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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRAITON

FOOD ADVISORY COMMITTEE MEETING

ON OLESTRA

VOLUME I

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

FOOD ADVISORY COMMITTEE MEETING

ON OLESTRA

Volume I

Monday, June 15, 1998

8:00 a.m.

Sheraton Reston Hotel
11810 Sunrise Valley Drive
Reston, Virginia

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
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Edward N. Brandt, M.D., Ph.D., Chairman
Lynn Larsen, Ph.D., Executive Secretary

MEMBERS

Rhona Applebaum, Ph.D.
E. Wayne Askew, Ph.D.
Stephen H. Benedict, Ph.D.
Henry W. Blackburn, M.D.
Bruce M. Chassy, Ph.D.
Katherine L. Clancy, Ph.D.
Fergus M. Clydesdale, Ph.D.
Owen R. Fennema, Ph.D.
Naomi K. Fukagawa, M.D.
Susan K. Harlander, Ph.D.
Morris E. Potter, D.V.M.
Donna R. Richardson, J.D., R.N.
Mary Y. Wang, Ph.D.

TEMPORARY VOTING MEMBERS

William S. Blaner, Ph.D.
Tim Byers, M.D., M.P.H.
Manning Feinleib, M.D.
Van S. Hubbard, M.D.
Steven H. Lamm, M.D., D.T.P.H.
Barbara A. Underwood, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

FDA Presentations

P R O C E E D I N G S

Convene

DR. BRANDT: Welcome to everybody. I am glad to see you all here smiling.

As you know, we are here to review the more recent studies on olestra since it was approved by the FDA sometime ago. Many of you are familiar with the issues, and we have been here before.

Introductions

To begin, we are going to go around the table and all of you say who you are and where you are from.

I will begin. I am Ed Brandt from the University of Oklahoma, Health Sciences Center in Oklahoma City. For those of you that asked, the tornado moved through about a mile and a half north of my house. I went outside and watched it and watched all the crud flying around, and we got a sprinkle out of the whole deal, didn't even get a decent rain which we needed, so that is the story for those of you that have already asked.

DR. LARSEN: Lynn Larsen, Food and Drug Administration, Executive Secretary of the Food Advisory Committee.

DR. BENEDICT: Steve Benedict, University of Kansas.

DR. FUKAGAWA: Naomi Fukagawa, University of

Vermont.

DR. FEINLEIB: Manning Feinleib, CDC and Georgetown University.

DR. BLANER: Bill Blaner, Columbia University, College of Physicians and Surgeons.

MS. RICHARDSON: Donna Richardson, Howard University Cancer Center.

DR. FENNEMA: Owen Fennema, University of Wisconsin.

DR. APPLEBAUM: Rhona Applebaum, National Food Processors Association.

DR. RULIS: Alan Rulis, Center for Food Safety and Applied Nutrition, FDA.

MR. LEVITT: Joe Levitt, Center for Food Safety and Applied Nutrition, FDA.

DR. HUBBARD: Van Hubbard, National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

DR. HARLANDER: Susan Harlander, The Pillsbury Company.

DR. BLACKBURN: Henry Blackburn, University of Minnesota.

DR. CHASSY: Bruce Chassy, University of Illinois.

DR. WANG: Mary Wang, California Department of Health Services.

DR. BYERS: Tim Byers, University of Colorado.

DR. LAMM: Steven Lamm from Consultants in Epidemiology and Occupational Health, Washington, D.C.

DR. CLANCY: Kate Clancy at the Henry Wallace Institute for Alternative Agriculture.

DR. ASKEW: Wayne Askew, University of Utah.

DR. POTTER: Morris Potter, Centers for Disease Control and Prevention.

DR. BRANDT: For those of you that are new on the committee, two or three things you need to know.

One. You have got to talk in the microphone. It's a firm rule. If you don't talk, I will just go to the next person, if you don't use a microphone, that is. We want you to have every opportunity to say what you want, but only if it's recorded for posterity. Just think of how many masters' theses may be written from all these transcripts, you know. You can't ever tell.

The second thing is that I have a little notepad up here. If you want to talk, raise your hand. I will write your name down, and I will get to you in order, so please don't just butt in if you can avoid it, so we will try to do that.

It is important that you get an opportunity, particularly today, to ask any questions you want to ask, to be sure you are comfortable. I remind you that we are here to discuss the science and to evaluate the science,

especially the scientific studies that have been performed since our approval -- or since our recommendation for approval November of '95.

So, that is what we are here to do. We are not here to evaluate the benefits of this. The law says that we are to recommend on the basis of reasonable certainty of no harm, and that is what we will attempt to do.

So, we do not take votes on this committee. At the end of the time, each one of you being an expert will be asked to give your own evaluation about what is going on.

For the press that might be here, don't talk to me. Talk to either Dr. Rulis or Mr. Levitt from the FDA.

You can also, of course, make suggestions about other studies that you think need to be done. You have, or will have if you don't have, a copy of the NIH's views about carotenoids with respect to cancer and eye disease, and that is the material I guess in front of you.

DR. LARSEN: Not yet.

DR. BRANDT: Not yet. You will have a letter at least. Some of you remember those anyway.

I think that is all I have to say. Now we will turn to Dr. Larsen for all of his administrative stuff.

Administrative Announcements

DR. LARSEN: The first thing I want to mention is to note a few agenda changes. The public hearing has been

changed from that originally announced in the Federal Register. We originally announced three sessions. There will be a single session on Tuesday morning from 8:00 a.m. to 10:00 a.m., and I believe all of those who registered ahead of time for the public hearing know that.

There have been a few changes to the agenda that was provided to the committee originally in your briefing books. Everyone should now have a copy of the latest draft in the materials in front of you, at least we think that is the latest draft.

The names of all the speakers who will participate in the P&G, CSPI, or FDA presentations, and the current expectation of what those presentations, the times, and the breaks, and so forth are on that.

I would like to have the one other member who has joined us in the last few minutes introduce herself.

