

Tab 104



MEMORANDUM OF INTERVIEW

Of

Steven B. Heymsfield, M.D.

On

Wednesday, October 18, 2001
10:00 AM

Weight Control Unit, St. Luke's Roosevelt Hospital Center
1090 Amsterdam Avenue, 14th Floor
New York, New York 10025

Attendees

Susan F. Laska, Investigator/DEIO/FDA (interviewer)

Lori A. Love, M.D., Ph.D., Senior Advisor for Clinical Science/ORA (interviewer)

Investigator Laska advised Dr. Heymsfield that we wanted to ask several questions in conjunction with his involvement and knowledge of the Ephedra studies conducted at the Weight Control Unit. Dr. Heymsfield agreed to voluntarily provide the information. There was no FDA-482 notice of inspection issued, credentials were shown to Dr. Heymsfield. Dr. Heymsfield provided a number of documents that are included in the appendices¹. Information about the New York Obesity Research Center of St. Luke's-Roosevelt Hospital Center and its programs, gathered from the web [<http://cpmcnet.Columbia.edu/dept/NYORC>], is included in Appendix B as B1.

The following is an account of the information provided by Dr. Heymsfield.

General Information:

Dr. Heymsfield is a physician who is medically boarded in Internal Medicine and has additional training in Cardiology. He is the Director of the Weight Control Unit affiliated with St. Luke's Hospital, New York, in addition to being the Deputy Director of the New York Obesity Research Center and Professor of Medicine at Columbia university's College of Physicians and Surgeons [please see B2 for a copy of Dr. Heymsfield's biographical sketch and curriculum vitae and attachment 2 for information about the New York Obesity Research Center]. He has conducted approximately 20 randomized clinical studies, including four dealing with products or ingredients that are considered dietary supplements [B3, page 2, marked with *]. Three of these trials used Ephedra as an ingredient in the tested product. From 1996-98, he was the principle investigator (PI) on a clinical trial testing Herbal Phen-Fen, an ephedra and St. John's wort combination marketed for weight loss. It was Dr. Heymsfield's opinion that the cardiovascular adverse events noted in this study indicated the need of an appropriate safety study for Ephedra. He has not

¹ Appendix A contains copies of all information received directly from Dr. Heymsfield, and are numbered sequentially as presented in the text of this memorandum. Attachment A lists all these documents in table format. Appendix B is similarly numbered, but contains information related to topics discussed in the memo that FDA obtained from other sources, including the internet.

published this study because the results, including adverse effects, were similar to those observed in the two ST&T clinical trials [described below].

Background to ST&T studies

Dr. Heymsfield explained his involvement with the ST&T Ephedra studies in which Carol Boozer, D.Sc served as the PI at St. Luke's. Dr. Boozer is currently the Director of the Energy Metabolism Core in the New York Obesity Research Center and an Assistant Professor of Nutrition at the Columbia University Institute of Human Nutrition [B4]. In about 1997, Dr. Boozer, approached Dr. Heymsfield regarding his opinion about participating in a study being monitored by Science, Toxicology & Technology (SS & T) San Francisco, California. The study was originally designed for Dr. Ming Singh from Vanderbilt, but he had left Vanderbilt and ST&T was looking for another investigator to conduct this study. Dr. Heymsfield stated that he had worked with Carol Boozer, D.Sc. on the Herbal Phen-Fen study. Dr. Heymsfield responded to Dr. Boozer positively that it would be reasonable and useful to conduct the proposed ST&T study.

Dr. Heymsfield indicated that Dr. Boozer had not previously served as a principle investigator in this type of clinical trial (pharmaceutical intervention) and he was unaware of any specific training she had in clinical research. He stated that she had served as co-investigator on a number of clinical trials in which he was the PI and that she was interested in this conducting this study protocol because she needed additional support for her lab.

8-week clinical study

Dr. Boozer was the Principal Investigator and Steven Heymsfield, M.D. was the co-investigator for an 8-week study investigating the efficacy of Ephedra for weight loss in 40 research subjects. The contract research organization (CRO) was Science, Toxicology and Technology (ST&T), with Michael Scott from ST&T serving as the study monitor. The sponsor was Metabolife and the active test agent was Metabolife 356, which is a currently marketed dietary supplement. This was the first Metabolife ST&T study in which Dr. Heymsfield participated. The study was entitled "The Treatment of Moderate Obesity with an Herbal Preparation Containing Ephedrine and Caffeine: A Double Blind Study." The study number was 97-104. The IRB was requested to review this study July 30, 1997² [A1]. According to the IRB protocol submission letter, the proposed study was "totally non-invasive study with the exception of blood samples...". Dr. Heymsfield emphasized that the sooner the approval was obtained and the study initiated, the greater the funding provided that would be provided the laboratory. This study was reviewed and approved by means of the expedited review process [A2]; the protocol approval was renewed by the IRB in 1998 [A3]. The study results have now been published in both abstract and manuscript forms [B5 and B6, see also further comments below].

