TAB 5

Public Meeting on the Safety, Effectiveness, and Possible Misuse of Phenylpropanolamine Hydrochloride as an OTC Weight Control Drug Product

May 9, 1991
Conference Room E, Parklawn Building

Between: Food and Drug Administration Representatives

Robert J. Temple, M.D., Director, Office of Drug Evaluation I (HFD-100)
Raymond J. Lipicky, M.D., Director, Division of Cardio-Renal Drug Products (HFD-110)
Heidi Jolson, M.D., Epidemiology Branch (HFD-733)
Martin Brecher, M.D., Division of Neuropharmacological Drug Products (HFD-120)
Philip L. Dern, M.D., Division of Cardio-Renal Drug Products (HFD-110)
William E. Gilbertson, Pharm. D., Director, Division of OTC Drug Evaluation (HFD-210)
Helen Cothran, Branch Chief, Gastrointestinal and Contraceptive Drug Monographs Branch, Division of OTC Drug Evaluation (HFD-214)
Mary Robinson, Gastrointestinal and Contraceptive Drug Monographs Branch, Division of OTC Drug Evaluation (HFD-214)
Robert Sherman, Gastrointestinal and Contraceptive Drug Monographs Branch, Division of OTC Drug Evaluation (HFD-214)

and

Public/Industry Participants

Richard Atkinson, M.D., Eastern Virginia Medical School
George Blackburn, M.D., Harvard Medical School
Thomas Q. Garvey, III, Garvey Associates, Inc.
Frederick S. Mayer, R. Ph., M. Ph., Pharmacists Planning Services, Inc.
Newell E. McElwee, Pharm. D., M.S.P.H., Rush Presbyterian St. Luke's Medical Center
Vivien Meehan, National Association of Anorexia Nervosa and Associated Disorders
John P. Morgan, M.D., CUNY Medical School, The City College of New York
Paul Raford, M.D., U.S. Public Health Service
David E. Schteingart, M.D., University of Michigan Hospital
Anthony Smith, State Center, Iowa
R. William Soller, Ph. D., Nonprescription Drug Manufacturers Association

Sheila Specker, M.D., University of Minnesota
Medical School
Joseph C. Veltri, Pharm. D., Intermountain Regional
Poison Control Center, University of Utah
Charles Winick, Ph.D., City University of New York

The meeting was held at the request of the Food and Drug Administration to gather information on issues regarding the safety, efficacy, and possible misuse of phenylpropanolamine hydrochloride (PPA), based on recent information submitted on OTC weight control drug products and a September 26, 1990 hearing, chaired by Congressman Ron Wyden, Chairman of the House Small Business Subcommittee on Regulation, Business Opportunities, and Energy, examining adolescent dieting behavior and the possible misuse of PPA-containing diet pills.

Presentations by various groups and individuals were made before a panel of four FDA representatives (Drs. Temple, Lipicky, Jolson, and Brecher). The panel was chaired by Dr. Temple.

A brief summary of the presentations and discussion at the meeting follows. A detailed record of these proceedings can be found in the transcript of the meeting which is part of the public record for the rulemaking for OTC weight control drug products, coded TR1 under Docket No. 81N-0022 in the Dockets Management Branch.

The meeting began shortly after 8:30 a.m. Dr. William Gilbertson, Director of the Division of OTC Drug Evaluation, opened the meeting with a review of recent events which led FDA to reopen the administrative record for OTC weight control drug products and ask for comments and any new data specifically related to the safety, effectiveness, and possible misuse of PPA for OTC weight control use. In a brief slide presentation, Dr. Gilbertson reiterated the questions relating to the safety, effectiveness, misuse, and labeling of PPA that were published in the Federal Register notice of April 1, 1991 (56 FR 13295 at 13298). Dr. Gilbertson noted that this was a fact-finding meeting, no conclusions were expected to be reached, and FDA's conclusions on the meeting will be published at a later date as a proposal in the Federal Register. He also noted that the administrative record would remain open until August 7, 1991, to include all data submitted since the record previously closed on July 26, 1982, and the proceedings of the public meeting. Dr. Gilbertson announced that anyone interested in participating, who had not previously notified his staff, would be given time to testify later in the day, and that time had been allotted to continue the meeting for a second day, if necessary.