DR. UNDERWOOD: Dr. Barbara Underwood.

DR. BRANDT: Where are you from?

DR. UNDERWOOD: I am a Scholar in Residence at the Institute of Medicine.

DR. BRANDT: I love that title. It's a wonderful title.

DR. LARSEN: Now, to your briefing books. Each member should have a packet containing the latest version of the agenda, as I mentioned, a list of the persons wishing to

speak in the public hearing, the charge and questions for the committee -- that is probably the most important piece of paper there -- and copies of a number of letters that we have received.

As of Friday afternoon, we had received more than 530 letters about olestra. Most of these were from individual consumers who were generally positive about the use although many of them expressed negative views about labeling.

The packet you received today should have about seven examples. These were selected to illustrate comments on labeling, on repeated use without problems, on the writer's desire to have a choice of foods recognizing that some consumers may have reactions, and on usefulness when on restricted diets. We note that even though I say "usefulness," Dr. Brandt will repeatedly advise the committee that we are concerned with the science, not the usefulness of the product.

Some letters were from individual consumers who experienced adverse GI effects or had concerns about adverse interactions with medications. Example of those are also in your packet.

Copies of the consumer letters are contained in two binders for viewing by the committee or the public out in the hall. Please see one of the staff if you wish to

leaf through that compilation.

We have received a number of letters from scientists, physicians, and various organizations also. These letters present views on both sides of the various scientific and medical issues. A copy of each one of those letters should be in your packet. Two were included in the original briefing books.

Finally, the packet should contain some submissions that we received in lieu of an appearance during the public hearing tomorrow.

Conflict of interest. Each member and guest expert has been screened for potential conflicts of interest. Three members were found to have minor potential conflicts of interest. In each case, the interest was evaluated and determined by the agency not to be so substantial as to likely affect the integrity of the services which the government expects from these individuals. The agency therefore granted waivers allowing the members to participate fully in this meeting.

Those three members are Dr. Brandt, who has a trust fund over which he exercises no control, and that includes stocks in Pepsico, Pfizer, and Procter & Gamble. Dr. Blackburn's retirement plan has a mutual fund which also contains stocks in Pfizer and Procter & Gamble.

Dr. Lamm's wife owns small amounts of stock in

Pepsico and Procter & Gamble. Another member, Dr. Clydesdale, who hasn't arrived yet, advised the agency that in May of 1997, he had served as a consultant to RJR Nabisco for which he received a small honorarium. The agency determined that under its conflict of interest regulations and due to the passage of time, this was not a financial conflict of interest.

We have one member, Dr. Hubbard, who was also found to have a minor potential conflict of interest. Dr. Hubbard's wife owns some stock in Unilever. The request for a waiver for Dr. Hubbard is still progressing through the review process.

Until we have confirmation that that waiver has been approved, Dr. Hubbard will be asked to abstain from any formal vote on the scientific issues before the committee. He will be able to vote on any administrative questions should such a vote take place. He will also be able to participate fully in the committee discussion and will be able to provide his comments and views for the record during the polling of the committee on the questions before them.

No other real or apparent conflicts of interests were reported. Because most of the standing members of the committee participated in a 1995 meeting on olestra, many, and perhaps all, have been sought out by the press and others to express their views on the committee process and

on their own scientific conclusions. In addition, some of our temporary members are also known to have expressed views on issues in the public, in letters to the agency, or both.

FDA's utilization of advisory committees is intended to elicit the best scientific and technical advice that can aid the agency in making decisions on difficult issues. When the issues presented to a committee are highly public and possibly controversial, it is anticipated that members may have expressed views prior to a meeting.

The Institute of Medicine of the National Academy of Sciences, in its 1992 report on FDA advisory committees, stated that committee members who bring strong opinions about specific matters to their assessment of the data are not necessarily and automatically biased. They must be judged on their willingness to hold personal views in abeyance while examining the pertinent data in a careful and impartial way.

The standing members of this committee were selected without any preknowledge of what issues would be brought before them. They have demonstrated that they hold a wide range of views on the issues about olestra. The temporary members were selected with an effort also to provide a range of views.

Because CFSAN values the views of each member of the Food Advisory Committee, we always seek to ensure that

each member's complete views are expressed for the record. The range and nuances of views expressed by the membership help the Center fully evaluate its options in resolving the issues presented to the committee.

We have full confidence that the personal and scientific integrity of each member, whatever views may have been expressed publicly prior to this meeting, will result in a careful, impartial, and balanced evaluation of the data.

That is the end of my administrative notes.

DR. BRANDT: Any questions?

[No response.]

DR. BRANDT: Seeing none, we will move on. Mr. Levitt, our beloved director, Center for Food Safety and Applied Nutrition, the floor is yours, sir.

Presentation of Mementoes to Outgoing Members

MR. LEVITT: Thank you. Good morning.

This is only my second meeting as director of the center with this committee, so I haven't gotten a chance to know you all very well yet, but I suspect over the next three days we certainly will.

Nevertheless, during the last four years, this committee has dealt with a lot of significant public health issues involving such things as dieter's teas, ephedra, and olestra not once, but now twice. Even though the term as

standing members of a number of committee members is drawing to a close, we are still going to be calling on your assistance to act as consultants or liaisons to the committee. We have a number of ongoing things going on. We have three working groups still finishing up on issues arising from the keystone dialogue, although two of those at least appear to be nearing completion.

We have a working group on meta-analysis, and we have three working groups on dietary supplement issues.

The "retiring" members are still going to be involved in one or more of these working groups, and we are pleased to have you continue to do so. Nevertheless, this is a milestone in your participation on the committee and we do have a token of our appreciation for those members that after this meeting will be officially rotating off of the committee as full members.

What I would like to do now is simply call them off, one by one, ask if you would come up here. We have a plaque and a certificate of appreciation from the agency for you.

Dr. Wayne Askew, Director, Division of Nutrition, University of Utah.