In discussing the 8-week efficacy study, Dr. Heymsfield stated that the participants in this study were not medically screened as well as participants in other trials that he has conducted. Dr. Heymsfield explained that he saw and reviewed all case report forms for research subjects from the first 8-week study. He stated that he believed that there were "a lot of adverse events for something sold as dietary supplement." The majority of adverse events occurred in the first 2 weeks of the study and were cardiovascular in nature, including palpitation and elevated blood pressure. His conclusions were that the study results did not support safety of the product, but rather indicated that further study was needed to appropriately evaluate the safety of the product. The primary interface during this initial phase of the study was Michael Scott, ST&T.

² Complete dates (MM-DD-YY) in this memo have been provided from and/or verified with the materials provided by Dr. Heymsfield.

On study completion, Dr. Heymsfield wrote an abstract for presentation of study results at the Federation of American Societies for Experimental Biology (FASEB) meeting in the spring of 1999 [B5]. This abstract was extensively reviewed [and "approved"] by ST&T and a team of Metabolife attorneys prior to submission. Suggested revisions made by this team included changing the wording "dose" to serving. Dr. Heymsfield stated that never before had a CRO come in with a team of senior level attorney's to review and approve an abstract for a clinical trial in which he had participated; his previous interactions with CROs/sponsors had always been with the medical staff. Dr. Heymsfield stated that he believed ST&T's/Metabolife's concerns related to the public presentation of the abstract. No requests were made to change data or comments regarding adverse events. No statistician was involved with data analyses of this first study. A manuscript was prepared and submitted to JAMA in the summer of 1999, but this manuscript was rejected. The manuscript was later revised and published³ in 2001 copy in B6].

6-month clinical study

About the time that the 8-week clinical trial protocol was submitted to the St. Luke's-Roosevelt IRB for initial approval, Dr. Boozer was approached by Michael Scott from ST&T to take part in a 6-month multi-center clinical investigation of the safety and efficacy of ephedra for the treatment of obesity. ST&T designed this study in consultation with Patricia Daly, M.D, an endocrinologist at Beth Israel Deaconess Hospital in Boston⁴. ST&T had consulted with Dr. Daly about clinical trial design issues, because she had conducted and published a number of small clinical trials evaluating the efficacy of combination of pharmaceutical ephedrine and caffeine for weight loss (some of these trials also included aspirin as a component of the active drug combination). Dr. Daly was the PI of the Beth Israel Deaconess study site (often referred to as the Harvard study site). According to Dr. Heymsfield, Vanderbilt had been considered as the other study site, but this changed because of issues raised by the Vanderbilt IRB about the study (the Vanderbilt IRB apparently required that the study be conducted under an IND, which the study sponsors and CRO were unwilling to consider).

Carol N. Boozer, D. Sc. was the Principal Investigator and Steven B. Heymsfield, M.D. was the Co-Investigator at the St. Luke's Roosevelt Hospital study site (note this is often incorrectly referred to as the Columbia site or study).. The study was entitled "Safety and Efficacy of an Herbal Preparation Containing Ephedrine and Caffeine in Overweight and Obese Individuals A Double Blind Study". The study protocol was submitted to the St. Luke's Roosevelt IRB for approval on 08/01/97 [A4], and was approved by means of an expedited review process on 08/12/97 [A5]

When questioned about the expedited review, Dr. Heymsfield stated that he was not aware at the time of approval that an expedited review process had been used for approval of the second clinical study.. He did indicate that the study sponsor was very anxious to start the 6-month study at St. Luke's-Roosevelt as soon as possible, because the study had already been initiated at the other study site, and that this message had been conveyed to the IRB [A4, page 1]. He explained there was a contractual agreement for funding in which Dr. Boozer would receive increased funding if the study was initiated quickly; consequently there was a major effort to capture this contract.

³ Boozer, CN, Nasser, JA, Heymsfield, SB, Wang, J, Chen, G and Solomon, JL. A study with a preparation containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial. *Int. J. Obesity*, 23:316-324, 2001.

⁴ Daly testimony at OWH Public Meeting in 8 2000, also Fax from telecon in 1995.

Dr. Heymsfield opined that this study was not a minimal risk study that would qualify for expedited review. He also revealed that a member of the IRB had informed him that the protocol approval for the previous study had not been unanimous as was the usual case, which he interpreted as meaning there being some concern about the safety [A6, see 12].

In addition to the documents cited above, Dr. Heymsfield provided a number of other documents related to the second clinical study [A 7 – A13], including drafts of protocol renewals.