Helen Cothran, of the the Division of OTC Drug Evaluation, served as the moderator. She welcomed all in attendance and reminded everyone that the times listed on the meeting agenda were subject to change. (See agenda attached.) She asked anyone in the audience who was not listed on the agenda, and who wished to make a presentation, to contact Mary Robinson so that time could be allotted after the scheduled presentations. Ms. Cothran noted that a representative of the Dockets Management Branch was present to accept any submissions to be entered into the record.

Dr. Temple introduced the panel and reiterated that this was not a decision-making meeting. He stated that the panel was prepared to listen to all views presented and, therefore, there was no planned time limit on the proceedings. Dr. Temple added that, after a presentation, questions from the audience would be taken following questions from the panel.

Dr. Paul Raford of the U.S. Public Health Service commented on the safety of PPA and proposed future investigations that might resolve some still unanswered questions. Dr. Raford pointed out that the vast majority of the clinical literature shows that most people can use PPA safely; however, there are some limitations to these studies. He stated that most studies were not designed to look at the small group of individuals that have shown dramatic increases in blood pressure following a single dose of PPA. He further stated that most studies on PPA used healthy, young individuals who were confined to a medical setting under strict supervision and these studies are not representative of how PPA is taken in the real world. Dr. Raford noted that although PPA should be used in a comprehensive program that includes calorie restriction, exercise and behavioral modification, epidemiologic data indicates that PPA is used without these other components and, as a result, most people find that it is largely ineffective. He said that the studies that the House Subcommittee focused on were designed to be representative of the population at large and they show that the majority of individuals misuse the medication and report, over time, it is ineffective. Dr. Raford commented on his comparison of PPA, acetaminophen, aspirin, and ibuprofen using the poison control center data and FDA's adverse drug reaction files. He attempted to find a standardizing measure, i.e., a common denominator, relating the number of side effects to the number of episodes of risk. He decided to use dosing episodes as the most appropriate measure for standardization and when examining the poison control center data and FDA adverse drug reaction data using this method, he found that the number of adverse drug reactions related to PPA diet pills outnumber those of other leading OTC medications. Dr. Raford concluded that there is a need for some standardizing measure so that the number of adverse reactions associated with PPA can be realistically compared to other OTC medications.

After Dr. Raford's presentation, he was asked by the Panel to expand on the three studies that he said showed misuse of PPA. The three studies were the studies by Vener and Krupka, done in 1985, the National Adolescent and Student Health Survey, done in 1987 by the Center for Disease Control (CDC), and a behavioral risk factor telephone survey that was also done by the CDC. The population in the Vener and Krupka study was college age individuals (18 and older) who were asked questions such as: (1) At what age did the first use of PPA occur?, (2) Had they ever taken excessive doses?, (3) Had they taken PPA despite medical contraindications?, (4) Had they had side effects?, and (5) Had they found it effective? According to Dr. Raford, the results indicated that use started as early as 12 years of age. By 16 years of age almost 50 percent of the teenagers had taken PPA and by 18 years of age almost three quarters of the teenagers had tried OTC diet pills.

The National Adolescent and Student Health Survey was a randomized study of nearly 50,000 individuals. Dr. Raford reported that the results indicated that use started as early as 12 years of age and 42 percent had used diet pills by the age of 16. Dr. Raford stated that none of the clinical safety studies and none of the efficacy studies had focused on this group.

The Behavioral Risk Factor Survey, a telephone survey of adults concerning nutrition and dietary practices, had a section on the use of OTC diet pills and the result was that a substantial number found that they were ineffective or were using them despite not being overweight.