Dr. Stephen H. Benedict, Associate Professor, Department of Microbiology, University of Kansas.

Dr. Henry W. Blackburn, Professor, Division of

Epidemiology, University of Minnesota.

Dr. Katherine L. Clancy, Henry A. Wallace Institute for Alternative Agriculture.

Dr. Susan Harlander, Vice President, Green Giant Research and Development, The Pillsbury Company.

Dr. Mary Wang, Senior Scientist, California Department of Health Services.

Also, "retiring," but not present today is Dr. Patricia Rodier, Senior Scientist, OB/GYN, University of Rochester, and soon to be present, but not quite here yet is Dr. Fergus M. Clydesdale, Professor and Head, Chenoweth Laboratory, Department of Food Science, University of Massachusetts. We will provide that when he is able to get here.

Thank you again, all of you. Please, a round of applause.

[Applause.]

DR. BRANDT: Thank you all very much for your service. I have enjoyed serving with you as the oldest member of this committee by far in terms of tenure and otherwise. I just have to point out to you that a good friend of mine once told me that the road to senility is paved with plaques.

Mr. Levitt, if you would give us our charge

Purpose of the Meeting; Charge to the Committee

MR. LEVITT: Thank you very much.

As I was going over my remarks last night, I am afraid the report that I was reminded a little bit of that famous quote from Mark Twain, who said, "I am sorry to have written you a 30-page letter, I didn't have time to write you a 5-page one." But if you will forgive our attempt at thoroughness, what I would like to do is three things.

Number one, I would like to kind of again provide some background both as a refresher course for those that have been here before, but also as an introduction to the new members.

Second, to go through the official charge and questions we are going to be asking you over the next three days.

Finally, to kind of sum up and give you some general views in terms of how we want to approach the meeting.

As you are all aware, approximately two and a half years ago, on January 30, 1996, FDA issued a final rule approving the use of olestra as a fat replacer in packaged, ready-to-eat savory snacks, for example, potato chips.

At that time, FDA announced that based on an exhaustive review process that involved consultations with experts outside FDA, as well as with this Food Advisory Committee, the agency concluded that olestra is safe for its

intended use.

Let me expand on that for a moment. As Dr. Brandt mentioned, an additive may be approved by FDA if it is safe for its intended use and under the Federal Food, Drug, and Cosmetic Act, safe means that there is "a reasonable certainty of no harm from the additive under the intended conditions of use."

The law places the burden on the petitioner to demonstrate safety, that is, that there is a reasonable certainty of no harm. The law, as you note, also uses the word reasonable. That means that the Act's safety standard should not be interpreted to mean proof beyond any possible doubt that no harm will result under any possible circumstance, but proof to a reasonable certainty.

According to the legislative history, an effect is harmful if it has an adverse effect on health.

Now, as many of you know, olestra was the first macroingredient of its type to be evaluated by the agency and its safety review presented several new challenges. For example, the evaluation of most new food additives depends primarily on the review of studies in which large groups of animals are fed the additive in amounts greatly in excess of levels that would be expected in the human diet.

In contrast, the safety decision for olestra was based in large part on data from human studies. In

addition, the effects of olestra on nutrient absorption presented questions not routinely assessed in review of food additives by FDA.

I want to emphasize that even though this review presented some novel issues, the agency found that the studies submitted were fully sufficient to conclude that olestra is safe under the intended conditions of use. However, because of the complexity and uniqueness of the issues involved with olestra, Procter & Gamble made a commitment to carry out post-marketing surveillance, and in the final rule, FDA acknowledged that conducts of such post-marketing studies by Procter & Gamble and review of such data by FDA are both prudent and consistent with the agency's mandate under the Act to protect the public health.

FDA also committed itself to a public discussion with this committee of the new data within 30 months. Thus, the FDA took the prudent step to create what I think of as a formal 30-month status check to ensure that any new information was reviewed and considered in an orderly fashion, and indeed that is why we are here today and for the next three days.

The purpose of this committee meeting then is to engage in that public discussion of the information and data generated in the post-marketing studies. The result is that we have a considerable body of new information and

scientific data to review and discuss. This includes data from passive surveillance reports, data from the first year of a study to measure the impact of olestra consumption on various nutritional measures, as well as data from several specific studies that Procter & Gamble has conducted subsequent to the olestra approval decision.

We very much appreciate Procter & Gamble's willingness and efforts to undertake this important work. We also appreciate the efforts of others in the community, including the Center for Science in the Public Interest, to collect new information.

Over the next two and a half days, you will hear view of data information that have been developed since January 1996. Specifically, today and tomorrow you will hear first the results from passive surveillance and the results of studies conducted by Procter & Gamble to further examine the potential gastrointestinal effects of olestra; second, information concerning issues other than GI effects, such as nutritional issues.

In each of these areas, Procter & Gamble, the Center for Science in the Public Interest, and other interested parties will be given an opportunity to present and critique the new information. In addition, FDA staff will present their views of the information and present their preliminary conclusions.

On Wednesday morning, we will also give interested parties an opportunity to present comments concerning the current olestra label. Finally, tomorrow morning, we have set aside time for open public discussion of all of these issues.

Now, as I have noted, FDA staff have been evaluating the new data and information, and based on that evaluation, have reached some preliminary conclusions about the significance of this new information.

I want to emphasize that the FDA staff analyses are preliminary and are intended to help provide a foundation and a context for this public discussion. Thus, we are anxious to have the benefit of your questions, your analyses, and your views, as well as those of the other participants.

In particular, at the end of each section of the meeting, as Dr. Brandt mentioned, the committee will be asked to address specific questions, so let me describe those for you.

In terms of a general charge to the committee, the committee is being asked to evaluate whether the newly available data and information regarding olestra raise significant public health concerns or other findings that were not anticipated at the time of the agency's January 1996 decision.

Specifically, we request your views in three areas. Number one has to do with gastrointestinal effects. FDA previously reviewed the potential for olestra to cause GI effects in consumers including special populations and concluded that olestra consumption may cause gastrointestinal effects, such as abdominal cramping and loose stools.

