed the wide use of this drug continuously by many physicians. There is no way of stopping that. That is a state regulatory device. The only control we have at present are our regulations. Thank you.

DOCTOR MEISCH: Thank you. Doctor Cicero?

DOCTOR CICERO: I would like to put this a bit in perspective because a number of things were thrown up there and you didn't have a denominator. It might help the committee to understand. When you threw up the CNS adverse events, for example, you had 159 during that 10-year period, serious events. There were 10 million patient exposures during that period of time. I think it is a bit misleading just this number of 159 as being significant. It is 159 out of 10 million. That incidence rate, acccrding to my calculation is .01 percent. That wouldn't even appear on the label as far as I know.

It is a little bit troublesome as to the definition of terms. You have indicated that there are a number of cases of dependency. In a prior report delivered by the FDA, and with which we agree completely, there were 0 mentions of drug abuse. I

don't know what dependence means under these terms.

You also listed 74 cases of withdrawal. And I will remind you COSTART defines withdrawal reactions as any adverse event which appears upon withdrawal. I don't think most of us in this room that know anything about drug abuse would classify that. Because you lump that, Doctor Lutwak. You lump that with --

DOCTOR LUTWAK: I stated very clearly that these -- that each of these reports may have occurred in more than -- more than one report may have occurred in the same patient.

DOCTOR CICERO: But if you've got 115 cases of dependency --

DOCTOR LUTWAK: Not 115 cases, 115 reports. 115 reports. That is not 115 cases.

DOCTOR CICERO: Thank you. If we are going to talk about risk/benefit --

DOCTOR LUTWAK: And these data, incidentally, are taken directly from the submission from the sponsor. These are not cases that were reported to us. These are cases that were reported to the sponsor. Submission number 019 to the NDA.

DOCTOR CICERO: Thank you. To put this into some frame of reference if we are looking at

risk/benefit ratios, and that was, I thought, the topic of your presentation, one thing we seem to forget is there are 290,000 deaths last year attributable to obesity. You see figures that demonstrated and documented that there can be protective effects of weight loss ranging anywhere from --

DOCTOR LUTWAK: That is a projection based on a hypothesis that has yet to be proven.

DOCTOR CICERO: I beg your pardon. That is CDC --

DOCTOR LUTWAK: I beg your pardon, sir. This is based on epidemiologic data which offer us the clue to where research has to be done. This is a projection. This is not 290,000 people dying off each year because -- this is a long-term, cumulative death result. You have not shown us that 290,000 patients can be prevented by giving dexfenfluramine.

DOCTOR CICERO: No, I said -- the statement I made is the CDC estimates that 294,000 people die each year from obesity related causes. I did not make any claim that dexfenfluramine is going to cure all 294,000. There is going to be some benefit to that. So I think you would have to put that into context when you are talking about any of

these other adverse side effects. That was an issue that really got hung up yesterday, and I just wanted to clarify that. We are not considering what are the tangible benefits of weight loss. Because truly your balance in your first overhead was risk/benefit. And what we heard you saying is a lot of risk things, which I think we can all question the assumptions underlying some of those, but the benefits. Let's not forget the benefits. That was my only point for getting up.

DOCTOR WRIGHT: Doctor Cicero, I would like us to not have an opportunity to replay what was clearly an extensive discussion yesterday on an approval decision for this drug. What I am interested in, and I thank you very much Paul, was your, I thought, reasonable presentation that an event with a relatively uncommon base rate in the population, fatal primary pulmonary hypertension, may be associated with the use of this drug and is one of the elements that should be looked for in any program of surveillance associated with its use.

DOCTOR CICERO: Okay. Absolutely. I agree with that.

DOCTOR MEISCH: Our next speaker will be Doctor Wadler.

DOCTOR WADLER: Thank you very much. I guess most of you are saying, who is Doctor Wadler, so I guess I ought to introduce myself because I work for no company. I work as a solo practitioner in sports medicine and internal medicine. But I do have some special knowledge and expertise as it relates to use of drugs in sports. I am an associate professor of Medicine at Cornell. I am a fellow at the American College of Physicians, the American College of Preventive Medicine, the American College of Clinical Pharmacology, and I am a fellow and trustee of the American College of Sports Medicine, and a trustee of the Women's Sports Foundation.

Some of you may have seen me over the years at the U.S. Open. I was the tournament physician for 12 years at the U.S. Open Tennis Championships, and I am proud to have been the recipient of the IOC President's Prize in 1993 for my work in drugs in sports.

I sat here this morning and listened to the past presentations and I am quite concerned about the decision to deschedule or decontrol these drugs. I am going to try to put this in a little bit of an athletic context. That is a different context than what you've been discussing today. I admit it is from

the mindset of drug use in sports and not the population at large, but I think there are messages here for the population at large.

The International Olympic Committee and the United States Olympic Committee defines doping as "the administration of or use by a competing athlete of any substance foreign to the body or any physiologic substance taken in an abnormal quantity or taken by an abnormal route of entry into the body with the sole intention of increasing in an artificial and unfair manner his or her performance. When necessity demands medical treatment with any substance which because of its nature, doses, or application is able to boost the athlete's performance in competition in an artificial or unfair manner, this too is regarded by the IOC as doping."

Now I wanted to talk briefly about some sympathomimeticamines, which have a long history in sport. I am very mindful that although fenfluramine is a sympathomimeticamine, its anorectic effect is somehow related to serotonin metabolism. Historically, the amphetamines have been shown in elegant studies by Beecher and Smith in the 1950's to be ergogenic or performance-enhancing in throwing, swimming, and running sports.

Now several points. To circumvent the Controlled Substances Act of 1970, the amphetamine look-alikes appeared, and I am sure many of you have great knowledge and much more knowledge than I have about the history of the look-alikes. The look-alikes most commonly were formulations of caffeine, ephedrine or pseudoephedrine and phenylpropanolamine, although clearly other sympathomimeticamines, and I suspect but do not know fenfluramine, could be substituted to simulate an amphetamine-like effect. The jurisdictional issues of the early 1980's to deal with look-alikes is well known to the FDA, and the problem with all of that, of course, remains, and all of you know and certainly all athletes know that one can easily swallow a Dexatrim, take it with some Sudafed, and down it with a thick, heavy cup of espresso.

The scientific evidence that therapeutic doses of sympathomimeticamines per se are, in fact, performance enhancing, is in fact a scam. In fact, the pharmacokinetics and pharmacodynamics of the sympathomimeticamines is not well enough understood to clearly show the difference between therapeutic doses and ergogenic doses. Despite that fact, Rip Dumont lost an Olympic gold medal in 1972 for having taken a therapeutic dose of ephedrine for his asthma. So why

do athletes take sympathomimeticamines? Two reasons, I think, are particularly relevant, but I will mention all three. One is related to a perceived aesthetic value to being thin, notably in sports such as gymnastics, diving, and swimming, and certainly in the art of ballet. Two, to make weight as in thoroughbred racing, boxing, and wrestling. Parenthetically, I will be travelling tomorrow with Angel Cordero, who is going to be reemerging as a jockey, and it is interesting to hear the abuse of these kinds of pills in the world of thoroughbred racing. Three, to simulate the amphetamine effect in the so-called look-alikes, that is, to gain speed and acceleration.

Now, how prevalent are weight loss products in the world of sports. In 1989 at Michigan State, Anderson McAid did a very nice study in which they looked at non-prescription weight loss drugs by gender and sport in 2,300 approximately NCAA student athletes. In men, these products were used by 2 percent of the baseball players, 3 percent of the basketball players, 3 percent of the football players, 7 percent of the tennis players, 2 percent of the track players. In women, in softball 11 percent used these weight loss drugs, in basketball 9 percent used these drugs, in tennis 8 percent, in track 9 percent,

and in swimming 14 percent. These sports constituted 10 men sports and 10 women's sports.

Now when looking at student athletes who had reported uses of non-prescription weight loss products in the preceding 12 months, 53 percent took them to improve their appearance. 37 percent took them to improve their athletic performance. 4 percent took them so that they would feel good, and then 6 percent for a variety of other reasons. But particularly disturbing, 13 percent initially used these drugs in junior high school, 46 percent initially used these drugs in high school, and the remaining 40 percent, either their first year of college or later on in college. 81 percent of all the student athletes that bought these products themselves, only 4 percent ever having obtained them from a physician.

Now the NCAA looked at its drug testing. Between 1986 and 1989 in 12,950 administered drug tests by the NCAA, there were a total of 392 positive drug tests. Of the 392, 292 were positive for sympathomimeticamines. Only 100 were for all other drugs including anabolic steroids. As a consequence, the NCAA no longer even tests for sympathomimeticamines. Now the IOC and the USOC bans

these drugs, including fenfluramine, and there are no published cutoff levels as to potential excess or large doses, although there are problems again with the interpretation of that data, and fenfluramine is banned by the IOC and the United States Olympic Committee.

In South Africa, to show the problem is not unique to the United States, 50 percent of all positive doping tests are for sympathomimeticamines.

Now I told you that I was a trustee of the Women's Sports Foundation, and I have a particular interest in women's sports, and I want to briefly define for you a spectrum of disorders which I am sure all of you have thought about but I want you to think about in the athletic context, and that is the spectrum from anorexia and anabolic steroid abuse. It is a spectrum in which the individual is obsessed with body image, preoccupied with mirrors, extremes, aberration of food intake, rationalization of behavior relative to performance, the use and abuse of drugs to manipulate their body appearance, and both are obsessed with the relentless pursuit of either bigness or thinness.