Other issues related to Dr. Heymsfield's involvement with ephedra clinical trials and Metabolife [see documents A14 – A 32]

During the time frame in which the 6-month clinical trial was conducted at St. Luke's, issues related to the safety of ephedrine alkaloid containing dietary supplements were very prominent in the media. Dr. George Blackburn, a physician from Harvard University who was prominent in the area of the treatment of obesity was interviewed by the Boston Globe. When asked his professional opinion about the safety of EADS he made a statement "to the effect that Metabolife can kill you⁵." Metabolife sued Dr. Blackburn [and the media] under an anti-SLAP law for defamation slander, trade libel and intentional and negligent interference with prospective economic advantage [B7]. Because he was a professional colleague, Dr. Blackburn asked Dr. Heymsfield if he would provide a factual declaration about the potential adverse effect of ephedra/ephedrine. After he agreed to do this for Dr. Blackburn, Dr. Heymsfield was contacted by Metabolife to provide a Declaration on their behalf in this lawsuit. Initially Dr. Heymsfield stated that he would provide a factual declaration. He later found out that he could not provide declarations to opposing sides. Because he kept his prior commitment to Dr. Blackburn [A14 – A 20], Metabolife informed Dr. Heymsfield that "they were at war" and subsequently they "terrorized me". The consequences were such that this "almost ended my career" [A26 - A29, see also B8 for additional information]. The lawsuit against the producer and Dr. Blackburn's was dismissed [B7], and recently on appeal, in (9/2001) the court's dismissal of the case against Dr. Blackburn was upheld. Besides, the deposition in the Blackburn case, Dr. Heymsfield has provided a number of depositions in other ephedra product liability cases, including one involving Metabolife [A6].

During this same time frame (1999), Dr. Heymsfield had heard a number of Metabolife commercials on a local radio station touting the safety and efficacy of Metabolife 356. He stated the similar information was printed in a product brochure [A 21] as well on the Metabolife website. The product brochure⁶ and the company website stated that safety studies for Metabolife 356 were on file. He called the listed 800 telephone number to obtain information about these "safety studies." In response to his call, he received a document that was signed by Michael Scott [A22 and A23] Dr. Heymsfield stated that he "felt very strongly that Metabolife was over emphasizing safety, given what I'd seen."

Dr. Heymsfield stated that he was contacted by the news show 20/20 requesting an interview regarding use of herbal weight loss products. The interview was approved by St. Luke's hospital Public Affairs, and was taped sometime in October 1999. Before the on-camera interview, he informed the producer and the interviewer that he was not able to discuss the Blackburn case. Heymsfield stated they had an agreement but soon after the interview commenced on camera, the interviewer "went straight for blood". Dr. Heymsfield in his opinion provided factual and fair accounts about efficacy and the need for monitoring when using herbal weight loss products including Ephedra. He was concerned however, because he perceived the interviewer as hostile

⁵ Dr. Blackburn's statement that is heard in the lawsuit "You can die from taking this product"
⁶ Direct quotes from the product brochure (see [A 21] Metabolife 356) is shown to be from "All safety studies are kept on file."
laboratories." "All safety studies are kept on file."

and he mentioned these concerns to Michael Scott, ST&T in a telephone discussion. Because of concerns [of negative publicity], Michael Scott commissioned a letter, which emphasized and restated Metabolife's position [A24], to the 20/20 producer that he wanted Dr. Heymsfield to sign. Dr. Heymsfield refused to sign and send this letter because he did not agree professionally with the drafted statements. Dr. Boozer was also approached to write a letter to 20/20 and shared her draft with Heymsfield [A25].

Prior to the airing of the 20/20 interview on or about November of 1999, Metabolife took out a whole page advertisement in the New York Times stating that herbal weight loss was safe and attempting to discredit Dr. Heymsfield. They made available the unedited tape of the 20/20 interview on their website. They contacted the hospital and Columbia University threatening to sue Dr. Heymsfield for breach of confidentiality agreement [A29]. They also threatened to withhold payment for Dr. Boozer's lab. Dr. Heymsfield explained that Columbia is located very close to St. Luke's. Dr. Heymsfield is on the academic staff at Columbia although, Columbia and St. Luke's are not affiliated with each other. According to Dr. Heymsfield, Columbia made it clear to Metabolife that Columbia was not involved and Metabolife dropped any interest in Columbia, concentrating their efforts instead on St. Luke's-Roosevelt senior staff.

Starting late in 1999 Metabolife reactions escalated, and they attempted to remove Dr. Heymsfield from the study. After the Metabolife's actions were brought to the attention of the hospital's legal counsel, David Engel, a St. Luke's attorney, in a discussion "suggested" that Dr. Heymsfield take himself off the 6-month safety study [see: A 26, A28, A 31. A similar request was made in a discussion with Dr. Boozer. Dr. Heymsfield responded to both parties that he believed it would be unethical and immoral to remove the medical doctor from the safety study.