Dr. Raford was asked if there was any information on the number of people who are likely to exceed the recommended dose. He said that the Vener and Krupka study and the behavioral risk factor survey indicated that 45 percent of 18-21 year olds had taken it in excessive doses or with caffeine. Dr. Raford was asked to comment on the higher rate of adverse events he found for PPA versus aspirin and acetaminophen. The Panel noted that the higher rate for serious adverse events reported to FDA and the poison control center for PPA versus aspirin and acetaminophen is dependent on the divisor used to convert from the number of doses to the number of episodes. The divisor being used for PPA is three times higher than for aspirin and four times higher than for acetaminophen. Dr. Raford explained that diet pills are taken for a much longer period of time, sometimes as long as three months. He said that if the appropriate risk measure is risk per continuous dosing episode, then the longer length of time that someone takes PPA would be reflected in the difference of the divisor. Dr. Raford felt that the appropriate number to use for PPA was 85.5 doses per course of medication. There was also a discussion about the differences between the poison

control center data, DAWN data, and FDA's adverse drug reaction data and how their interpretations might differ.

The Nonprescription Drug Manufacturers Association (NDMA) made a presentation which included a number of speakers who presented data on PPA's effectiveness, safety (including its role in cerebrovascular events and eating disorders), and commented on the House Subcommittee Report and PPA's benefit-to-risk ratio. Dr. William Soller, Senior Vice President and Director of Science and Technology of NDMA, introduced each speaker.

Dr. David Schteingart of the University of Michigan Medical Center presented data on the effectiveness of PPA. He described three recent studies, including one that he conducted, which he said demonstrated the effectiveness of PPA for weight control. He stated that there was much greater weight loss with diet plus PPA compared to diet plus placebo, and these differences were statistically significant. He concluded that PPA is safe and effective when used for the treatment of mild-to-moderate obesity. Dr. Schteingart also said that there was no data to suggest that PPA causes the loss of lean body mass rather than fat. Dr. Schteingart explained that loss of lean body mass is usually associated with rapid and large weight loss, whereas the weight loss associated with the use of PPA is slow and small in quantity, and such weight loss is consistent with the recommendations of the American Dietetic Association.

After Dr. Schteingart's presentation there was a discussion on the difficulties in doing a study that tries to reproduce the conditions that exist in an OTC setting, and how applicable the study results are to an unsupervised environment.

Dr. Schteingart was asked about the kind of supervision that the patients received and whether he felt that the mere presence of a professional would provide additional incentive and influence the results. He said that he tried to conduct the study with minimal supervision and that the measurements were taken by a research assistant who would not have affected the way the patients felt about succeeding. Dr. Schteingart was asked if there were any data on rebound weight gain after the studies were discontinued. He replied that he would anticipate that anybody who stops any weight loss program would regain their weight but had no information on this particular group of individuals. When asked if he felt that the use of PPA diet pills outside of a formal program was beneficial, Dr. Schteingart said that they are useful in inducing people to maintain a lower weight and avoid the health complications associated with obesity.

Dr. George Blackburn of Harvard Medical School presented data on the role of PPA in weight loss, the composition of weight loss, and weight cycling. He claimed that the loss of lean body mass was associated with large and rapid weight loss and not the slow and relatively small weight reductions associated with the use of PPA diet aids. He stated that weight loss of twenty-five pounds or less is safe, does not lead to weight cycling, and can result in dramatic health benefits. Dr. Blackburn later discussed his 1989 study and concluded that people benefit most from PPA in conjunction with a nutritionally balanced hypocaloric diet and that obese hypertensive adults are at the lowest risk for the pressor effect of PPA.

The Panel asked Dr. Blackburn about the health benefits of weight loss, the amount of weight reduction, and the time needed before any therapeutic effect could be seen. He said that his studies have shown that, as soon as you adopt a healthy diet, you start to see the metabolic changes and that cholesterol, blood pressure, glucose tolerance, and sensitivity can be affected within two weeks. Dr. Blackburn was also asked what relationship the amount of protein consumed had on the loss of fat versus the loss of muscle mass. He stated that the type of diet can determine whether one loses muscle mass or fat. If someone is restricting calories and is on a low protein diet the weight loss is more likely to be lean body mass rather than fat.