Now the American College of Sports Medicine has recently brought to the public's

attention the so-called female athlete triad which affects anywhere from 15 to 62 percent of the female athletes, and I realize that is a broad range. The prevalence is not clearly defined but the problem is clearly defined. The female athlete triad is made up of 3 components, disordered eating, menstrual disturbances, and osteoporosis.

First for disordered eating, the prevalence or estimates, as I said, are between 15 and 62 percent of female athletes. The spectrum of the disordered eating ranges from normal eating behaviors disorder to control one's weight to frank poor nutrition and inadequate caloric intake to various forms of binging and purging to the extremes of anorexia and bulimia. We know that disordered eating is particularly prevalent in certain sports, those sports where there is subjective or appearance judging, such as gymnastics, ballet, diving, and figure skating, or where there is a perceived correlation with performance such as in long-distance running. Other correlates are individual versus team sports and sports which the athlete peaks at a particularly young age such as tennis and gymnastics.

With respect to anorexia, the relentless pursuit of thinness, it wasn't very long ago that we

all read the story of Christy Heinrich, who had died. A criteria, just to reiterate, and I am sure many of you are familiar with it, is a refusal to maintain body weight over a minimum for age and height, an intense fear of gaining weight even though one is overweight, a distorted view of one's body weight, size, and shape, the absence of three consecutive periods, and the incidence is a half and one percent of adolescent women and two and a half percent among young adult women. Of course, 5 to 10 percent of these are male. They may engage in extreme physical activities to be thin and they clearly abuse drugs. They abuse anorectics, laxatives, caffeine, emetics, and diuretics. Their behaviors aside from drug abuse and, of course, excess exercise and food restriction is self-induced vomiting, and suicide rates and mortality as high as 9 percent.

Bulimia, the criteria briefly there is binging twice a week for at least 3 months, a sense of lack of control over eating, where eating is a discrete period definitely in excess of normal where they can consume 20,000 calories, recurrent, inappropriate behaviors to prevent weight gain, vomiting, and again anoretics, laxatives, diuretics, and excess exercise. The incidence is 1 to 2 percent

of adolescent college women and 10 to 15 percent of men are bulimic.

Now I talked about the female athlete triad, so why is this important? Well, it turns out that most of the women who have significant eating disorders have secondary amenorrhea. The secondary amenorrhea occurs in about 2 to 5 percent of the general population. In female athletes, it is between 3 and 66 percent. Up to 20 percent of runners and casual runners, 50 percent of elite runners, and 30 to 50 percent of ballet dancers. It is frequently associated with eating disorders, excess amounts of training, changes in body composition, and so on. Of course, athletic amenorrhea is always a diagnosis of exclusion.

Now the public health problem relates to the development of osteoporosis. Because premature bone loss from inadequate bone formation is a consequence of low estrogens with increased risk of fracture. Amenorrheic athletes, women in their 20's, have bone densities of those of women in their 50's, where estrogen, again, is the major contributor to maintenance of bone density. Estrogen levels in amenorrheic athletes and anorectic women approach those of post-menopausal women.

I cannot help, as I just conclude my remarks, reflecting on an article by Goldstein and Kalant in Science 1990, "Drug Policy, Striking The Right Balance", in which clearly availability affects consumption. The use of a drug clearly correlates with its availability. We know this from alcohol in times of prohibition, criminality aside. We know it from the very origins of the Controlled Substances Act of 1970. We know it from the State of New York where triplicate prescriptions are required for benzodiazepine.

When you make your decision, and I hope the decision this morning -- I am not familiar with your process and I wish these and future remarks would have been heard prior to that, with all due respect -- that you do not make this decision in a sociologic vacuum. The world of sports consumes us. We all are consumed by it one way or another, either directly, passively, or your children, and I must tell you that we are in an epidemic. I don't care what the prevalent statistics are. We can argue forever. They are just almost anecdotal. But everybody in this field -- everybody I know in this field is assured and convinced that we have a serious problem with drug abuse in sports and we have a serious problem with

eating disorders in sports, and I, for one, need to be convinced that there is an advantage to decontrolling it, since as a prescription I can write the prescription. So somebody would have to tell me why we run the risk of increasing the availability, increase the risk of the abuse of the drug, when currently that drug is available for legitimate use as it exists today. Thank you.

DOCTOR MEISCH: Thank you. Doctor Seiden, you are the next speaker, please.

DOCTOR WRIGHT: Mr. Chairman, did Doctor Wright have an opportunity to make all the comments he wished to make? We asked him to limit it to one topic.

MR. POLLITT: Doctor Wright had to leave and he is going to submit a written statement to me.

DOCTOR SEIDEN: I shall not go over all of the remarks that I made yesterday regarding my views of the potential neurotoxicity in humans for fenfluramine and its neurotoxicity to animals. I just want to highlight a few things that came up this morning and to reiterate some of what I consider my more important comments. So I am going to be brief and then Doctor Ricaurte will present a few brief comments as well.

I am glad that the committee as well as the sponsoring agent has come to see that neurotoxicity is something that they must be aware of and they could even, at least, according to Doctor Cicero, name as such. So that means we are probably moving a little bit closer together in what is obviously a very contentious area.

The highlights of yesterday's presentation might be well reiterated. One, in every species that we have had the opportunity to do experiments in using fenfluramine and taking their brains out for assay, we have found neurotoxic events, what we consider neurotoxic events, that persist long after the drug has been discontinued. That is true of mice, at least some species of mice or strains of mice, rats, guinea pigs, different strains of monkeys, every species that we looked at.

The fact that it occurs in all these different species leads me to believe that it might occur in humans as well. I see no reason to exclude humans from the continuum of the animal species. So just on a genetic basis, I would not expect humans to be somehow protected.

Also, the fact that in both rodents and non-human primates, the dose of fenfluramine required

to engender 5HT neurotoxicity are very close to the doses that are required to suppress intake by 50 percent. This is a point I made yesterday. I understand that a lot of you are seeing this slide for the second time.

Then in the next slide from Doctor Schuster Johanson, they noted, and along with some studies that we did in collaboration, that fenfluramine also produces a long lasting depletion of serotonin in the striatum, the hippocampus, and the rest of the brain at a dose of 5 mg. It produces toxicity at a dose of 6.25 and 12.5 mg per kilogram. In the case of other anorectics, the minimal dose necessary to produce a prolonged neurochemical effect varied from 10 to 40 times the ED_{50} dose. So fenfluramine is only 1.25 the ED_{50} dose. And it does appear that fenfluramine is a significantly more toxic drug than the other drugs tested. This, I believe, is a key consideration in assessing the potential neurotoxic effects of fenfluramine.

Doctor Moore showed a very interesting slide comparing the levels of neurofenfluramine or fenfluramine in the brains of humans with those in animals that engendered 5HT depletion. The slide apparently showed that you had a very minuscule amount

of fenfluramine generalized in the brain of humans compared to the animals. I have a couple of reservations about this slide.

One, I am not quite sure that the data obtained in humans was obtained using the same techniques that the data obtained in animals were.

My second reservation is that I am not completely convinced that levels in the brain are necessarily predictive of the neurotoxic events that take place. We don't know the mechanism that causes the long lasting depletion, and we have to hold, I think, in reservations something about interpreting the levels found in the brains of various species to make any kind of prediction about the long lasting or the possibly neurotoxic effects of fenfluramine.

I would like to hold that in reservation for myself, and I enjoyed the opportunity to review that data. I agree that the fundamental issue, that is, does toxicity occur in the brains of human beings is a fundamental one that needs to be addressed. And I think with that said, I will ask Doctor Ricaurte to further address those issues, with the chair's permission.

DOCTOR MEISCH: All right. Briefly.

DOCTOR RICAURTE: Thanks very much, Lou,

and members of the committee. I realize the hour is late, so my comments will be brief and will center around the issue that was discussed yesterday and that is, how can we find out if the neurotoxicity produced in animals, at least by the data that has been presented

-- how can we determine whether or not that neurotoxicity also occurs in human beings. I think we all are in agreement that that is a key question. And what I am willing to comment on is how that issue might be addressed in humans.

This is a slide taken from an early study from Chase and Shoulsen performed at the NIH back in the 1970's. What this slide is intended to illustrate is that the concentration of 5HIA, the major metabolite of serotonin -- the concentration or the amount of this compound in lumbar spinal fluid of human beings given fenfluramine is decreased after administration of fenfluramine. What I have to emphasize is that this decrease in the concentration of 5HIA observed in fenfluramine treated individuals was noted shortly after discontinuation of the drug.

The question is, would this kind of reduction in CSF 5HIA concentration persist and could it be used as an indicator of possible CNS serotonin

neurotoxicity in humans. To the best of my knowledge, that study has not been done, specifically that of taking individuals previously exposed to doses of fenfluramine, anorectic doses of fenfluramine, and determining whether their level of CSF 5HIA is persistently decreased.

What I am not showing you because of time is that this CSF 5HIA method has been validated in animals treated with a related amphetamine analog. We know that in the animal model, CSF 5HIA is a useful indicator of CNS serotonin neurotoxicity. So the first suggestion or question is, could CSF 5HIA in humans previously exposed to fenfluramine perhaps be used as a possible indicator of a long-term effect of fenfluramine on the human serotonin system.