In actuality, Dr. Heymsfield was removed from the study: he did not see any patients, he did not review any charts, the study results were not shared or discussed with him and he was not a co-author on any abstract or presentation of study results. He was not aware of any notification to the IRB to the effect that he was no longer involved with the study, although he was named as a co-investigator in the protocol approved by the IRB. Later in the interview he recalled that there were 2 interns working under him who may have performed physical examinations on the research subjects, but he was not certain and could not confirm that this was the case. The two interns were Dr. Abderrahane Saddouck and Abdelhakin Dinar. According to Heymsfield these two interns did not have any investigator training regarding the nature of this particular study. He did state that Dr. Saddouck had participated in other "routine" drug studies in which Dr. Heymsfield was the PI. Dr. Heymsfield stated that he was aware that a cardiologist in Los Angeles was reviewing the data generated from the 24-hour Holter Monitoring and the 24-hour blood pressure monitoring that was required by the protocol for the 6-month safety study. Dr. Heymsfield stated that he did not see any patients or charts from the 6-month study.

Dr. Heymsfield related another adverse interaction with Metabolife that grew out of a professional invitation at the North American Association for the Study of Obesity [NAASCO] meeting in November of 1999 where he was to review herbal weight loss products. Since this presentation occurred after the published abstract and the presentation at FASEB, Dr. Heymsfield thought that he could include the results of the 8 week study in his talk. He intended to use only general information that did not go beyond what was mentioned in the published abstract. ST&T and Metabolife objected to his saying anything about the 8 week study or the 6-month study on the grounds that this violated the confidentiality agreement that he had signed. Although Dr. Heymsfield pointed out that that the 8-week abstract had been "approved" by ST&T and Metabolife prior to submission, and was never intended to be released from that any further, ST&T and Metabolife still considered this a violation of his confidentiality agreement [A32]. It was during this time, that Metabolife's actions

peaked and he felt personally terrorized [received many phone calls that were hang-up and was tailed prior to the meeting, at which time he called the police].

According to the study protocol, equal numbers of research subject were to be enrolled from each study site. However, after Dr. Daly left Beth Israel Deaconess Hospital sometime in 1999, the remaining patients were recruited at the Boozer study site. Dr. Heymsfield stated that he believed that the majority of patients were recruited from St. Luke's for the 6-month study, and that he was unaware if the IRB had been notified of and approved this protocol change.

Dr. Heymsfield was asked why the dosing regimen changed from 'bid' dosing to 'tid' dosing in the 6-month study. He indicated that he was aware that a change in the dosage regimen had occurred at some time during the study and he conjectured that this was because of adverse events that were occurring. He noted that about this time, Metabolife also raised the issue of gradually "building up" to the recommended dose of the product and that at some time this recommendation was adopted for the labeling of their marketed product. Based on his knowledge of clinical findings from the first study, he stated that one out of 5 patients could not tolerate that initial dosing. Heymsfield speculated that he doubted that this change in dosage would have been submitted to the IRB. Dr. Heymsfield stated that there was an investigators' meeting for the first study, but he did not attend an investigators' meetings for the 6-month study. Dr. Heymsfield stated that he was aware that Dr. Boozer and ST&T had been meeting, and that at least one of these had occurred when Dr. Heymsfield was out of town.

When asked his professional opinions on the 6-month study related to an appropriate study design to demonstrate safety, Dr. Heymsfield stated that he believes an adequate safety study would be at least 2-years in duration and have at least 2000 subjects. He explained that the cardiovascular adverse events associated with Ephedra-caffeine combination products were worse than those associated with the use of phentermine and explained further that Ephedra-caffeine combinations could not be considered benign treatment by any means. He raised a number of other issues associated with the 6 month study design and conduct. These included his doubts that study personnel were adequately trained to elicit appropriate responses to the questionnaires [symptoms, etc.], the issue of potential biases induced by the questionnaire that was used, the issue of whether there was appropriate blinding ("people were almost unblinded by the side effects") and the lack of appropriate training for the staff monitoring blood pressures during the trial. Although he was the clinical investigator on this study, he was not informed of any adverse events that occurred during the second study, and raw or summary data were not shared with or evaluated by him.

A copy of the information that Dr. Boozer had submitted to the FDA was shared with Dr. Heymsfield, and he was asked his professional opinion about the study results and conclusions [B9]. He stated that this was the first time that he had seen any results from this clinical trial.