FDA further concluded based on the record at the time of approval that these effects were not adverse health consequences. In light of the prior consideration of resolution of the issue, at the request that the advisory committee consider the following question: Based on new data or other information, are there any significant unanticipated gastrointestinal effects captured in the passive surveillance reporting or in the post-marketing studies that could be attributed to the ingestion of olestra and that are adverse to health? So, that would be the first question. You will have that in the charge in front of you.

Number two goes to the studies pertaining to active surveillance. FDA concluded based on the record at the time of approval that olestra can have an effect on the absorption of the fat soluble vitamins, vitamins A, D, E, and K.

FDA also concluded that it is possible to add these four vitamins to olestra-containing snacks in such a

way as to compensate for the amounts that are not absorbed from the diet due to the consumption of olestra.

The agency also concluded based on the record at the time of approval that olestra can have an effect on the absorption of lipophilic carotenoids. At that time, FDA concluded that while fruits and vegetables that are good sources of carotenoids provide health benefits, there was no direct evidence that carotenoids themselves are responsible for specific health benefits. That was the conclusion at the time.

Accordingly, the agency concluded that there was no justification or need at that time to require compensation with specific carotenoids, however, the agency also concluded that it had a responsibility to evaluate any new data that bear on this issue, such as data and information on the health significance of carotenoids along with any new data generated in post-marketing studies.

So, in light of the prior consideration of resolution of the issue, FDA requests this committee to consider the following question, and this is the second of the three questions: Do the new data from the first year of active surveillance, or any other newly available data, show that consumption of savory snacks containing olestra has a significant adverse effect on health due to interference of absorption of fat-soluble vitamins or other lipophilic

substances? Again, you will have that question before you and we will come back to it at the appropriate time.

Finally, the third issue relates to labeling. FDA concluded in 1996, based on the evidence available at the time, that the possible association of olestra consumption with GI effects, such as abdominal cramps and loose stools, did not represent adverse effects, as I mentioned.

However, FDA further concluded that consumers should be provided with information to enable them to associate olestra with these GI effects. Thus, the agency required a label statement to inform consumers of possible effects of olestra consumption, and I believe you are all familiar with that label.

Also, because of the requirement to list all ingredients on the label, the agency was concerned that consumers might interpret the listing of four vitamins in the ingredient statement as evidence that the snacks were fortified for nutritional benefit.

This was not the case as you know. Therefore, FDA also determined that the label for olestra-containing products should disclose the inhibition of absorption of some vitamins and other nutrients and that fat-soluble vitamins A, D, E, and K, have been added to the snacks to compensate for such loss.

So, finally, in light of the prior consideration

of resolution of this issue, FDA requested the advisory committee to consider the following third and final question: In light of the new data and information concerning consumption of olestra, should the label of olestra-containing products be changed in any way? If so, what factual information, if any, regarding the consequences of consuming olestra-containing products should be disclosed on the product label?

You will see the theme of all of this is again as a post-market safety check, what is new, what has changed, and how do we address that today.

So, let me then use that as a wedge into some concluding comments.

First, I know that this is the final Food Advisory Committee meeting for a number of members, as I noted, and it is clearly an important one. For other members, particularly those new temporary voting members whose expertise is needed for this discussion, it may be your first meeting and I want acknowledge and welcome your participation also.

As I said, the 1996 approval of olestra was arrived at based on an exhaustive review and outside consultation. Now, everyone did not agree with that decision, but it was the agency's decision, arrived at through a fair and open process.

We are not here today to redo or second-guess that decision or the decisionmaking process at that time, and I think that bears repeating. We are not here today to redo or second-guess that decision or decisionmaking process two and a half years ago.

Now, you may hear presentations during the next two days of information that was available prior to January 1996, and to the extent that such information provides context for your discussion, that is entirely appropriate, but I want to remind you that your recommendations should be based on new information and data developed or reported subsequent to the approval of olestra.

I also want to remind you that under the law, as Dr. Brandt mentioned, a petitioner is not required to show, and FDA in fact is not even permitted to consider, whether a food additive has benefits, that is, we are not here to draw conclusions about the usefulness of olestra. Rather, the agency's sole focus, and the sole focus of this committee needs to be, on the new information relating to the safety of olestra.

Finally, I want to remind you that the 1996 decision was not a provisional approval to be recertified after 30 months. Rather, it was a full approval, like all other food additive approvals, with the additional commitment to have a formal, 30-month status check of those

post-marketing surveillance studies that the petitioner had committed to carry out, as well as of any other new information that would bear on the safety of the use of olestra in savory snacks.

Therefore, what we are here to do is to follow through on that original commitment to have that formal status check, to look at new data or new information to see if anything significant has changed. That is the key question: do the new data or new information present us with a significantly different picture regarding public health and safety of this product?

If the answer is no, then, we will have fulfilled our important commitment of January 1996 to the public regarding our post-market surveillance and evaluation of the product. Of course, as with other ingredients added to food, we will continue to monitor the safe use of olestra.

If the answer is yes, then, it will become FDA's job to translate the significance of that new data and information into appropriate actions. Whether that may mean, for example, modification of the olestra label, a request for more focused post-marketing studies, or even potential reconsideration of olestra's marketing status, but the key for us here today is to be sure that the new scientific data and information, and your expert evaluation of those data, are what drive any FDA future actions.

I would finally point out that in any event, Procter & Gamble is planning to continue its post-marketing monitoring studies including, for example, number one, continuation of the passive surveillance; number two, completion over the next three years of the "active" surveillance studies on nutritional effects; and, three, collection of data on national consumption patterns of olestra snacks.

Procter & Gamble has also committed to continue to report the results of these data collections to the FDA, and, of course, we will evaluate them. The agency will consider this information and any other relevant information as part of its continuing responsibility to monitor the safety of the food supply.