This touches on a second possible methodology that is available and it relates to positron emission tomography, and in this case, using a ligand for the serotonin transporter. This is a method that over the last five to six years, along with my colleagues at the Johns Hopkins School of Medicine, we have been developing. It is still at a stage of development, but I dare say that it is at a stage where at least in animals treated with the related toxic amphetamine analog, in this case MDMA,

seems to provide us a reliable measure of long-term losses of the serotonin transporter following exposure to an amphetamine toxic derivative.

What you see here in the top panel is labeling of serotonin transporters in a controlled baboon, and on the bottom panel, I am not sure how well it shows, but what is evident not only in this slide but from the quantitative data that has been analyzed is that there is a marked and persistent reduction in the number of serotonin transporters following exposure to fenfluramine. This is a fenfluramine treated baboon.

And what I would like to emphasize is a point that Doctor Seiden just made, and that is the importance of anchoring the "toxic dose" to the therapeutic dose. And what I would highlight is that according to studies of Fulton and colleagues at our institution, the ED_{50} dose for anorexia in the baboon is in the order of 2 mg per kilogram, and what I am illustrating here are the effects of a dose of 5 mg per kilogram given twice a day for four days. I think we could all agree that that is not a large margin of safety. Now this, I have to emphasize, is a pre-clinical study, and what I am suggesting to you is that perhaps similar methodologies under well-

controlled conditions could be applied to assess the question of whether or not the neurotoxic effects of fenfluramine observed in animals generalize to humans.

The next slide simply underscores the fact that the loss of transporters that I have illustrated in the baboon with PET scans was demonstrated up to approximately 3 months beyond the period of drug administration. This is not a short-term event. In comparably treated animals, what you see is depletions or losses of all of the serotonin axonal markers that we measure up to a period in the baboon of 9 months, and in squirrel monkeys up to a period of 14 to 17 months.

Let me just make one final point, and it has to do with the issue of clinical consequences of possible, and I underscore possible, serotonin neurotoxicity in humans. There seems to be the, I think, logical expectation that if serotonin neurotoxicity occurs in humans, one might logically expect neuropsychological or neurobehavioral consequences. As Doctor Mann elegantly touched on earlier this morning, the issue of detecting neuropsychological or neuropsychometric differences that are directly linked to a selective and specific depletion of brain serotonin is not a simple one.

So one note of caution I would add is that the absence of changes in routinely performed neuropsychological studies somewhat similar to those presented by the sponsor, my concern would be do those tests have the appropriate validation to convince us that they have the required sensitivity and specificity of detecting the functional consequence of serotonin depletion if it exists. So what I am suggesting is that methods need to be developed, particularly along the neuropsychological function, methods not dissimilar from the type that Doctor Mann is describing, to see if, indeed, there are behavioral or neurobehavioral consequences associated with the serotonin depletion, not only in animals but also in human beings should that be the case in the clinical setting.

So to close, based on the considerations that Doctor Seiden has outlined for you and based on these few comments, what is recommended is that it may be useful to carry out more detailed toxicology studies in baboons, making an effort to identify a non-neurotoxic dose in a species that at approaches a comparable weight as a human being in an effort to see how close does this non-neurotoxic dose relate to a clinically effective anorectic dose, that is, use

baboons, use animals to get at how large or small the margin of safety for this particular drug might be in human beings.

Secondly, that a controlled, long-term, double-blind study is in order. Testing for not only the rare pulmonary hypertension effects, which I am not prepared to comment about, but also for possible neuropsychological effects in which serotonin has been implicated, specifically depression, anxiety, impulsivity, cognitive function, changes in aggression, sexual function, neuroendocrine function, and sleep. It is only logical that if serotonin has been implicated in these behavioral spheres, it is in these spheres that we should begin to look for changes.

And finally, I must comment that I am somewhat surprised that given the natural history of these disorders ranging from depression to anxiety and cognitive problems, given the natural incidence and occurrence of these disorders in adults ranging from age 30 to 65, it is somewhat surprising to me that of 30 or 40 million people that have been screened, none of these individuals are having any problems in these behavioral domains. I would submit to you that it is not an issue of whether people exposed to fenfluramine

have problems in any of these behavioral spheres. The real issue is characterizing the baseline occurrence of these disorders in the unexposed population and determining whether or not the incidence of these problems is any higher in individuals previously exposed to fenfluramine and doing this in a highly controlled manner.

With that, I will conclude the comments and I would be happy to entertain any questions.

DOCTOR MEISCH: Doctor Wright.

DOCTOR WRIGHT: I actually have a question for Doctor Schuster. Was that quote that was put up by Doctor Seiden written by you and Doctor Johanson? In the quote, it appeared that you were concerned about a smaller therapeutic index for this drug than for others of the class. Has the time that has passed since that was written caused you to modify your opinion in any way?

DOCTOR SCHUSTER: Let me first of all state that I confess that I have not followed the neurotoxicological data since I became the director of NIDA. My interests have been elsewhere. And I cannot state too much more than what was stated at that time that it was our opinion at that time that this should be taken very seriously because it appeared as if the

doses that were necessary to produce a 50 percent decrease in food intake, given acutely, and bear in mind that this was an acute administration of the drug and it was also based upon a slightly different kind of anoretic measure, and that is we were looking at decreases in the eating of a highly preferred substance, which oftentimes elevates the ED_{50} dosage. So with all those caveats, but it was the same across the anorectic doses, it is true that we saw this difference between agents.

I am not in a position right now to make any comment about the neurotoxicity issue. I think that it is something that we should all be concerned with in terms of FDA. I will say, as I would have said this morning if I had made a presentation, however, that I think that as far as the Drug Abuse Advisory Committee is concerned, that the issue of neurotoxicity, liver toxicity, or whether it makes your hair fall out, has to be secondary to the prime characteristic, which is the defining characteristic in the CSA, and that is, is it a drug of abuse. And it is still my opinion very strongly that it does not meet any of the criteria for being a drug of abuse.

DOCTOR WRIGHT: Thank you, Doctor Schuster.

DOCTOR MEISCH: Doctor Schuster, you are here on your own behalf or on behalf of the sponsor?

DOCTOR SCHUSTER. Yes, I'm sorry?

DOCTOR MEISCH: The question is, are you here totally under your own expense or are you here --

DOCTOR SCHUSTER: No. I am here at the request of the sponsor, and I would like to make it very clear that my reason for being here is simply because -- it is not a question of being a purist as far as the application of the Controlled Substances Act is concerned. I am concerned about its dilution, and therefore, if it is used inappropriately that we might be on a slippery slope in terms of a policy that would allow the admission of substances that we wish to deter physicians from prescribing perhaps, because we either think the prescribing is frivolous or because there is the potential for some toxicity --to control substances of that sort in the absence of abuse liability or actual abuse, I think is a misapplication of this Act, and that was why I was willing to come here and testify.

DOCTOR MEISCH: Thank you. Just a second. Doctor Wright, we need to have Doctor Mann and then Doctor Cicero wants to speak. What are your thoughts?

DOCTOR WRIGHT: Well, I simply wanted to

know -- we had one of the scientists who had been quoted here and I wanted to give him an opportunity to speak about his work. Doctor Mann, I believe, has presented most of what he wished to present. Am I correct on that?

DOCTOR MANN: Yes. I might have one or two comments.

DOCTOR WRIGHT: Please feel free if they appear appropriate.

DOCTOR MANN: Well actually, I did want to respond to a couple of things that arose. I wanted to comment on the suicide rates that were presented as a potential consequence of the use of fenfluramine by referring people to the fact that we had published a paper about two years ago in JAMA, two or three years ago, looking at -- which I think was the first of its kind that looked at incidences of suicide attempts and completions in people taking psychotropic medications. This was an issue with fluoxytine. And in that context, one can actually examine the data that was presented with fenfluramine, and I think that one would have to conclude that based on the information that is available now, there is on evidence that a drug does one thing or another. So I think there is little to conclude on that score.

The second point I wanted to make is that one of the issues that arose in relation to neurotoxicity is what does it matter if you lower serotonin. On one hand, we may have some evidence based on the materials presented by the sponsor that you can lower serotonin considerably without any apparent consequences. I think I would like to reiterate that actually there is evidence from both animal and human work that there are measurable behavioral consequences of lowering serotonin of the order of 30 or 40 percent, and that many of the measures that have been employed and presented thus far in relation to fenfluramine really don't address adequately those kinds of effects, and I would like to endorse the speaker over there that mentioned that we need a different sets of measures. This really needs to be followed up more thoroughly in a controlled way.

With regard to the PET scan data that was presented, I think that I have a caveat about that. It looked very impressive, but McNeal 5652, which is a serotonin ligand, has a significant handicap in assessing the effects of drugs like fenfluramine, which potentially can compete for the receptor directly and displace binding as well as release endogenous levels of serotonin which will displace

binding, and therefore, you get a reduction of binding which may potentially have nothing to do with the toxicity or otherwise of the drug and just merely illustrate its expected pharmacological effect. I think the approach in general has merit, but there may be some problems with that specific recommendation.

And finally, my last comment relates to surveillance. I think there are high risk groups that need to be surveyed more specifically rather than just an equal effort across the entire population. I think that is the point of the presentation on sports medicine. One obvious group that one would have to consider are people with eating disorders that go well beyond sports medicine. These represent anorexia nervosa and anorexia bulimia. They represent a significant number of individuals in the general population that are clearly at risk in terms of these kinds of anorectics. And a specific target of surveillance of the use of drugs like fenfluramine in that group I think would have merit. Thank you.

CO-CHAIRMAN MEISCH: Doctor Wright?