Dr. Blackburn was asked if he feels that teenagers are following the dietary guidelines for increased protein intake along with reduced calories and are not losing muscle mass. Dr. Blackburn said that it would be difficult to identify the amount of protein consumption in teenagers who are dieting. He stated that 50 percent of teenagers who are using PPA are using it for weight maintenance and that this figure is often misinterpreted as people who are inappropriately on a diet.

Dr. Richard Atkinson of Eastern Virginia Medical School, substituting for Dr. Louis Lasagna of Tufts University, spoke about the risk/benefit ratio of PPA and said that even a small weight reduction has a beneficial effect. Dr. Atkinson also presented Dr. Lasagna's conclusions about the questions raised in the Federal Register as follows: (1) PPA is effective, it causes a slow steady weight loss and weight tends to stay down as long as people are on the medication, (2) the fact that studies were done in a medical setting does not invalidate them, (3) there is no evidence that PPA causes rebound weight gain or a loss of lean muscle mass rather than fat, (4) there is no evidence that small increases in blood pressure cause any serious long-term effects, (5) the incidence of strokes is not different from that which would be expected to occur by chance, (6) there is no evidence that PPA plays a pathogenic role in the causation of anorexia

nervosa or bulimia, and (7) there is no scientifically sound evidence that PPA misuse is a widespread problem in any age group.

There was a discussion following Dr. Atkinson's presentation on whether PPA would have to be used on a long-term basis to maintain weight loss. Dr. Atkinson felt that comprehensive programs of diet and behavior modification generally show a poor success rate if the patients are followed over a five-year period. Dr. Atkinson said that there is a small group of people who should use PPA as a life-long treatment just as some individuals must use medication for hypertension. He mentioned his on-going research in animals and humans to try to identify those individuals who might require life-long medication. Dr. Atkinson said that he believes there are multiple types of obesity with specific biochemical defects that will have to be treated pharmacologically, and that there is a need for continued study.

Because of the lengthy discussion periods following each speaker's presentation, the meeting was well behind schedule. Because of these time constraints, NDMA allowed their presentation to be segmented in order for the panel to hear the testimony of several individuals who spoke about the consequenses of PPA misuse.

Frederick Mayer, President of Pharmacists Planning Services, Inc., stated that PPA should be sold only by prescription or be placed in a special class of drugs that could only be sold by a pharmacist, with patient education and counseling, or be taken off the market entirely. He claimed that there was wide misuse of PPA by adolescents who often ingested more than the recommended dose. He stated that conclusions reached on PPA using healthy subjects in controlled clinical studies are not applicable to a population that includes children as young as 12 taking the drug without medical supervision over an extended period of time. He also had concerns about mixing OTC drugs, such as PPA, with other drugs. Mr. Mayer strongly urged FDA to change the labeling of PPA-containing products so that the elderly could more easily read instructions and cautions regarding their use with certain illnesses such as heart disease, high blood pressure, or diabetes. He mentioned legislation in California directed toward increasing the ability of consumers to read and comprehend the labeling of OTC drugs. Mr. Mayer read the testimony of a 74 year old woman who had lost conciousness while driving on a Los Angeles freeway after taking one Dexatrim capsule. She was taken to a nearby emergency room and was told that she had gone into shock and passed out as a result of extremely high blood pressure. She said that Dexatrim had caused her extremely high blood pressure.