Let me thank you very much for your time and attention, for your willingness to take time from your busy schedules, and most importantly, for your willingness to take three days out of your lives and really commit yourselves to thinking what does the data mean, what does it mean for public health. We want your advice, and we look Forward to the presentations and your evaluation of them.

Thank you very much.

DR. BRANDT: Are there questions from the committee of Mr. Levitt and the charge? Everybody is clear about what we are here to do?

[No response.]

DR. BRANDT: If any legal issues come up, we are blessed with the presence of legal counsel, Catherine Copp, someplace around here. Stand up so everyone can see you.

If any of you have a question that has to do with the legal aspect of what we are doing, why, we have got immediate help or at least immediate words. It may or may not be help, but we will see.

Any other comments, questions by anybody on the committee? All right. Dr. Clydesdale has joined us and we are delighted to have you, sir, one of our "retiring" members. Do you want to give him his thing?

MR. LEVITT: I will be happy to give you your thing if we can find it. Kathy.

Dr. Clydesdale, while you were out, we have a plaque and certificate of appreciation for the "retiring" members with the proviso that we know that you are continuing working with us as consultants and liaison members on a number of working groups and other assignments, and really want to express our appreciation to you for that.

Yours is actually on its way here. If you will come up here for a moment. As other people have seen, this is a certificate of appreciation in recognition of distinguished service on the Food Advisory Committee.

[Applause.]

DR. BRANDT: Did anybody else sneak in that I missed? I don't see anybody that I didn't see before.

Dr. Rulis, you are on, please, sir. Dr. Rulis is Acting Deputy Director for Programs.

Introduction and Overview of Olestra; Review of the Safety Decision Process and Commitment to Post-Market Surveillance; Expansion on the Charge and Questions

DR. RULIS: Thank you, Chairman Brandt.

[Slide.]

Good morning to you and to members of this Food Advisory Committee. I am Alan Rulis, Director of the Office of Premarket Approval, and I am Acting Director of the Center for Programs.

I guess one reason I am here is to show that all things are relative. If Mr. Levitt believes that his presentation was long compared to the ideal, mine is going to be extremely long compared to the ideal. For every word that Mr. Levitt spoke, I am going to speak probably three or four, and probably not say a whole lot more, but what I am hoping to do is to be able to provide you with some context and some background, a sense of history and perspective about how FDA has reviewed food additives for the last 40 years, and what may be some unique aspects of the olestra evaluation that you need to keep in mind as we think back to

those times when we reviewed it and also look at the new data that we are to focus on in the next two and a half days.

During the next two and a half days, you will be provided with summaries of information that has been gathered to date about olestra consumption in the real life marketplace, as well as the results of several controlled studies performed by Procter & Gamble and their associates to further evaluate olestra.

There will be presentations by Procter & Gamble, by the Center for Science in the Public Interest, and by FDA, as well as other information and views from interested members of the public. Mr. Levitt has just described for you your charge and read to you the questions that we would like you to deliberate on.

My goal today is multifold and some of the points that I am going to try to cover are laid out here on this overhead for you.

[Slide.]

First, for those of you who are new to the advisory committee, it is to provide you with essential background information on FDA's food additive review process, reminding you of the statutory standard under which FDA works and the way in which that standard is currently interpreted in light of the scientific data that the agency

reviews.

Second, to provide context, I will provide a very brief overview of the types of information FDA evaluated before determining the use of olestra in savory snacks is safe and how the approval process was enhanced for olestra beyond that used for a routine food additive petition. This will be necessarily a brief overview, of course, because we are not focusing on those data in detail.

Because our deliberations in this follow-up session of this advisory committee will be focused on new data generated since the approval, I will be necessarily brief in describing the approval data, but I want to point towards a lot of the data that you will be hearing about in some detail for the next two and a half days. I will not be describing those data in detail, however. You will hear that over and over again from other participants here.

Finally, I would like to explain what FDA's approval for olestra meant and the actions and agreements that were attached to that approval that bring us here today, and finally, give a brief overview of the information that you will be considering in some detail.

Now, let's take a look at the next overhead.

[Slide.]

This is just a little chronology of major aspects relating to olestra approval. The petition was filed in May

of 1987, and the Food Advisory Committee met in November of 1995. During that time period of almost 10 years, almost a decade, the FDA received and evaluated over 150,000 pages of data. It put to work on the order of 60 reviewers and generated 150 memos analyzing those data.

The approval was granted in January of '96. Test marketing of olestra snacks began in Colorado, Wisconsin, and Iowa in April of '96. That marketing was expanded into Ohio and Indiana in October of '96 and February of '97 respectively.

National marketing of olestra-containing snack foods began in February of '98, and, of course, today we are here to participate in the follow-up for the advisory committee meeting.

[Slide.]

Let's talk a little bit about FDA's responsibility under the food additives amendment of the Food, Drug, and Cosmetic Act, as amended in 1958. That amendment to the FD&C Act defines food additive. I won't read that definition. You can be sure that olestra is included in that definition.

The Act requires premarket approval of new uses of food additives. It also establishes a standard of review, which we will talk about. It establishes a standard of safety, as well, and it establishes formal rulemaking

procedures.

[Slide.]

Now, the FD&C Act, in Section 409, says, "A food additive shall with respect to any particular use be deemed to be unsafe unless there is in effect a regulation prescribing the conditions under which such additive may be safely used." That is the impetus for bringing to the agency a petition that we would review and determine whether the petitioner has met the burden of proof, and until that is done, the additive is not safe on the market.

[Slide.]

Petitions generally have these basic elements: the identity and composition of the additive, the proposed used in food, the amount that will be added to food, data that established that it will accomplish its intended effect, quantitative detection methods sometimes are included in the petition.

Full reports of safety studies, the data. This is the core, this is the heart of the petition, and, if needed, any proposed tolerances, and, of course, environmental information in compliance with the National Environmental Policy Act.

[Slide.]