DOCTOR CURTIS WRIGHT: I'd like to hold general comments until later.

CO-CHAIRMAN MEISCH: Good.

DOCTOR CURTIS WRIGHT: Since the issue of

Doctor Schuster commented very directly on the question of control of the practice of medicine and his perception that it was inappropriate to use the CSA to try to impose such controls, we are very fortunate to have Doctor Fleming here.

CO-CHAIRMAN MEISCH: Doctor Fleming?

MR. FLEMING: Mr. Chairman and ladies and gentlemen of the Committee, thank you very much. I thought it was the Board of Medicine that bestowed medical licenses. I am not a physician. I am an attorney.

I am the Executive Director of the Massachusetts Board of Medicine and I'm very happy to be here to speak with you this afternoon. Unfortunately, not so much for what I have to say to you, but for the wonderful testimony and comments that I got to hear from the physicians and scientists about this very interesting subject. So, thank you for inviting me for that reason.

However, I am also not prepared to comment on the neurotoxicity of the drug either. I was asked to talk about the law in Massachusetts in regard to drugs and their anorectic effects. I also understand that the time is late. I was supposed to catch a plane about ten minutes ago. I think I can boil

things down in a very short order, to give you a rough idea of the history of at least Massachusetts and maybe a comment or two about boards in general, as the issue of state medical boards came up earlier this morning.

As I'm sure all of you know, we're charged with the authority and responsibility to adopt rules and regulations governing the practice of medicine in order to protect the public. I think that all state medical boards try very hard to do that, unfortunately, with limited resources. In keeping with this directive, our board in 1988, considered a variety of prescribing practices and issued a policy to foster competence and public protection. Those regulatory changes included a prohibition on prescribing steroids for athletic enhancements, restrictions on self-prescribing to physicians and prescribing to immediate family members, and a proscription against prescribing drugs for their anorectic effect. In fact, the regulation in Massachusetts has been quite strict. The regulation read: "A licensee is prohibited from prescribing any drug, including but not limited to amphetamines and sympathomimetic amines for its anorectic effect." I think that you would agree that that's quite a

limiting regulation in view of what I'm listening to today.

That regulation remained in effect for quite some time -- well, it was promulgated in 1988. In my business, that's quite some time for a regulation to stay in effect. Since the time of the passage of that regulation, as you may expect, there has been a great deal of pressure on the board from pharmaceutical companies, physicians and consumers to revoke, or at least amend, the ban against prescribing anorectics for weight loss. The board has resisted that, since then, for a number of reasons.

As I promised I'd be short, I will be short. I won't go through all the stories that I have for you, but it had to do with the cases that came before the board, of physicians obviously trying to meet the need of their patients who, unlike most drugs that are prescribed for people because the physician thinks that they need it, these are drugs that the people want their doctors to prescribe for them because they think they need it for a lot of obvious reasons. As a consequence of that, motivational effect on the physicians, the pressure on the physicians, the board was getting a number of cases of something that, I guess, is not -- well, I won't say

that. That's too flippant -- that is the other side of the coin here that hasn't been talked about which is misuse, as opposed to abuse.

The Board of Medicine in Massachusetts and other states is concerned with both things: abuse and misuse. However, as a consequence to some very learned proposals to the board, notably Doctor George Blackburn and his colleagues from New England Deaconess -- I hope that's right -- the board did consider, and in fact, amended its regulation, this prohibitive regulation, last year to allow for a waiver of that regulation banning the use of these drugs, so long as the use of drugs were part of an institutional review board approved protocol that was submitted to the board in advance for its approval. The board passed that regulation and there is such a test going on now.

Since that time, with the introduction of some new board members, a fairly profound change has come across the land in Massachusetts. In the early summer, the board instructed me and the staff -- based on some of its thoughts about what you all are talking about here and what the board members have been presented with by some of their colleagues in the industry and patients -- asked us to come up with a

regulation which allowed the board to think about what its role was in this regard, and to think about what the FDA's role was in this regard, and actually who was doing what, and who should be doing what. They didn't give us much more of a guidance on that except to say that does our restrictive regulation -- is it an attempt to second-guess what, in fact, is the job of the FDA to do? That is, to decide what drugs ought to be available for what uses and what the labels should say, as opposed to what the licensing board ought to do.

We thought that was somewhat of a change. We understood where it was coming from. The day before yesterday, the board voted to put out for public comment, the following amendment to its regulation. Remember what the past one said. This one says "the licensee is prohibited from prescribing any controlled substance in Schedule II for its anorectic effect." A very profound change.

We also presented and it will be put out for public comment -- it's still in draft form. I'll give you my address in a minute and if you would like it, I will be happy to send it to you -- a policy statement which takes the issue for the medical board, rather than banning a drug for what it does and for

what the motivations are and brings it into a discussion of off-label use. That is, instead of just banning a drug per se, the board wants to put out for public comment and hear people's thoughts about looking for substandard uses of that drug, or misuses of the prescription off-label. So that we can rely on what the federal government is telling us in terms of what these drugs should be used for, looking at doctors who are using these drugs in ways that they shouldn't be used and dealing with them on that regard.

It's a very controversial issue. I'm sure you all know that better than I do. It's very controversial in Massachusetts. As you've heard, it's controversial in Virginia. It's going to be debated in Florida in the context of state boards. If anybody is interested in receiving our draft regulation or this policy statement and would like to provide comment, you can send it to me. My name is Alexander Fleming at the Massachusetts Board of Medicine. The address is 10 West Street, Boston 02111. If you feel inclined to comment, ask me, I'll send you this and we'd like to hear your comments. Thank you very much.

CO-CHAIRMAN MEISCH: Thank you.

We have now Doctor Tolliver of the DEA.

DOCTOR TOLLIVER: My name is Doctor James Tolliver. I'm with the Drug and Chemical Evaluation section out of the Office of Diversion Control at DEA. I'm here in an official capacity, being asked to provide information on DEA, or law enforcement encounters with the drug, fenfluramine. I actually mention the fact that I'm here in an official capacity because I understand according to one of my colleagues that attended the meeting, that there was some comment to the effect that DEA did not have any information. We did not send any individual to this conference yesterday, giving them the authority to make those kinds of statements. But I am here today in that capacity.

I want to provide you with this information because, although it's not necessarily evident today according to what has been done, the diversion from legitimate sources is one of the criteria that's used for consideration of scheduling of drugs. It is data that should be considered before any kind of a decision is made to do a scheduling action. So, at this point in time, we simply want to provide you with what we have in terms of information on the encounters with this drug by law enforcement officials.

The sources of the information are up here on the board. The screen here that I have used for this talk, and it includes the system to retrieve information from drug evidence, our STRIDE system. Whenever a drug is encountered, it is sent to the DEA laboratory for confirmatory type analysis. Additional data can be obtained. We can get the file number from STRIDE information, and then we can subsequently go to the case file and collect additional information on that particular case.

Another data source that I've utilized is the United States Customs Laboratory, the scientific and services database. We'll talk more about that shortly. The United States Customs Office of Intelligence and what is, basically, the customs database, another separate database of law enforcement Customs encounters with drugs. It's called TECS, for short, and it stands for the Treasury Enforcement Communications Systems.

Again, by way of introduction, DEA Laboratory System, these are the locations of the laboratories where the drug analyses are done. Virginia, Washington, D.C., New York, Miami, Chicago, Dallas, and two in California. The United States Customs also has their own laboratory system in the

New York, Savannah, Georgia, Chicago, New Orleans, Los Angeles, San Francisco, and San Juan. I don't know that much about the Customs laboratory system, but the DEA laboratory system accepts exhibits from both state and local laboratories, as well as from Customs. You'll see a combination of the both.

I'm going to start out by talking about the STRIDE system. These are encounters by DEA. You can see in the first column is the year. The second one is the agency. I told you already that we accept drug exhibits from state and local, as well as Customs and DEA. You'll see Customs on the next page. And you can see the location as to where the encounters were made. You can see how it was obtained, whether it was a seizure or some kind of a purchase. Or in some cases, it's simply unknown. The last one is the quantity on the side. 500 tablets in the first case, down to just as low as one tablet, for example, if you look at 1975. These are all obtained in DEA cases and have been submitted to the laboratory. This is what has been analyzed.

This takes us through 1978. Then we skip a few years and go up immediately to 1984 and then to '85. There are Customs' cases in '88 and a limited number of cases in 1990, '91, '92. Then we go up to

'94. The Customs' cases, we'll see a lot more of those cases shortly, but you can get a good idea as to what kinds of cases they are. A lot of them, at least in this case, they were all coming from the Laredo, Texas border. They were individuals that were attempting to smuggle into the United States from Mexico, the drug Ponderex, which is benfluramine.

Just to give you a flavor of a couple of the other cases, if you look at 1990, DEA in California sees 71 tablets. This was a medical clinic for weight loss. The nine tablets was a pharmacist who was dealing out a lot of controlled substances from his pharmacy. A particularly interesting case -- well, 1992, I should mention since this is a powdered material. In this particular case, it was a chemical company that had ordered some dexfenfluramine and brought it into the country, and they did not have a DEA registration to do so. So, it was seized and subsequently destroyed.

In 1994, there was a case of particular interest to us. The bottom case here in which there were three different exhibits: one exhibit of 360 tablets, another exhibit of 6,000, and still a third exhibit of 12,000 tablets. This particular case involved a Chinese herbal shop located in Houston,

Texas, who was bringing in large amounts of a variety of drugs including fenfluramine. In this particular case, we seized 30 million what are called black pearl tablets. These are usually made of diazepam. Diazepam is being seen everywhere in all kinds of drug cases, and you'll find diazepam mentioned in the Customs' cases in just a minute. And this case also involved steroids.