A discussion followed on the merits of a third class of drugs and Mr. Mayer was asked if there is any evidence that pharmacists controlling the sale of drugs would decrease the rate of adverse events. Both Mr. Mayer and Mr. Brian Hyps of the American Pharmaceutical Association said there is documentation that a pharmacist's intervention does reduce the number of adverse drug reactions. Mr. Hyps offered to submit this documentation to the administrative record. Mr. Mayer stated that the Pharmacists Planning Service was more in favor of removing PPA products from the market than for including it in a third class of drugs. He asked that, at the very least, FDA require a large warning on the label that could be easily read by elderly consumers who might otherwise use PPA despite medical contraindications. There was a brief mention of NDMA's voluntary label readability program.

NDMA continued its presentation with Dr. Sheila Specker of the University of Minnesota Medical School who spoke about the role of PPA in eating disorders. She stated that most individuals with eating disorders are not adolescents, but adults. She said that the median age of onset for anorexia nervosa is about age 17, and age 18 for bulimia. She commented that patients with eating disorders use other substances such as laxatives and diuretics, and most find that the effects of diet pills are not powerful enough to sustain their usage. Dr. Specker said that the main problems in these individuals are binge eating, vomiting, and laxative abuse. She concluded that there appeared to be no evidence that the use of diet pills was a primary contributor to the development of eating disorders.

Dr. Specker was asked if there was any reason to think that diet pills provoke or stimulate eating disorders, and if she thought the rate or course of these conditions would be altered if PPA diet pills were not so readily available. Dr. Specker said that her patients do not exclusively use one substance, and if they are using diet pills, they are also using laxatives and alcohol to try to suppress their appetite. Dr. Specker was asked if there were any reports of adverse effects from people who were taking laxatives and why such effects were generally not reported to adverse drug reaction systems or poison control centers. Dr. Specker thought that these events were under-reported because individuals experiencing these events were using the products surreptitiously and would not want it to be known. She added that their symptoms might not be as severe as would be experienced with excessive doses of diet pills. She said she doubted that the rate or course of eating disorders would be affected if PPA was not available.

Dr. Joseph Veltri, Director of the Inter-Mountain Regional Poison Control Center, Dr. Newell McElwee of Rush Presbyterian, St. Lukes's Medical Center, and Dr. Charles Winick of the City

University of New York followed with NDMA's commentary on the House Subcommittee report. Dr. Veltri talked about the poison control center data used in the House Subcommittee report, serious methodologic problems he found in that report, and his contradictory findings on the number of calls to poison control centers, reports of adverse events, and the severity of those events. The problems that Dr. Veltri found in the report included improper generalization of the poison control center data to the general population, the arbitrary use of "dosing episodes" which would artificially inflate the number of adverse events, and the use of a combination of three generic categories to construct a new category which includes PPA diet aids, PPA and caffeine combination products, and PPA containing look-alikes. After review of the data reported by poison control centers, he was unable to find evidence to support the Subcommittee findings and found that PPA diet products did not differ from other common OTC products in terms of mentions to poison control centers (i.e., number of calls) or reports of adverse reactions, and in terms of severity of the outcome of those exposures.

Dr. McElwee presented information on the methodologic problems with the House Subcommittee report, and contradictory findings regarding teen use, adult misuse, and the frequency of adverse events. Dr. McElwee said that he found epidemiologic information that should have been included but was not, and errors in the accuracy of the information contained in the report. He concluded that the data were often misquoted and misinterpreted in the report. Dr. McElwee disagreed with the House Subcomittee's exclusion of the Drug Abuse Warning Network (DAWN) data from the report because, according to the Subcomittee, the data were not relevant in an evaluation of PPA safety. He stated there was no evidence that a large number of purchasers of PPA products misuse the drug and do not follow current label instructions, or that OTC PPA products represent a serious hazard to consumers, especially those under age thirty.

Dr. Winick discussed epidemiologic data, the relationship of the use of PPA products to lifestyle, and comparative studies of PPA versus other products. Dr. Winick talked about two epidemiology surveys, the National Adult Survey and the Adolescent Survey. He stated that they were essentially modules of questions that were part of a much larger survey, and that the central goal of these surveys was not to do an intensive examination of the subject of weight reduction or diet aids. The surveys were conducted at one time and gave no information on trends. Dr. Winick felt that the data were extremely underanalyzed with no information on lifestyle, background, or other difficulties the subjects may have had. He said that these surveys do not present the complete picture and it would be difficult to make sweeping generalizations based on the information we have now.