The standard of reviewing food additive petitions is fair evaluation of the data. Now, this is a very

deceptively simple phrase, but carrying it out is tremendously challenging. You can imagine 150,000 pages of data, 12 shopping carts full of data, 60 reviewers going over the data in great detail, writing memoranda the best possible analyses that their scientific credentials provide them the ability to do.

What is necessary is to synthesize all of that information and take the weight of the evidence together and reach what is essentially a binary conclusion. It is not possible at the end to say, well, here are some good points and here are some bad points.

What the FDA is charged with is reaching in the approval stage a binary conclusion. That is not your charge, as Mr. Levitt has carefully pointed out and which you must remember today, but in the approval of a new food additive, the binary decision is the outcome, very difficult because there are many countervailing factors including very strong opinions of many reviewers on one side or the other of an issue.

We encourage our reviewers to be very critical of the data, to shred the data, to analyze the data, to be as intensive about their analysis of the data as possible, and yet in the end, we must bring all of this together and ask ourselves where are we on this binary conclusion - is it a positive or a negative.

[Slide.]

The House of Representatives, in their report on this bill, anticipated this, and in some very eloquent language wrote, "The committee feels that the Secretary's findings of facts and order should not be based on isolated evidence in the record, which evidence in and of itself may be considered substantial, without taking account of the contradictory evidence of equal or even greater substance." So the Congress put more words around that subtle phrase, but it still is quite a challenge.

[Slide.]

With respect to the safety standard, let me just point out here that the statute in Section 409(c)(3)(A) says no such regulation shall issue if fair evaluation of the data before the Secretary fails to establish that the proposed use of the food additive under the conditions of use to be specified in the regulation will be safe, so there is the requirement of premarket safety evaluation. Unfortunately, Congress did not provide us the definition of the word safe.

It did provide us with the Delaney clause, which is this famous sentence that follows that is not pertinent to olestra, because olestra is not a carcinogen, but it does go on to say that if the additive is found to induce cancer when ingested by man or animal, that it cannot be approved,

but we are looking at the general safety provision, and we concentrate on the word safe here.

[Slide.]

Again, Congress came to the rescue of FDA because even though it didn't put the definition of safety in the statute, it provided a legislative history that helps us, and in this House report, you can see that the Congress said that the concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not and cannot require proof beyond any possible doubt that no harm will result under any conceivable circumstance.

[Slide.]

So, the standard of safety is a reasonable certainty of no harm, and the burden is on the petitioner to prove that, and the agency reviews the data and determines whether the petitioner has met that burden.

[Slide.]

Now, that was easy, too, that sounded easy, too, but over the years we have wrestled with this at FDA and we have tried to ask ourselves what are some ways in which we can think about the safety standard, the actual elaboration of it as we do our daily work.

What this safety decision that we make is not, is it is not an academic inquiry. It is not an opportunity to ask interesting questions that are perfectly fine to want to answer from a scientific point of view just for the sake of getting the answers. It is not a search for complete knowledge.

The questions we ask, the knowledge we try to find is pertinent to the health consequences of the use of the additive. It is not intended to ensure, nor is it possible to ensure, safety with absolute certainty, that is, reasonable certainty no harm.

We are not trying to prove with certainty that there is no theoretical possibility of harm although we probably would like to if we could, we can't. That is the statutory standard. It does not weigh risk and benefits. Unlike drugs which provide the ability to look at a therapeutic ratio and decide whether there are any benefits that countervail over the risks, we are looking in a sense at a stricter standard, safety per se. It is not intended to enforce or limit consumer choices among safe food. The benefit question is out of bounds for us in this sense.

[Slide.]

What the safety decision does do is it, in fact, ensures safety and it has been doing that for 40 years. It is a consensus decision made under uncertainty, that is,

there will always be some residual uncertainty, but it provides that essentially it is based on a fair evaluation of the data of record, and it must protect the public health in the end.

It is made in the absence of complete knowledge, absolute certainty is not there. It will withstand scientific procedural and legal challenge from all sides, and the residual uncertainty that is there is not out of line with what has been previously tolerated in the context of all similar safety decisions, so doing this for 40 years helps because you can look back and say, well, you know, we think this is about right, and we can show that it is about right because we have these examples in our historical past.

[Slide.]

Finally, the statute, as I said, provides for formal rulemaking procedures. It says that we will by order establish a regulation that prescribes conditions under which an additive may be safely used and the reasons for such action.

The agency, in its approval of olestra, published a 50,000-word preamble in the Federal Register explaining the linear thought process, the synthesis of all the data, and the basis for its binary conclusion.

[Slide.]

As I said, FDA has been reviewing food additives

since 1958. We have evaluated somewhere between 3- and 4,000 petitions, and they have been for food additives, color additives, GRAS ingredients, and other food ingredients, and almost all of them have followed this basic outline.

It is a toxicologically based data review. We are looking for toxicological impact of the compound on living systems. We establish the estimated daily intake, a lifetime averaged EDI, estimated daily intake.

Then, looking at the data that have been accumulated and presented to us by the petitioner, we observe whether there is, in fact, in those studies, and particularly the longest studies, the most sensitive studies conducted in animals the highest no effect level, HNEL, highest dose that causes no adverse effect in animals.

We then make the assumption that those effects that we see demonstrate what we call threshold behavior for toxic effects, that is, at some dose those effects will not manifest themselves, there needs to be some minimal level of dose that will cause an effect to occur, so that below a certain dose there will not be that effect, and we apply a safety factor, typically, a factor of 100 or sometimes it is called an uncertainty factor to the highest no-effect level from the lifetime animal studies, and we achieve what is called an ADI, an acceptable daily intake, and we compare

that acceptable daily intake to the estimated daily intake, and if the comparison is favorable, we say that we have met the general safety criterion of the Act.

We have shown that the additive will be associated with the reasonable certainty of no harm, it is, in fact, safe, the binary conclusion is secure, and we go on about our business. There are no effects at estimated consumption levels, there will not be any.

[Slide.]