So, steroids, black pearls with diazepam, and the fenfluramine was coming out of China. It was labeled as being used as an anti-obesity substance, and also as an anti-diabetic agent. It was found in cabinets in the back of the Chinese herbal shop in Tucson. This particular case was also of significance in that it involved not just Tucson, but it also involved Los Angeles and a few other areas as well.

That is what we have in terms for DEA in terms of DEA encounters with the drug. We're going to next look at the U.S. Customs database. We've only recently obtained this information. These are seizures that occur directly off of people. In other words, you're at a Customs' port, entering into the country and you're asked to declare what you have. You don't declare it, they decide to search you, and they find the substance on you. They immediately

seize it because you basically lied to them and you've attempted to bring it into the country. This is all coming in from the Laredo port and it was purchased in, for the most part, Nuevo Laredo in Mexico.

You can see that a lot of these cases involve, also, diazepam. Esbelcaps is a combination preparation that also contains diazepam as well. But the other diazepam there, for the most part, is valium, the ten milligram tablets. The two tablets, you're going to see that over and over again. That is not an indication as to how much was seized. It is strictly an indication as to how much was submitted to the laboratory for confirmatory analysis. I have not been able, in the time, to get the actual amounts that were seized.

This is 1988. If you look at the next slide, it continues with 1988. You see some other drugs here, diethylpropion. The diethylpropion is in the form of tenuate dospan which is quite often seen in many of the southern forensic laboratories because it is an extremely popular drug that's brought into the United States from Mexico. Down towards the bottom here, if you look at 4/1/89, Laredo, you can see also clorbenzorex. Clorbenzorex is not a controlled substance right now. It's name is Acylex

and a lot of laboratories now in the South, forensic state and local laboratories, et cetera, are encountering this particular drug. You can also see flurosimide, a diuretic.

Again, it continues to '89, Laredo, Texas, and here you see you more of the ponderex is what you're going to see throughout. All right, there's no pondimin, per se, it's strictly ponderex and you can see it in many cases with diazepam, diethylpropion, phentermine. And then you see two other different brands, actually again, combination products containing diazepam coming out of Mexico.

That brings you up to 1990. 1990, same thing, basically, going down the list. I see meprobamate there. Into 1992, dexfenfluramine, clear, colorless liquid, that's what the report said. I have no idea, really, what that is. All these, for the most part, are tablets or capsule type preparations. Nothing, actually, in 1993 at all that was analyzed in the Customs' laboratory.

We get up to 1995. You can see it in San Francisco. This is coming primarily from the airport. Again, I want to stress that the one tablet or the one capsule is only what was sent to the laboratory for analysis, okay? It doesn't say anything about how

much was actually seized. And that's it. That's as far as the database has gone so far. The laboratory system in general is supposedly about -- although you do see one 8/11/95, the laboratory system is usually a couple of months behind in terms of their analysis work on drug samples submitted.

Now, what I've showed you up to this point is Customs' seizures coming off of individuals at ports of entry. The next thing that I would like to show you are seizures from United States Customs that have occurred through the mail. That is, coming into the country here via the mail. You only have data back to 1991. You know, it's pretty much tabulated out here for you. I have put the quantity. I put tabs when I knew what the tabs were, how many tablets were involved. GR stands for grams. In this case, we're talking about mail facilities and they did not submit these. These are not submitted to any laboratory for analysis. They seize the material. They record what it was, based upon the packaging material and what they know about what the tablets, capsules, whatever look like, and then they simply destroy it, dispose of it.

The gram weight is the total weight of both the fenfluramine and the valium. So, they did

not make a distinction there as we would in DEA laboratory, for example, or a Customs laboratory, how many tablets in the cases of the GRs. So, I don't know and I do not have a decent conversion into dosage units for that. But you can see, again, valium is in many of the samples.

You can see where it's coming from. I have up here the date and the next column is the origin. It's the country from where the mail originated. The destination -- you can see that the mail is going to various locations, whether it be Massachusetts, Ohio, Florida, California, New York, Illinois, Indiana, Washington State, et cetera. And quantity, and then finally, the drug that was put down on the form. You see that the United Kingdom, Greece, Belgium and a particular note -- you need to look at Thailand. In '94, you can see that basically all of that, with the exception of two mail orders from the United Kingdom and from Greece, all of it is from Thailand.

I was able to get information from the TECS system. The TECS is a very secretive type of system strictly for law enforcement, but I was able to download some information from that system. They let me into it for that purpose. What I was able to

determine is that -- what the TECS allowed me to do was to actually get the name of the individual to where this was supposedly going, okay? It also allowed me, if it was known, to get the address of where it was coming from. We know it's Thailand. We know it's somewhere in the United States, but it doesn't tell us anything, just based upon this, where it's coming from, where it's going to.

An examination of the TECS for these Thailand cases, what it showed is that the vast majority of these people were Asians. So, it was going from Thailand to individuals that are Asians located within the United States. The other thing though on the other side of the coin, trying to find out where it came from, we were able to determine that it's Thailand. But it was not possible because the people did not put, for the most part, the addresses on as to where they came from. So, you see that.

I think I have one more just giving a few more -- whoops, is that all? I thought there was one more. Maybe not. Yes, there is.

The rest of this is Thailand as well. So, we don't know the origin of it, with the exception of two. Actually, two of the cases, we were able to get an address but we don't know whether it was a

pharmacy, whether it was just a private individual or what. It's coming in from Thailand and it's going to a variety of locations. The data system, at this point, basically, just hasn't been updated. It stops at around June, July. So, we don't have any data more current than that.

This is all that we have in terms of law enforcement encounters at this time. I will mention one other thing. By the nature of what I do, very frequently I talk to a number of forensic laboratories each and every week across the country on various drugs, whether it be benzodiazapenes or whatever to find out what is being found in their laboratories. I can tell you that most of the laboratories, particularly in the South, are aware of fenfluramine and have encountered it from time-to-time, but it's not that frequent. But they do encounter the drug. When they're encountering it, it is part of a case. Right now, there is not a laboratory system in place in which we can funnel all the data from state and local laboratories into one database. This is something that we're working on. We can't do that yet. But that's as far as we've taken it. So, there are, in fact, law enforcement cases involving this particular drug.

CO-CHAIRMAN MEISCH: Okay, thank you.

Doctor Wright?

DOCTOR CURTIS WRIGHT: Well, I have a couple of questions to try to characterize what this trafficking involves. From the slides, as I tried to keep a rough tally as he showed them, it seemed that there was a large collection of border cases involving Mexico, a significant number of mail cases involving Thailand, and then a scattering of cases involving the UK and other Commonwealth or similar countries.

Do you know the control status of this drug in Mexico or Thailand, or can the company provide us with some information on that?

DOCTOR CICERO: It's not controlled in any country in the world.

DOCTOR CURTIS WRIGHT: We're the only country in the world that controls this?

DOCTOR CICERO: That's correct.

DOCTOR CURTIS WRIGHT: Under those circumstances, how would a traveler or an Asian know that it was a violation of our law to bring this across the border or to mail this into the states.

DOCTOR TOLLIVER: They wouldn't know. I don't know of any way in which they would know that.

DOCTOR CURTIS WRIGHT: I'm sorry. I

didn't mean to interrupt, Elizabeth.

Do you have any cases that have a smattering of diversion to more traditional illicit drug trafficking, known purveyors of illicit substances to whom substantial quantities are being brought into the country?

DOCTOR TOLLIVER: No, not really. Only a couple of those cases involved, really, cocaine, for example. Most of them involve other anorectic drugs and so forth.

DOCTOR KHURI: Doctor Wright has spoken to my confusion, to some extent, but I found Doctor Tolliver's presentation of seizure evidence of interest, especially the geography and the range of doses from one pill to many, many grams. I'm not fully sure I understand how germane it is to the focus of our deliberations today because the seizures were made because of the law of Schedule IV control and are not evidence of abuse, is the comment.

DOCTOR TOLLIVER: Well, I think what you're considering here is the potential for abuse. Under the law, that is one of the considerations that you make. In fact, it is an or. There are four considerations that you make when you're looking at whether or not a drug should be abused. Each of those

considerations is followed by an or statement and not an and. One of those is whether or not the drug is found in the illicit traffic.

Yes?

DOCTOR LUISADA: On the mail seizures by the Customs Department, were those packages labeled on the outside with the contents?

DOCTOR TOLLIVER: No. No. And some of them were hid in the -- to give you some examples that I can remember off the top of my head, one case involved hiding the tablets in children's books. Another case involved hiding the tablets in-between blankets. These are the mail coming in. Just another one that I can remember out of Laredo, for example, the guy had strapped -- this was the 360 tablet one. The guy had actually strapped the tablets around the knees and the legs, with tape and so forth. So, hopefully, it wouldn't be detected.

DOCTOR CURTIS WRIGHT: So, there was a presumption that at least these individuals knew that what they were doing wasn't acceptable?

DOCTOR TOLLIVER: Yes. Well, yes, if I go back and I think in those terms and I go back and think of your question, all these, for the most part, coming out of Laredo, certainly, all right, were

hidden, all right? I only have information on those coming out of Thailand. The Customs' inspectors have told me that there was no indication on the label, on the box, on the package, that they contained fenfluramine. In fact, a Customs' agent if he looked at the package by itself, would not be able to tell that this was a drug. That happened with all of them, okay? That, I can tell you.