Dr. Heymsfield stated that it was very unusual to have 102 out of 269 eligible subjects fail screening in a 6-month study. 167 subjects were randomized and 87 subjects completed the trial. Regarding the number of dropouts observed in this 6-month study (80 subjects or 47% of those enrolled), Dr. Heymsfield stated a 60 - 70 % completion rate was normal or typical for this kind of drug study, including those conducted over a much longer duration than 6 months. As an example he stated that the clinical trial with Merida, which was 2 years in duration, had an approximate 60 - 70% completion rate. He stated that analyses of all data by study site would be useful.

In reviewing the published posters for the 6-month safety study, Heymsfield stated that both the heart rate and mean blood pressure increased in the active treatment group. Because of the manner in which the data were collected, the greater the heart rate, the greater the blood pressure.

treatment on individuals, particularly those sensitive to the effects of ephedrine, would not be readily identified or characterized. During normal weight loss, a decrease in blood pressure is expected, however, this did not occur in the active treatment group. He noted that this pattern (no decrease in BP with weight loss) was the "same story as Merida."

Dr. Heymsfield stated that he would want to see the individual blood pressure data, particularly that on any outliers, and not just the group mean values. As a clinician and researcher, he would also want to evaluate data on blood pressure over time for each research subject. He stated that rather than presentation of mean blood pressure over time, a more useful evaluation would be to present the data in the content of changes in diastolic/systolic blood pressure over time that exceeded a specified threshold. In his opinion, these data do not appear to be analyzed and presented objectively.

Dr. Heymsfield stated that the majority of adverse events occurred in the first two weeks of the study and were cardiovascular in nature, including palpitations and elevated blood pressure. He stated that the pattern and types of adverse cardiovascular events were similar to those occurring with higher dosages of phentermine, and were "predictable for this type of agent". He was concerned about the ventricular events observed in the study [tables in B]. He questioned why a subject in the active treatment group was kept in the study when the evaluation indicated changes at baseline [table] He stated that ventricular events indicate that this product is not safe for the general population. When asked about whether he considered this a drug, Dr. Heymsfield stated that he does consider this a drug and certainly not safe for the general population.

Dr. Heymsfield repeatedly stated that he was not aware of any medical monitoring for the 6 month clinical trial. He was not aware of anyone who would have interpreted the adverse events. Dr. Heymsfield stated he tried to get access to the Holter monitoring tapes from the initial screening because of his interests on the cardiac physiology of the obese and the effects of dieting on cardiac function. He stated that little is known or published in this area, but that such information is potentially very important; consequently he was interested in reviewing and publishing this information in the peer-reviewed scientific literature. The study coordinator, JA Nasser, refused his request for this information. Dr. Heymsfield stated that he did not push the request any further or raise the request to a level of greater authority such as the Principal Investigator Carol Boozer. Dr. Heymsfield did state that he did request from Carol Boozer the safety data information for the 6-month study. He characterized this request as a routine request and that he was given no reason for a refusal. He speculated that the Dr. Boozer was informed by Metabolife not to share data with Dr. Heymsfield. The study records are securely stored in the same building where Heymsfield's Weight Control Clinic is located. He is aware of only 2 keys, which are kept by Drs. Boozer and JA Nasser. Dr. Heymsfield does not have any copies or access to case report forms. Other personnel involved with the first study were Grace Marin, who is a certified phlebotomist. The routine laboratory analyses were performed by (which later became Quest Laboratory).

Regarding the specific roles that the authors listed in the abstract for authors on the published abstract he "did not have a clue" as to what the roles all of the authors played. He knows that JA Nasser and JL Solomon were Dietitians working at the New York Obesity Clinic. P. Homel was a Statistician. He was able to identify Ruth Strauss as the cardiologist in California who evaluated the Holter monitoring data.

Dr. Heymsfield stated that subjects for the first study were recruited by newspaper advertisements and posters around the Columbia community and speculated that similar mechanisms would have been used to recruit subjects for the second study.

Dr. Heymsfield stated that Dr. Boozer would have developed the informed consent for both studies. For both studies, either Dr. Boozer or the study nurse would administer the informed consent. Dr. Heymsfield stated that he did not administer or witness any informed consents for either study.

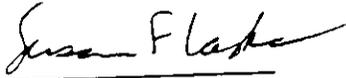
Dr. Heymsfield states that he did not have copies of and was unaware of any investigator's brochures for either study. He denied having any labeling or proposed labeling.

Because of concerns about the reliability of the stated dosage of ephedrine alkaloids, Dr. Nassar had analyzed 5 – 10 samples of the product used for the first study. In addition, these samples were sent out for independent testing laboratory [GC analysis and GC/MS quantitation of ephedrine and related alkaloids]. Dr. Heymsfield did not know the name of the independent testing lab, but stated that Dr. Nasser would have these results.