What is different about olestra? I tried to figure out a way to explain this to you, and I have drawn this little road, this little spectrum, this little road map. Some people at our agency call it the yellow brick road. I don't know why they refer to it that way.

It is a spectrum of all of the food additives that we could ever review starting with those of the lowest possible exposure, which we call threshold indirects, on the order of half a part per billion in the diet, migrating to food possibly from contact with food packaging materials, very, very low exposures, very low likelihood of any toxicity, all the way up through higher exposure, indirects, that is, packaging materials of high exposure, all the way up through direct additives like artificial sweeteners, saccharine, sucralose, aspartame, and then into a realm which we call macroingredients, which are becoming more

visible now as food ingredients in the marketplace and in our petition shelves. Some of those are macronutrient substitutes, such as olestra, it is a macroingredient.

You can imagine taking the spectrum all the way down to whole foods although we don't approve whole foods as food additives because they are considered to be generally recognized as safe. Potatoes put into beef stew, for example, could technically be considered to be food additives under the statute except for the fact that they are generally recognized as safe. We don't evaluate them.

Now, much of the work we have done for the last 40 years has been a tox-based review. We have been looking at toxicity in animals. What is unique about olestra and other macroingredients is that there needs to be attention paid to other issues besides toxicology. There needs to be a nutrition-based review, as well as a tox-based review, and there may have to be physiological and gastrointestinal issues addressed.

So, the basic picture of what we have to look at and the data we have to evaluate is expanded considerably as you move down this spectrum. The Congress, in their wisdom, when they put together the Food Additives Amendment, probably did not have this type of food additive in mind. The toxicology of industrial chemicals was well developed by the time of the '58 amendment, but the way in which one

would evaluate safety of a macroingredient was not in anyone's mind at that time probably.

[Slide.]

For the macroingredients, we need to look of course at the identity and specifications. We need to look at the exposure estimation and obviously, because the ingredient may occupy a large fraction of the diet, we may have to be very careful about exposure estimation.

We have to focus our toxicological evaluation on what we call ADME, absorption, distribution, metabolism, and excretion studies, where is this additive going in the human body. We evaluate the potential gastrointestinal effects. We assess potential nutritional effects. We look at clinical data. We even do post-market surveillance or what I call post-approval monitoring, another way of talking about it. And we invoke advisory committee meetings, such as this one.

[Slide.]

Now, this is a little graph that I dreamed up that I should show you. I am afraid it is probably not the best thing to do, but I will just give you an idea of where my mind is in trying to think about the approval of food additives and what actually happens when the agency reviews the data.

I think of it this way. I think of a vertical

scale that somehow is called the degree of certainty, and you can imagine one is being absolute certainty. It is the Holy Grail. You never get there, but you can approach it asymptotically, and you can do that by adding breadth, depth, and rigor to your data, and ask questions and get adequately documented answers to your questions of probative value.

That is what we do for a living, and as you do that, you see, you quickly learn about those additives even by asking a few questions, what is the chemical structure, what is the likely human exposure, your level of certainty about the safety of that material goes up quickly or it could drop, but for an additive that is ultimately safe, this is what happens, you learn a little bit, you learn a lot in a little bit of time.

Eventually, though, you come around what is sometimes referred to as the knee of the curve or, for mathematicians, the inflection point. This is where you begin to expend a lot more effort learning a little bit, and you can go off to infinity learning just a little bit more.

Threshold indirect additives rise quickly. We just look at the chemical structure and the estimated human exposure, and I can tell you very quickly without much toxicological review that you are within a reasonable certainty, you are within this range of approvability.

For a direct food additive, you may have to examine quite a bit of data. You may have to go through the entire retinue of chronic feeding studies in several animal species. You may have to subject animals to histopathological examination of 30 or more organ tissues, studies of reproduction and teratology, full-blown toxicological evaluation treatment.

At some point out here, after answering the questions or after looking at all those data, you reach an area that is reasonably close to certainty, and you say I have achieved reasonable certainty of no harm.

For other additives, this curve is even shallower. You may have to proceed further out to the right. But at any rate, at some point there is a point at which the questions that you ask are not of probative value, they are of speculative value, they are of conjectural value perhaps, and they may cost you a lot of effort and time to get much higher on this curve, but at some point the binary decision needs to be made, and it is.

[Slide.]

I am going to swing very quickly through the original olestra review. We are not going to focus on it in this committee, but I do want you to hear the basic major points of how olestra was reviewed just to refresh your memories.

There was a parallel review of all the data by FDA reviewers and scientists as I mentioned. There were consultations with outside subject matter experts. We pulled together a regulatory decision team of senior managers to listen to our reviewers and to go over their memos and to consolidate and to accumulate the information together in one place and to weigh the evidence.

We conducted a working group of this Food Advisory Committee for two or three days prior to the November meeting in '95, and then this advisory committee met. We had further consultations with experts at NIH. We also looked at other data that was made available, and we finally published the final rule with its associated preamble.

[Slide.]

I wanted to show you, if you have never seen a space-filled model of an olestra molecule, this is one way of looking at it. This is a 6-substituted sucrose. Normally, it's almost all 8-substituted, but in order to be able to see the structure, we have got 6 on here, but this is a chemical combination really of sucralose with either 6, 7, or 8 fatty acids that are commonly found in edible oils and fats. These fatty acids are either saturated or unsaturated, and they have typically chain links from 12 to 20. This is a view of how the molecule looks.

[Slide.]

We estimated the intake, the lifetime average EDI, the estimated daily intake to be 7 grams per day of olestra, but we also considered higher levels of intake based on other scenarios, such as the short-term consumer, for example, a 2-ounce bag of chips every day for 12 weeks, and that would represent this individual here.

The 99th percentile, 14-day average in the highest consuming group, the 99th percentile, single-day intake for olestra. Typically, this might be a 13- to 17-year-old boy who from time to time is eating a large amount, but only in an acute setting.

[Slide.]