Dr. Winick disagreed with the contention that the widespread availability and vigorous marketing of PPA products made it difficult for people to engage in other approaches to losing weight such as exercise and calorie reduction. He stated that, in three different surveys, when people were asked what things they would do to lose weight, the vast majority cited the need for increased exercise and the wisdom of eating fewer calories. Regarding use of diet pills by young people, Dr. Winick stated that there appears to be a downward trend and in the last 7 years, the use of these products has dropped by 50 percent. He also disagreed with the perception that the use of these products by people who are not overweight is undesirable. He said that evidence from a number of studies showed that these products are often used for weight maintenance, and there is no information to show that they have significant aftereffects, that they lead to disease, or that they have any major negative consequences.

Dr. Winick stated that the dosing episode concept used by Dr. Raford is not a viable one because the rate at which OTC products are used in the home is unknown. He mentioned that a product like aspirin, which is used for so many different purposes, does not lend itself to simple generalizations. He noted that, when looking at the poison control center reports, PPA is significantly less represented than aspirin and acetaminophen. Dr. Winick disagreed with the 85.5 per dosing figure for PPA used by Dr. Raford. Dr. Winick said that the only recent data on PPA dosing episodes that he is aware of states that the median number of doses per dosing episode is 16.2. Dr. Winick said that PPA should not be singled out as being any less safe than other very widely known and used OTC products, such as acetaminophen and ibuprofen.

After the presentations of Drs. Veltri, McElwee, and Winick, there were questions about the poison control center data and how relevant it is to the general issue of the safety of PPA, about the number of people who used PPA products despite not being overweight, and about trends both in the number of reports of adverse reactions and in the use of diet pills in general. There were concerns that some of the reports involve accidental exposure in children or the use of PPA in combination with caffeine or other ingredients. There were questions about the use of "dosing episodes" as a standard of measure and whether this would arbitrarily inflate the rate of adverse events.

At this point in the meeting NDMA interrupted its presentation to allow Vivien Meehan and Anthony Smith to speak about PPA misuse and its role as a contributing factor in eating disorders.

Vivien Meehan, President of the National Association of

Anorexia Nervosa and Associated Disorders spoke about the widespread availability of PPA diet pills, laxatives, and diuretics as a contributing factor in anorexia nervosa among female adolescents, and the need for stronger label warnings. She stated that there was strong evidence that PPA products are a significant contributor to the deterioration of patients with anorexia nervosa and bulimia nervosa. She further stated that many adverse reactions are not reported by adolescents because they do not want their parents to know that they are taking the drugs. She stated that there should be massive and continuous educational programs aimed at restricting the use of diet products by teenagers. Ms. Meehan concluded her presentation by saying that current labeling of OTC diet products is not adequate and that warnings about proper dose and the need to consult a physician before use should be enlarged and stated much more strongly.

After Ms. Meehan's presentation there was a discussion on whether laxatives and diuretics are also widely misused. She said that diuretics and laxatives together were responsible for electrolyte imbalance in many people. She was asked if a substitute would be found for PPA if it was removed from the market. Ms. Meehan stated that her primary concern was to protect teenagers from the damaging effects of starting to diet at too early an age and suggested that the only way to protect them is to try to make it more difficult for them to get the drugs that can contribute to this behavior and possibly lead to the development of eating disorders. It was also suggested that data be gathered from countries where there is more intervention by health professionals and some of these substances are not so readily available.

Mr. Anthony Smith of State Center, Iowa stated that his teenage daughter had recently died from complications of anorexia nervosa. He told the panel that, because of their easy availability, he was unable to prevent his daughter from using diet pills, laxatives, and diuretics well in excess of the recommended doses. He urged FDA to remove PPA diet pills from the OTC market.