Dr. Heymsfield did not have copies of all materials submitted to the IRB over the entire duration of this clinical trial. He was not aware as to whether certain protocol changes, such as the change in dosing regimen from bid to tid (which he considered a significant change) or the change in the number of individuals recruited, were specifically identified for and approved by the IRB. Dr. Heymsfield stated all the raw data for the first study was in hard copy form, although the data were eventually entered into an Excel file. He was unaware of how data were collected, stored and analyzed for the 6 month study?.

He stated that in comparison with prescription drugs that he has studied such as Merida and Xenical, the stimulant effects were stronger with Ephedra-caffeine combinations such as Metabolife 356. Dr. Heymsfield stated he believes that "Ephedra is a drug but not a safe drug" because of its cardiovascular side effects.. He stated that safety has not yet been adequately established or evaluated for these products (even if one could pool all the world data for analyses). He re-iterated a number of times that he was never requested by Metabolife to alter or adjust data, but he was 'encouraged' (pushed) to adjust his interpretation of the data. Dr. Heymsfield stated that he believes Dr. Boozer does have a lot of scientific integrity. He believed Dr. Boozer laboratory was to receive approximately \$100,000 to 200,000 for the first study. Dr. Heymsfield stated that these clinical trials were "not done with the same rigor" as a pharmaceutical trial, and that the study budgets reflect this.

The interview with Dr. Heymsfield concluded at 2:30 p.m.



Susan F. Laska, M.S.
Investigator/DEIO



Lori A. Love M.D., Ph.D.
Senior Advisor for Clinical Science/ACRA/ORR

Investigator recommendations:

1. Consider IRB inspection of St. Luke's-Roosevelt's Hospital to evaluate among other items:
 - Procedures for expedited review
 - Copies of the expedited reviews, minutes of IRB discussions of protocols
 - How was this study article classified? Drug or supplement
 - Correspondence with PI (changes to protocol, at least annual review, final report, adverse events etc.)
2. Consider IRB inspection of the second study site, Beth Israel Deaconess Medical Center to obtain similar information as listed above.

Enclosures:

Attachment A
Appendix A
Appendix B

Cc: HFC-1 Baker
HFC-2 Love
HFC-200 Taylor

Draft: 10/19/01 sfl
Revised: 10/22/01 and 11/01/01 lal
11/16/01 sfl
Reviewed: J Taylor HFC-200 11/16/01
Dbaker, HFC-1 01/09/02
S Laska 1/30/02
Revised 01/23/02 lal

Attachment A: Documents Obtained from Dr. Steven Heymsfield

| Description | Comments |
|--|--|
| <p># Study 1: 8 week trial</p> <p>A1 Protocol submission to IRB:</p> <ul style="list-style-type: none"> Letter to Chair, IRB, (1 page) from C. Boozer, dated 7/30/97 submission of new protocol "The treatment of moderate obesity with an herbal preparation containing ephedrine and caffeine: A double-blind study" Protocol (5 pages): Page title "Institutional Review Board" with project title: "The treatment of moderate obesity with an herbal preparation containing ephedrine and caffeine: A double blind study" Project duration 10/01/97 - 3/30/98 - Consent form (3 pages): St. Luke's-Roosevelt Hospital New York City New Drug or Procedure Consent Form; "Treatment of moderate obesity with an herbal preparation containing ephedrine and caffeine: A double-blind study." Interoffice correspondence from IRB to Carol Boozer, 08/12/97 - approving of protocol and consent form for 97-104 "The treatment of moderate obesity with an herbal preparation containing ephedrine and caffeine: A double blind study." Protocol (5 pages): Page title "Institutional Review Board" with project title: "The treatment of moderate obesity with an herbal preparation containing ephedrine and caffeine: A double blind study" Project duration 10/01/97 - 3/30/98 - Consent form (3 pages): St. Luke's-Roosevelt Hospital New York City New Drug or Procedure Consent Form; "Treatment of moderate obesity with an herbal preparation containing ephedrine and caffeine: A double-blind study" "ST&T 97104 Physical Examination Form: Screening" "ST&T 97104 Physical Examination Form: Screening" Form (1 page) labeled "Appendix " and "Advertising Copy" Renewal approval for Protocol: "The treatment of moderate obesity with an herbal preparation containing ephedrine and caffeine: A double-blind study" from A. Cameron, IRB to C. Boozer dated 08/21/98, 1 page. <p>A2</p> <p>A3</p> | <p>Protocol not signed by PI or Director of service, includes consent form no protocol number, but 40 research subjects and 8 week study of...</p> <p>The study was approved by means of the expedited review process. Protocol signed by PI [7/1/97] and Director of Service [8/1/97]. Checked as no investigational drugs or devices</p> |