So, in that sense, there was concealment. So, I would assume that they would probably know. The one other thing that would seem reasonable to me is, if you send a package and it doesn't reach its source, and then you send another package and it doesn't reach its source, then it might start telling you that something is wrong. Although they continue to do it. But we don't have any indications that it all came from one source. This was one of the things that we were trying to do is by looking into TECS, to figure out whether or not it was coming from different parts of Thailand. For the most part, a return address was not provided, nor was the address of origin provided.

DOCTOR CURTIS WRIGHT: And the large commercial seizure involved its sale as an anorectic agent, apparently?

DOCTOR TOLLIVER: We don't know exactly

what they were using it for, all right? That is what the labeling that was on the packages of fenfluramine -- it was coming in from China. It was labeled in Chinese on one side; American on the other. It had in big letters up at the top, "anti-obesity, anti-diabetes." It said the Chinese Institute of Pharmaceutical Medicine or whatever on the other side.

Yes?

CO-CHAIRMAN MEISCH: Doctor Klein?

DOCTOR KLEIN: Could you characterize the type of drugs, in general, that you're seeing coming across at the Laredo port of entry?

DOCTOR TOLLIVER: Okay. I think Mike saw my one slide that I did not put up here. If I could have that slide for just a minute?

Back in July, I spent some time down at the Laredo border crossing. The purpose of the time down there was to characterize in detail exactly what drugs are coming across the border from Mexico into the United States at that one crossing. What I was able to do during that time, as these drugs are declared. They're purchased in Nuevo Laredo for the most part and then they are brought across. As long as you have only what's considered personal use quantities of the drug, which is a certain amount

above which if you go the drug is seized, but below which you're able to declare. The people at the border station have got to put it out in writing. There is a declaration form that they have to fill out.

Wnat I did is, I spent a week there and looked at declarations for three weeks, over the time period of July 1 to July 21, 1995. I examined a total of 1,679 declarations. This is a breakdown of the most popular drugs that were found on the declarations. There are a whole slew of drugs underneath, all of which have been found less than 17 times. But you can see here that valium was, by far, number one. I can not stress enough -- we're analyzing this more and more now -- the extent to which valium is appearing in everything that law enforcement is really encountering in terms of drugs. It's everywhere. We're encountering it constantly now.

So, you see here, the declarations. 1,156 were valium. Rohypnol is a drug of real concern to us. That was number two. It is a hypnotic that is not available in this country. It was the second most popularly mentioned drug on the declarations. Tafil is alprazolam. So, right here, you have three

benzodiazapenes in a row. Then you get to tenuate dospan which is diethylpropion. You can see asenlix which is not controlled. Clorbenzorex was number five. Then you have three analgesic preparations in a row. Then you get to the next one, diminex, which is phendermine. Then you go down to diestet which happens to be mazendol. Then a couple of others down there -- the neobes also happens to be diethylpropion which, by the way, is Schedule IV. And then ponderex which is the benfluramine, was next in line. It was fairly low down on the list in terms of what was declared at the border crossings.

DOCTOR KLEIN: All right, thank you.

CO-CHAIRMAN MEISCH: Any more questions?

DOCTOR CURTIS WRIGHT: I would just like to thank Doctor Tolliver for coming. That was extremely helpful.

DOCTOR KLEIN: I just have one more question.

In the seizure, since they're personal use items, was there any antibiotics seized?

DOCTOR TOLLIVER: Antibiotics? We saw them very occasionally, less than three or four of the declarations, for the most part. It was very, very rare to see antibiotics, anti-viral medication,

anything like that.

One of the things, if you noticed, on this list, the vast majority of them were controlled substances that were found. In fact, if you look at the declarations on the whole, over 90 percent of them had benzodiazapenes of one form or the other. Over 97 percent of all the declarations had controlled substances in them.

DOCTOR YOUNG: In our packet, Doctor Tolliver, there was a letter dated December 2, 1991, from Robert Bonner, the Administrator of DEA, concluding on the basis of, apparently, data up through 1991 -- DEA said there was not an abuse and did not indicate any significant levels of abuse. I gathered from your presentation that you would not change that reading of the situation?

DOCTOR TOLLIVER: Well, that's for you to decide. At the time, we did not have Customs' data either. We had very little. It was very limited. We also did not have information -- all I can tell you is what I've talked to from the phones and so forth. I wrote that letter and it was signed by him, but it was based upon, basically, on what DEA had. We had no Customs' data at all, and very little in terms of state and local at the time, all right?

DOCTOR KRAMER: If I may, I don't recall you mentioning that any of the seizure data that you had from your last list included amphetamines. That it did include other anorectic agents, but it didn't include amphetamine proper?

DOCTOR TOLLIVER: That's right, yes. Amphetamine was not one of them. Bring amphetamine across, it's going to be seized. It's just that simple. There's no such thing as putting it on a prescription form, Mexican prescription and bringing it in, or anything like that.

CO-CHAIRMAN MEISCH: Doctor Wright, what are you wishes at this point?

DOCTOR CURTIS WRIGHT: Well, I think we have two more parties to hear from. We have CPDD and the Stimulant Society.

Have they managed to hang in here? No, they've departed.

I'd like to take about four minutes and talk about what we've done in the past with surveillance when there's a concern about a substance that either we did not schedule, or that we're concerned about in some way.

This is an evolving business because we are learning how to do this. It was driven by the

fact that in some recent high-risk approvals -- I think probably the best one is the fentanyl oralet which had a safety concern in terms of children. Vigorous control by the marketing company has resulted in a perfect safety record in the first year of marketing which is unheard of for a narcotic. I mean, zero serious adverse events. So, it became clear to us that just as with Parke-Davis and oral chloroenphenicol, if a pharmaceutical firm chooses to take vigorous action, it is possible for them to be very effective.

The things that we required usually in the various meetings of this Committee over the iterations that we've been through in the last six years have been that there be sufficient scientific study to adequately describe the probable risks associated with the compound. That specific plans be made to place surveillance systems that will detect potential problems. That any reports of problems be evaluated. That an intervention of significant problems be placed, and that the report of those interventions be provided to the Agency as part of the annual report.

In this particular case, I have heard a number of things. I've heard a suggestion that a CSF study was appropriate. I've heard a suggestion that

a long-term study in patients looking with sensitive measures. I really do not have the energy to ask Doctor Mann to go into those in detail at this time, though I think he would. It was described. In terms of the terminal events, or the events that people appear to be concerned about, certainly, suicide was one, drug abuse was one. I think that the primary division is concerned about primary pulmonary hypertension and neurotoxicity and will take of that quite well.

The populations that I heard today were eating disorder populations, drug abusing populations, school populations, criminal justice populations in the context of parolees or individuals in, for example, methadone programs where urinalysis is commonly done. Athletes, and as part of that, the body-building athletic culture and possibly female athletes as a group particularly at risk.

I think that if you have a recommendation to make about post-marketing monitoring, that it should be that a specific program be implemented. That it be negotiated between the Agency and the sponsor, and that it sample those kinds of areas or others that you may recommend. I also am very sensitive to the comment that was made by Doctor

Tolliver. I do think that it is important that we acknowledge the importance of criminal justice information in making an abuse determination. And if we still have a quorum, you may wish to readdress your decision of earlier today, in the context of any post-marketing data that you may or may not want to request.

CO-CHAIRMAN MEISCH: All right. Any comments from the Committee members on surveillance post-marketing agreements?

Yes?

DOCTOR BORHANI: I think, based on what we have heard, I have no question in my mind that definitely, there ought to be a set of very rigorous and well designed, and if I may be permitted to add the word "controlled and supervised" surveillance program in conjunction not only between FDA and the sponsors in the pharmaceutical industry but the DEA and all the other agencies that we just heard. Because it is definitely clear to me now that there is a good database available and this database could be tapped if the confidentiality is preserved, which I'm sure will be if FDA and the DA work on this.

So, I think that will give us not only information that we could use in terms of any abuse or

potential abuse, but in terms of other aspects of the use of this particular drug, especially neurotoxicity, psychological behavior and other personal behavior that the people who legitimately take these drugs will develop these kinds of symptoms that hopefully, we will have a good database.

If I may add, I would like to suggest if it is possible, perhaps you would like to consider CDC people involved in this so that they can work together. Because they collect these kinds of data and other aspects of the American people's health. So, it would be good for us to have a good database at this point. So, I definitely think that's going to be a good thing to do, and I hope we end up doing it.

CO-CHAIRMAN MEISCH: All right.

Yes?

DOCTOR KHURI: Indeed, I agree with Doctor Borhani. My original vote was, of course, predicated and it assumed that we would decide question three in such a manner. I would add, of course, the list of targeted surveillance which Doctor Wright has delineated is extremely important. It would obviously be the most effective, as well as cost effective way of doing this.

But I would also say that surveillance is

detection, but we are also interested in evaluation and intervention in cases of abuse as mentioned in the question. I think I would be very interested, although it not be implemented yet, in knowing what the interventions would be.

CO-CHAIRMAN MEISCH: All right, thank you.

Doctor Bone?

DOCTOR BONE: Thank you.

It seems to me likely that the type of misuse I asked about earlier when we were trying to draw a distinction between abuse and misuse with respect to, in effect, illicit use for the intended purpose by, for instance -- this might be an overlap with the school-age population, but it might not entirely -- is probably more likely to be a problem than abuse of the drug for purposes of the user's becoming intoxicated in some way, that they would seek to be intoxicated.