NDMA continued its presentation with Dr. Thomas Garvey of Garvey Associates, Inc. who reviewed published reports of severe adverse reactions to PPA drug products, particularly those that (1) occurred in women between the ages of 15 and 44 years of age that involved hemorrhagic stroke, and (2) involved a dose of PPA that was two-fold or less the recommended dose and for which there were no obvious confounding elements, predisposing illness, or concomitant medication. He discussed the 1990 paper by Lake, published in the American Journal of Medicine, in which cerebrovascular accidents (CVAs) were reported in connection with

PPA use. Dr. Garvey also included an additional case from a recent report by Dr. Forman, a physician. He stated that the majority of the cases could not be potentially related causally to PPA because they involved either massive overdoses or confounding factors such as concomitant medications or pre-existing problems. He stated that, of the 42 cases studied for the years 1973-1990, a total of 4 involved hemorrhagic stroke in women 15 to 44 years of age who appear to have taken up to two times the recommended dose of a non-combination PPA diet formulation. They were taking no confounding concomitant medication and had no pre-existing medical problem which might predispose to hemorrhagic stroke.

After Dr. Garvey's presentation there was a discussion on what factors he considered to be confounding. Members of the Panel pointed out that, in the real world, patients may have concomitant medication which may or may not predispose them to having an adverse reaction, and that some important information can be lost if too many cases are discarded.

Dr. John Morgan of CUNY Medical School stated that a group of case reports associating a drug with severe adverse reactions may yield misinformation because the adverse event may be related to other drugs or other conditions, and that sometimes events are caused by doses which greatly exceed the usual or recommended dose. He noted that the slight elevation in blood pressure associated with PPA use is far less than would occur following common daily activities and is unlikely to be the cause of hemorrhagic strokes. He further stated that an adverse event may occur at its usual background rate and be associated with a commonly used drug completely by coincidence. Dr. Morgan discussed vasculitis (inflammation of the blood vessel), stating that there is no proof that vasculitis is associated with hemorrhagic stroke. Dr. Morgan reviewed case reports of CVAs associated with the use of PPA from FDA's spontaneous reporting system, the medical literature, and reports from manufacturers and sellers of PPA diet products. Over a period of 11 years, 92 cases of hemorrhagic stroke were reported, of which 48 were putatively associated with PPA diet products. Twenty-one of these cases had no obvious confounding factors and 13 involved first dose cases. In females 15 to 44 years of age, he found 8 first dose cases associated with PPA.

Dr. R. William Soller of NDMA ended with a review of the National Hospital Discharge Survey (1979-1989), and foreign data bases regarding the background rate for CVAs. Dr. Soller stated that over the past 11 years, there have been 10 reports of hemorrhagic stroke associated with first dose use of PPA diet aids at less than or equal to twice the recommended dose. Using the hospital discharge survey data, he estimated that over the same period of

time, the number of cases occurring by chance alone in the female diet aid consumer population would be 15 (assuming one first day, first dose effect) or 30 (assuming two first day, first dose effects). Therefore, he concluded that the number of CVAs seen for PPA over an 11-year period appear to be the number that would be seen by chance alone. He reiterated NDMA's main points and made a summary statement of PPA's benefit-to-risk ratio. He concluded that PPA is safe and effective when used in a comprehensive weight loss program that includes diet, exercise, and behavioral modification, that there are no scientifically sound studies that demonstrate wide misuse of PPA, and that the safety data for PPA compares favorably with other common OTC medications.

Dr. Soller was asked how he would make a correction for the fact that not all cases are reported. Dr. Soller said that under-reporting occurs with respect to medical literature, company reports, and FDA's spontaneous reporting system, and that he did not know what conversion factor to use. Members of the Panel agreed that it would be very difficult to determine the number of unreported cases in an OTC setting.

Dr. Gilbertson made a final call for additional testimony. Since there was none, the meeting was adjourned at approximately 7:00 p.m.

Robert Sherman