Attachment A: Documents Obtained from Dr. Steven Heymsfield

| | | |
|----|--|---|
| A4 | <p>Study 2: 6 month trial</p> <p>Protocol Submission: "Safety and Efficacy of an herbal preparation containing ephedrine and caffeine for the treatment of obesity"</p> <ul style="list-style-type: none"> Boozer submission letter to IRB, dated 8/1/97 [1 page] Draft protocol 97-002, includes consent [8 pages] Faxed protocol from P. Daly "Safety and Efficacy of an herbal preparation containing ephedrine and caffeine for treatment of obesity" fax date 8/1/97 [pages: "8 -17 out of 28 "per Fax] | |
| A5 | <p>"Symptoms Questionnaire" (sic) [2 page]</p> <p>Letter from Chair, IRB to Boozer dated 8/12/97 stating that 97-105 "Safety and Efficacy of an herbal preparation containing ephedrine and caffeine for treatment of obesity" had been approved by "means of the expedited review process"</p> <ul style="list-style-type: none"> IRB, SLR Hospital Center application face sheet signed by Boozer on 8/1/97 and by the Division Chief and Service Director on 8/4/97 Copy of Protocol & consent, now labeled as 97-105 [7 pages] ST&T 97-104 "Screen Visit" form [1 page] Consent Form [3 pages] "Symptoms Questionnaire" (sic) 2 pages ST&T 97104 Physical Examination Form: Screening Medical Screening Form 97-104" [1 page] | |
| A6 | <p>Faxed copy [10/26/99] of SH deposition in Yolanda Perez v Metabolife, Case number 733138, Superior Court of the State of California for the county of San Diego – document contains handwritten edits, 4 pages.</p> | <ul style="list-style-type: none"> States that SLR's IRB sent SH a note stating that one IRB member had written against the proposal, usually unanimous – SH's discussion with IRB member to believe there was some safety concern "The IRB would not let us pass. I with study that placed patients at risk. We received no reports from the study. Metabolife International, Inc. of the existence of any adverse effects. After the study with the ingestion of Metabolife 356 prior to starting our project, we were told that millions or even billions of servings were consumed daily contrary we were told that millions or even billions of servings were consumed daily consumers without ill effect. We would not have been able to conduct a Metabolife study if adverse side effects that showed potential for the product." SH first became aware of adverse events with Metabolife on the afternoon of the 20/20 program in 10/99 |
| A7 | <p>Protocol: Safety and efficacy of an herbal preparation containing ephedrine and caffeine in overweight and obese individuals. A double blind study" P1 CN Boozer, co-investigator SB Heymsfield, 11 pages.</p> <p>Footer: " 07/28/98 Patricia A Daly, M.D."</p> | <p>Protocol title has changed from 1997 [now "w in overweight and obese individuals instead of for "treatment of obesity"</p> |
| A8 | <p>Protocol: Safety and Efficacy of an herbal preparation containing ephedrine and caffeine in overweight and obese individuals. A double blind study" P1 CN Boozer, co-investigator SB Heymsfield</p> <p>Footer: " 08/06/98 Patricia A Daly, M.D."</p> <p>Numbered as containing 11 pages, but page 10 is missing. Document contains highlighting, handwritten edits and bolded text [? Revisions]</p> | <p>Note: Original had only front, not back of copy. SBH faxed the complete document to me. Protocol title has changed from 1997 [now "weight management" instead of "treatment of obesity"</p> |
| A9 | <p>Protocol: "Safety and efficacy of an herbal compound which contains ephedrine, ginseng and caffeine for weight management." P1 Patricia A Daly - "current 9/98 in</p> | |

Attachment A: Documents Obtained from Dr. Steven Heymsfield

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| <p>A10</p> <p>Study 2: 6 month trial</p> <p>Boston" handwritten in right upper corner, but footer states "March 28, 1998", 13 pages IRB Continuing Review form, marked as IRB# 97-105 and Appendix C, 1 page with handwritten responses; signed by CN Boozer on 8/10/98</p> | <p>"treatment of obesity" States: 67 subjects enrolled, 17 withdrawn " One change to protocol described in the in memo. No changes to consent form (ignore bolding) Note: Do not have copies of memo or attachment described on the Page numbering starts with 2 Changes in protocol are in bold type: <ul style="list-style-type: none"> changes in protocol name different from 1997 and draft documents </p> |
| <p>A11</p> <p>Approved Revised Protocol consent: "The treatment of moderate obesity with an herbal preparation containing ephedrine and caffeine: A double blind study" stamped "IRB Approved Jul 15 1998 Consent Form " with "97-105 " in handwriting. 15 pages, page numbering starts with 2 <ul style="list-style-type: none"> Sheet 1 "Ephedrine & Caffeine Study, B/P Measurement (sitting vs. standing [1 page] ST&T 97-104 "Screen Visit" form [1 page Consent Form [3 pages] "Symptoms Questionaire" (sic) 2 pages ST&T 97104 Physical Examination Form: Screening "Medical Screening Form 97-104" [1 page] <p>Form for research subject to records study medication, exercise and diet, 5 pages, undated.</p> </p> | |
| <p>A13</p> <p>Protocol: Safety and Efficacy of an herbal preparation containing ephedrine and caffeine in overweight and obese individuals. A double blind study" P1 CN Boozer, co-investigator SB Heymsfield, 11 pages. Footer: " 07/28/99 Patricia A Daly, M.D. "</p> | |