It strikes me that that kind of use would probably involve maybe slightly different channels from those that are usually thought of as drug abuse. It might add also, the mechanisms of actually seeking to survey the populations at-risk will be somewhat different and will require, perhaps, an active approach that might be less dependent on law

enforcement agencies' usual approaches. Although I'm certainly a neophyte with respect to that kind of question. Also, it would be helpful in that way to track back to, perhaps, an appropriate prescribing it as being an original source for some of those users, if there are such users.

There is obviously an interest, from the standpoint of the Committee, who is concerned about safety and efficacy primarily in surveillance for the kind of adverse effects that were either expected or postulated based on earlier discussions. I don't know whether it's going to be possible to blend those, as Doctor Borhani suggested, into the same surveillance program, but certainly it would be useful if a complimentary approach can be worked out. So, I think attention to those issues would be valuable.

DOCTOR CURTIS WRIGHT: Just so that you know, we do have precedent for tracking to the level of the individual prescriber. There is very good literature tracking back to individual prescribers, both in the oncologic literature for inappropriate use of oncologic agents and also in the literature with respect to using Medicaid and Medicare databases to track for inappropriate prescribing of oral chloroenphenicol.

DOCTOR BONE: I see.

Do you have experience in, for example, looking amongst high school age girls in schools to determine whether there's a prevalence there that can then be backtracked, that kind of thing?

DOCTOR CURTIS WRIGHT: Our program that's currently running that's most like that is the dextromethorphan program where a combination of spontaneous reports from schools and surveys of school nurses and school contacts looks for evidence or reports of misuse of dextromethorphan in that school age population. This is a new field and it's limited only by the creativity of the folks at the company and in some of the things that the guidance committees have been able to come up with.

CO-CHAIRMAN MEISCH: Doctor Cicero?

DOCTOR CICERO: Yes, I think that a more complete description, we've actually got school counselors. There's a group of school counselors, high school -- the athletes, the coaches, trainers, all of those can be contacted by surveys.

I think the outline that Doctor Deitch laid out was, in fact, just that. I think clearly, this needs to be thought about. And as he indicated, not only a consultation with the FDA, but you're going

to need an expert committee to get together to actually help in the design of this. What should it look like? I think what we're sort of asking for today, which is very helpful, is the type of input. Clearly, this will have to not only be negotiated with the FDA, but I think there needs to be some expert group of people who do know sports medicine, who do know the areas that were brought up today that could help and say, "okay, what makes sense in this case?"

Clearly at this point, it appears that we have no abuse. It seems like there's very little misuse. I hear the concerns that people seem to be expressing that there may now be because it's de-scheduled. Well, if it is, then we ought to be able to target which groups that it's likely to occur in, and get in there and take a look at it. With the wealth of the talented people in this field, I would think that that's certainly feasible.

What I heard the company saying -- and if we didn't all hear it, I think the commitment was there to basically to do the very best job possible with an expert committee helping, obviously, in that judgment.

CO-CHAIRMAN MEISCH: Doctor Deitch?

DOCTOR DEITCH: Let me just give you an

example. Maybe we're talking about the same thing.

Around the time AH Robbins was acquired by American Home Products Corporation, we became aware of abuse of Robitussin. By setting up a fairly well thought out program to intervene -- which I think is what you'd like to hear, what was said -- using local pharmacists, local educators, essentially SWAT teams went into the areas where this was occurring. They essentially drove it down to a zero base within, I think, about a three to six month period of time. They continued to educate. They continued those programs in those places where there were vulnerable populations. I think, really, what we have to think about is where are the vulnerable populations?

One thing we certainly can start with is when you have this unique situation of going from a database of about a million to a 1.2 million prescriptions, we have an excellent way of looking at where is it being used now and using that as the starting point and being able to detect very quickly once it is de-scheduled, if there are changes in patterns.

Just go back to the point of the fact that 97 percent of the uses now have been shown to be for obesity treatment. We need to go a little bit further

and drill down and be sure that that is exactly what's happening. Look at prescriptions themselves, how many tablets are being prescribed, what the average dose is. There's a thing in the industry we call dacons, daily counts, how is it being used and so on. So, there's a wealth of data. We are certainly willing, as we always are, to meet with the Agency and to hear your suggestions, and come up with a program that is acceptable to all.

CO-CHAIRMAN MEISCH: Go ahead.

DOCTOR KHURI: A quick question and then another question.

As someone interested in adolescent drug abuse, was the Robitussin abused for the alcohol or what?

DOCTOR DEITCH: No, it was Robitussin. I mean, I'm a pediatrician also. I couldn't understand why in the world they would want to abuse ordinary Robitussin which makes you sick.

DOCTOR KHURI: Right.

DOCTOR DEITCH: But in fact, rapid ingestion of large amounts, four ounce bottles -- maybe it was a placebo effect, maybe it was a hysterical effect. We don't really know exactly what it was. Maybe some of the drug abuse people here are

more familiar with it. But it came up. We put it down and it disappeared.

DOCTOR KHURI: Well, I'm a drug abuse person and I don't know about that. But we do know about garbage heads.

DOCTOR CURTIS WRIGHT: We actually have two advisory committee reports on that --

DOCTOR KHURI: Yes, okay.

DOCTOR CURTIS WRIGHT: In the quantities that these were consumed, this was a psychoactive drug. It was predominantly, probably, a sigma effect.

DOCTOR KHURI: Okay. I did have a question. I was extremely interested in the pulmonary hypertension data shown by Doctor Luisada. We might add, actually, pulmonary clinics to our list of surveillance places.

But I was a little confused because Doctor Luisada's excellent presentation to me assumed a definite causality. I had understood that this detection was an association and not an absolute risk. There was a strength of association, but it's still a remaining question, in my mind, because there could be so many other factors in the diagnosis, causing the disease -- admittedly rare, but terrible disease.

DOCTOR LUISADA: Initially, this was an

association. Because of this association, the sponsor, Servier commissioned the study that was conducted by Doctor Abenhaim of Montreal, a very carefully controlled epidemiologic study, case-controlled study that was just completed. We heard part of the initial report yesterday. There will be additional reports coming out over the next few years which showed a very definite relationship.

DOCTOR KHURI: That may have been in the briefing materials of the other committee and I missed your presentation yesterday. I'm sorry.

DOCTOR LUISADA: Right, right. No, I'm sorry. I assumed that that had been discussed and I should have pointed that out.

DOCTOR KHURI: No, we discussed other things yesterday.

DOCTOR LUISADA: All right. Well, that's my defect. I should have really pointed that out. This has been an established relationship. The quantification of it is still very indefinite and there are additional reports coming out.

CO-CHAIRMAN MEISCH: All right.

Other questions or comments?

DOCTOR CURTIS WRIGHT: I'd like to hear Lisa's venue.

MS. MOJER-TORRES: I'm still thinking.

DOCTOR CURTIS WRIGHT: We're getting down to closure. I think we do need to know -- we do need a definite signal from you as to whether you think that -- I heard a number of opinions and a number of comments, but I need a real definite signal as to whether you think that a post -- and it's really not a post-approval, but a post-decontrol, a monitoring plan, is essential. I'd appreciate it if you would address that question as a Committee.

DOCTOR BORHANI: Do you need a motion to discuss this formally?

CO-CHAIRMAN MEISCH: I don't think so.

DOCTOR CURTIS WRIGHT: It's Question Number 3. We need an answer to Question Number 3.

CO-CHAIRMAN MEISCH: Go ahead, please.

DOCTOR KHURI: Well, my answer to that is an extremely strong recommendation. I for one, and I believe the other members of the committee would not have voted for decontrol at all, which is not voting for unbridled use of this substance, but simply to perhaps have more use and to learn more about it. I would say it is absolutely essential to have good detection of use and misuse if it comes up.

I think our task was narrowly defined with

a narrow definition of what it abused. We decided "no, it was not a drug of abuse" by our narrow definition. But we must have surveillance and evaluation of that surveillance. Not just counting the numbers, but evaluation of what it means and in addition, interventions have been addressed. I believe it is the good intention -- and I hope will be actuated -- of the sponsor to do so.

MS. MOJER-TORRES: Well, in terms of listening to everything that's been said, I was particularly impressed with what you said about the fentanyl. I wasn't here at that time, and I have a feeling that the issues, the safety issues, were more directed. Whereas here, they seem to be a little all over the place. They're with the female athletes. They're with the hypertension. The concerns seem to be so spread out.

But I was so impressed with the fentanyl, that in a year, there wasn't one incident, one reported incident. I think we should really take a clue from that. I don't know if we can learn -- as I said, I wasn't here, so I don't know -- maybe you can review what --

DOCTOR CURTIS WRIGHT: I can spend a few minutes talking about that. That was an extremely

high priority concern of the Commissioner, personally. He attended the Advisory Committee, personally. He made it very clear to the director of the Center for Drugs that it was important. Doctor Lumpkin, in an extraordinarily able way, and Lucy Rose worked very well to make a very explicit program that was negotiated very clearly with the company. It was made very clear that if this program was not implemented as agreed to, that the drug would come off the market, no ifs, ands or buts. That was very effective.

CO-CHAIRMAN MEISCH: A comment on that, actually, in relation to what we're dealing with here.

We're not dealing with a potent opioid such as fentanyl, and we're not dealing with children. The kind of rigor -- and the drug with children, it was, what, only for use in-hospital.