Attachment A: Documents Obtained from Dr. Steven Heymsfield

| | Metabolite related issues |
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| <p>A14 Fax sheet with Burns & Levinson LLP letter head to SH from Bob O'Reagan, dated 8/27/99 hand written notation about Metabolite's filing and typed pages from the Faber deposition re: Metabolite v. Blackburn [contains p 1, 2, 8, 9, and 10], 6 pages total.</p> <p>A15 Fax sheet with Burns & Levinson LLP letter head to SH from Bob O'Regan, dated 9/1/99, includes a draft copy of SBH's deposition [6 pages] with handwritten editing and 2 typed pages of insertions.</p> <p>A16 Fax [10 pages, dated 9/03/99 4:46 PM] for Dr. Heymsfield from JM Childs, Esq re: Blackburn v Metabolite. Contains draft declaration [2 pages], a Lexis-Nexis copy of a May 24, 1999 Washington Post story written by Charles Babcock on Michael Ellis & Metabolite [7 pages]</p> <p>A17 Letter dated 9/6/99 from SBH on Columbia letterhead to a "Mr. Childs" re article Mr Child sent re "Fat Burners", 1 page.</p> <p>A18 a: Fax of draft Deposition to SH from Gregory Roper dated 9/7/99 4:51 PM - this copy contains handwritten edits and a handwritten notation on the right top of the transmittal form "7443686 to: Greg Roper" 6 pages + fax sheet, a second identical document [A18b] is labeled on the bottom of the page "Deposition Exhibit 51, Marlene Lee, CSR, RPR, CPR" Printed copy of an email dated 9/7/99 from G Blackburn to SH - SH's declaration was scanned and provided as an electronic copy, 7 pages. Fax from George L. Blackburn, Beth Israel Deaconess Medical Center dated 9/8/99 to SH, page 2 is a copy of an email from GB to SH thanking him and telling where to send the declaration.</p> <p>A21 Copy of Metabolite 356 product information [undated] - English and Spanish versions, undated.</p> <p>A22 Metabolite International, Inc. "Thank you for your interest..." form signed by Health Advisory [1 page], undated.</p> <p>A23 Report signed by Michael Scott, ST&T entitled "ST&T report Summary - Product #356", 2 pages, undated</p> <p>A24 Faxed letter from Michael Scott, ST&T to SBH dated 9/10/99 re: 20/20 clarification regarding Metabolite study [2 pages] Includes a 1 page letter drafted by ST&T & dated 9/9/99 to Ms. Van Horn [20/20 Producer] to be signed and sent by SH</p> <p>A25 Fax sheet dated 9/23/99 from CB to SH and draft of CB's 1 page letter to 20/20 [marked DRAFT 2 in handwriting] [2 pages total]</p> <p>A26 Memorandum from SH to D Engel dated 10/6/99 re: Metabolite, labeled as "confidential", 5 pages</p> | <p>Discusses roles in clinical trials and the Blackburn deposition</p> <p>"Metabolite 356 is shown to be safe by two independent laboratory studies." <ul style="list-style-type: none"> "All safety studies are kept on file..." When SH requested it, the data was sent printed materials from the Health Advisory (1 page), and a copy of the report signed by Michael Scott, ST&T entitled "ST&T report Summary - Product #356". Discusses recommended dosage regimen - start lower & gradually increase.</p> <p>Discusses how ST&T was asked by Foslip of California, the distributor of Product #356 to assess safety, and describes types of studies performed. The data contained in this report.</p> <p>SH refused to sign & send this letter which had multiple bullet points regarding the safety of Metabolite, a safe dose of ephedrine, etc.</p> <p>CB states that ST&T & Metabolite want her to send a letter to 20/20 and make this topic will be a subject of a meeting the next day with Michael Scott.</p> <p>Gives background on history & issues with Metabolite. About 1st trial</p> <ul style="list-style-type: none"> "A relatively large number of subjects on the active treatment dropped out early because of adverse effects..... there were no early dropouts in the control group for adverse effects. This is an unusual finding among drug studies. I have |