DOCTOR CURTIS WRIGHT: The specific restrictions on that was that during the roll-out period, that particular drug was limited to use under conditions of adequate monitoring. A great deal of attention was placed on the label to the detection and prevention of adverse events. It, in essence, resulted in individuals who were trained at the level of an anesthesiologist using the drug. The result was that, under those circumstances, there's remarkably

little risk associated with a very potent opioid.

I am not clear how that would translate into this class of drugs. I think that's where the creativity comes into play in developing a system. But it is very clear that companies can exert a substantial influence on the marketing of their products should they choose to do so. It's very clear that we are watching very carefully.

MS. MOJER-TORRES: See, that's what I was impressed with, the fact that the company took such an active role. Then it wasn't just a bunch of recommendations, and you got your deregulation so, see you later. I was very impressed with that.

CO-CHAIRMAN MEISCH: Yes?

DOCTOR KHURI: In a way, however, we also are dealing with children here. I get back to my bailiwick.

One thing we want to monitor very carefully is, obviously, teenage girls looking to lose weight. We've mentioned that. But also, a bunch of kids trying to have hallucinogenic experience on this drug and getting it. We know that although a lot of things are not sold to under 18 or under 21 year olds, they certainly are highly available.

We also know the effect of the media and

[redacted]

least bit reluctant to ask for emergency scheduling. And you are empowered if you, in the course of looking at a surveillance program, find an emerging problem.

DOCTOR KLEIN: No, emergency scheduling is only for non-approved substances which are in Schedule I.

DOCTOR CURTIS WRIGHT: There is no provision for -- I stand corrected. That's why we have Mike. I do not claim to be an expert in that law.

The answer is, you would make a recommendation to us or we would make a recommendation through the Secretary to the DEA that this be rescheduled. In general, those go a little easier than de-scheduling, historically.

DOCTOR KHURI: Okay. So, in a way, there is an emergency scheduling.

DOCTOR BORHANI: If it is all right, I would like to ask a question that I have asked my other friends in FDA before.

How difficult is it for FDA, as a whole, taking these recommendations and discussions as you always do, I'm sure, when you consider. Finally, the Commissioner makes a recommendation in this case through the Secretary to do something. How difficult

is it for FDA to work -- and I mean work very hard -- with the pharmaceutical industry and to get a commitment from the pharmaceutical industry that becomes part of your recommendation? That based on et cetera, et cetera commitment and contribution or whatever, we recommend that we do this. Because this recommendation involves education of physicians, education of pharmacists, public education, surveillance, evaluation, reporting, and they're all going to cost money. Therefore, if you are accepting our recommendation and going through the Secretary, we would like you to know and pass it on to Congress and the President when the time comes, that these recommendations will not affect adversely too much, the national budget that we'd like to balance.

You see, I'm really trying to get a handle if FDA could tell -- to be very frank -- to the sponsor sitting behind me, "listen, Buddy, we are going to do this. I think we'll do it, but you're going to commit yourself that so much percentage of your income that comes from this cash flow is going to come to implement this recommendation." I'm just talking that very frankly to see, is it possible to even approach or discuss this so that the taxpayers will not be saddled with another $2 or $3 billion for

implementing these kinds of recommendations? Or am I just totally naive?

DOCTOR CURTIS WRIGHT: You've covered a lot of territory.

DOCTOR BORHANI: I know. I know.

DOCTOR CURTIS WRIGHT: Let me try to answer it. Then we'll ask the company to answer it.

From our perspective, in general, the amount of money that is spent on clinical development -- excluding some pre-clinical work and development work -- but on clinical development and the implementation of clinical monitoring is usually modest in relationship to the amount of money that firms have to spend in terms of promotion of their products. The marginal cost, if you will, of implementing additional attention at the level of the detail person is relatively bearable.

It does get passed on to the consumer. It does appear on the price of the drug. I mean, they don't cost it out and say, "FDA's monitoring program, three cents per tablet," but the reality is that when you ask for things, they do cost money and you do have to make sure that they're needed. That's why we don't ask for your recommendations unless we feel we need them. And when you give them to us, we take them

seriously and convey them to the sponsors. I think a responsible firm implements them.

I'd like to hear what the firm has to say.

DOCTOR DEITCH: Am I on the spot now?

Let me say a few things. First of all, Wyeth Ayerst Laboratories and Interneuron -- but Wyeth Ayerst Laboratories has been in the business of marketing pharmaceuticals in this country since before many of us were born. We are one of the largest pharmaceutical companies in the United States. We have products in many different categories. We have products in categories that we have concerns about. We have instituted programs of education and monitoring to be sure that valuable equity isn't lost somehow because they are misused.

It's a business decision just as well, but I'll give you an example: oral amiodarone, an anti-arrhythmic agent which had been marketed in Europe for many, many years, was approved with a lot of caution back in 1985. Amidst a lot of concern not only inside the company but also in the community of arrhythmologists or electro-physiologists that, in fact, once out on the market, while it was only being approved for severe life-threatening arrhythmias, ventricular tachycardia, ventricular fibrillation --

ie, last resort -- because it had a very high incidence and still has a high incidence of severe limiting side effects: pulmonary fibrosis and things like that. That it would be misused to treat atrial arrhythmias at a lower dose, as it is throughout the rest of the world.

We've been very, very successful in continuing to educate through our sales force, through speaker training and so on, on the absolute proper use of the product. Now, the vested interest we have in that not only is to be a good public citizen -- because we are concerned about misuse of the drug -- but because we certainly want to protect equity just as well. We're not interested in seeing a product used improperly.

You've given us a responsibility today that we don't take lightly. We understand in the first instance that the patients are waiting out there. There are many patients who are not getting treated for obesity, not because the drugs are not available but because physicians are not happy prescribing drugs on triplicate prescription, having to refill the product every so often and having limitations and so on. A lot of plans won't reimburse and so on and so forth. So, the opportunity is there

to be able to extend treatment to those people who need it.

At the same time, we'd be very foolish to risk the opportunity by not participating and not working as closely as we can with reasonable solutions to all the problems that you've brought up today. We stand ready to do that. We'll meet with Doctor Wright and with others in the Agency, tomorrow if you wish. I think we've been here long enough this week, maybe next week, and begin that process.

DOCTOR KLEIN: You should appreciate also that there is an additional cost to the government, at least to the FDA, because whereas the NDAs, the 90s, are stacking up in my office, they need a certain amount of time as well, and attention. As we are nurturing some sort of a new type of system and following it, they -- exceedingly time consuming as well.

CO-CHAIRMAN MEISCH: Yes?

DOCTOR KHURI: A small point, but I'm thinking of the cost of surveillance. I want to put the flashlight where the cases are as much as possible.

The small addition -- in my experience with abuse of hallucinogenics in young people, you

don't find them as much in drug abuse clinics, believe it or not, even methadone clinics. You find them on college campuses. I would alert college infirmaries dealing with bizarre behavior just to screen for this, because they won't think of it unless we tell them.

DOCTOR KLEIN: I'd like to ask Doctor Young, hallucinogens are not generally self-administered? Is that correct?

DOCTOR YOUNG: Those of the LSD type.

DOCTOR KHURI: But almost anything that changes mental state or consciousness -- it's a broad range -- can often be classed as an hallucinogenic experience, although not strictly hallucinogenic.

DOCTOR CURTIS WRIGHT: I get the feeling that we're all running out of steam, at least I am. Perhaps I'm projecting as Doctor Luisada would say. I'd like to have an answer to Question 3, and I'd like to know if you want to reconsider one? I'm not suggesting either way. I'm just asking, in the light of the new information you've heard, do you wish to reconsider?

CO-CHAIRMAN MEISCH: Comments?

DOCTOR KHURI: Do you want a poll? I, for one, do not want to reconsider number one.

CO-CHAIRMAN MEISCH: I don't either.

DOCTOR BORHANI: I'm comfortable with the way I decided.

CO-CHAIRMAN MEISCH: All right.

DOCTOR BORHANI: I have to guarantee I really want -- thank you.

CO-CHAIRMAN MEISCH: Now, to address Question Number 3: "If decontrol is recommended, does the Committee recommend the sponsor implement a risk management plan to detect, evaluate and intervene in cases of abuse?"

DOCTOR KHURI: Yes.

DOCTOR BORHANI: Yes.

MS. MOJER-TORRES: Yes.

CO-CHAIRMAN MEISCH: Show of hands?

DOCTOR CURTIS WRIGHT: Is that a quorum, Steve?

CO-CHAIRMAN MEISCH: Opposed?

Abstain?

That was unanimous.

DOCTOR CURTIS WRIGHT: Yes. I just needed to make sure we had enough members left.

The other question I would -- I'm very sensitive to what Doctor Tolliver had to say. Does the Committee wish to reconsider one?

CO-CHAIRMAN MEISCH: We were just polling

ourselves on that.

Doctor Young?

DOCTOR YOUNG: No.

DOCTOR KHURI: No.

DOCTOR BORHANI: No.

DOCTOR KHURI: Are you still abstaining?

MS. MOJER-TORRES: Yes.

CO-CHAIRMAN MEISCH: No need, no desire.

DOCTOR CURTIS WRIGHT: Want to close?

CO-CHAIRMAN MEISCH: Yes. We're adjourned.

(Whereupon, the meeting was concluded at 4:34 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in

the matter of: Drug Abuse, and Endocrinologic and Metabolic Drugs Advisory Committees Joint Meeting

Before: Food and Drug Administration

Date: September 29, 1995

Place: Rockville, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.