The toxicology data, the ADME data, the mutagenicity, genotoxicity data, subchronic studies in a variety of species, chronic toxicity and carcinogenicity studies in mice and rats, reproduction, teratology resulted in these conclusions. Olestra is not metabolized, it is not toxic, it is not carcinogenic, it is not teratogenic, it is not genotoxic.

[Slide.]

Of course, as I said, we went on beyond the toxicology framework to look at a whole series of nutrition related, gastrointestinal-related studies in the left column human studies, in the right column pig studies.

Most of the emphasis was on the 8-week studies,

clinical dose response study and the clinical vitamin restoration study. You have heard that described in detail before.

The highest dose in these studies was 32 grams per day, and in the dose-response study, the highest dose of olestra was associated with about a 20 to 25 percent incidence of diarrhea-like symptoms, loose stools on a percentage of available days in which that kind of effect could exhibit itself.

That number, 20 to 25 percent, for 32 grams per day, you might want to remember because you will be hearing data later and you might want to compare that to data you will be hearing later. These other studies were important, but contributory to the top two.

The pig studies were the two largest, the longest duration pig studies are the top ones here. They received the most emphasis, and we studied the effects of olestra in full-grown pigs. The data that were provided here were done in pigs by P&G in order to simulate the human gastrointestinal tract. When we looked at those data, we were able to get more information about vitamin compensation levels.

[Slide.]

This just summarizes those. You know about these, Vitamin A, E, D, and K levels. About a third of an RDA for

Vitamin A, about an RDA for Vitamin E, about a third of an RDA for Vitamin D, and about an RDA for Vitamin K were considered to be appropriate for adding to snack foods that contain olestra in order to compensate for any losses in those vitamins that might result from the partitioning of fat-soluble vitamins into the olestra fraction in the gastrointestinal tract.

[Slide.]

On carotenoids, we determined that olestra will not have adverse health effects due to interference of carotenoid absorption, and we had several main points associated with that conclusion, one, in association with epidemiological studies, that is seen, may be simply an association with fruit and vegetable consumption. That connection between carotenoids and fruit and vegetable consumption will undoubtedly be an issue we will discuss here.

No cause-effect relationship was established for carotenoids except for the provitamin A function, and most carotenoids are not consumed with savory snacks, and therefore, the effect on the levels is likely to be small. The effect is observable under certain conditions, but in real life conditions it is likely to be small.

[Slide.]

Finally, our conclusions. We approved it based on

a reasonable certainty of no harm. We did require compensation of the fat-soluble vitamins, and, of course, the label statement was required. It is an interim label statement. We are still technically in rulemaking on that label statement, and it will be a subject for discussion on day three.

[Slide.]

As was just noted by Mr. Levitt, because of the complexity and uniqueness of the issues involved with olestra use, Procter & Gamble made a commitment to carry out post-approval monitoring.

In its final rule, FDA acknowledged that the conduct of such post-approval studies by P&G, and review of such data by FDA scientists, are both prudent and consistent with the agency's mandate under the Act to protect the public health.

One of the primary aspects of this 30-month status check is to ensure that the new information generated since approval has a public opportunity for discussion and description before this public body.

The new data are arrayed out in this slide here. The passive surveillance data at the top, P&G has provided periodic reports during test marketing. They were the results of calls to a toll-free number. P&G has supplied at this moment in time about seven reports including over 1,300

people over an 18-month period.

Five test markets are included in those data - Wisconsin, Colorado, Iowa, Ohio, and Indiana for a combined population of 2 1/2 million persons. P&G continues to provide information on all the products out there containing olestra including P&G's Pringles, Frito-Lay Wow chips, and Nabisco fat-free Ritz and Wheat Thins.

There have been efforts to get medical records of those contacting medical professional help, and we have that information to talk about from the FDA view, and I am sure other presenters here will talk about that in detail.

With the national expansion, Frito-Lay and other marketers of olestra products have been cooperating with P&G to prepare a single report for the agency, so we can digest this information more expeditiously. With the advent of national marketing, approximately 1,500 individuals reported in the first six weeks, and the majority of the reports that we have received, as with the test markets, relate to the GI complaints.

The Center for Science in the Public Interest also set up their own toll-free number, and they also have a web site for electronic compilation of complaints, and they have been compiling those and sending them to the FDA, and we have been looking at them, as well.

We have received three reports from CSPI for a

total of about 1,300 individuals, and we have medical records for about 15 individuals.

The re-challenge test, those reporting to P&G's toll-free line were asked to participate in a re-challenge test. The final report of this test was submitted to the agency. It included 98 individuals. It was a double-blind, cross-over study with the possibility of consuming full-fat chips twice and olestra chips twice. Then, there was a telephone contact made three to five days later.

The stool composition study, double-blind, placebo-controlled clinical study. It measures whether people experience diarrhea-like symptoms as measured by increased stool output, water output, and electrolyte loss, and greater than three bowel movements per day.

It's a two-week study conducted in 66 individuals on a metabolic ward, and all bowel movements for every individual were collected and analyzed. Telephone surveys on the incidence of GI effects, there were two surveys conducted by P&G to assess the prevalence of GI complaints before olestra's introduction into the market, one in Indianapolis, and another nationwide after introduction, and we will be hearing about that.

The acute consumption study. That is a movie theater setting. You will be hearing about that in some detail. That was published also in JAMA. 1,092 subjects

got a 13-ounce bag of chips and a 32-ounce beverage, two hours of ad libitum consumption. Chips were weighed afterwards and about 960 subjects called back between two and four days later, and 125 subjects were called back within five to 23 days later to describe their symptoms.

The home consumption study is a large study to assess the real life consumption scenarios of olestra-containing snacks. 1,100 households, 1,381 individuals, over a six-week period. It included children, teenagers, and the elderly.

A daily dairy of snack consumption and GI symptoms was conducted. It was a double-blind study. The test group got olestra-containing chips, and the control group got olestra-labeled triglyceride-containing chips. Both groups could also select full-fat chips that were labeled as full-fat chips.

In this study, there were 130,000 subject days, 66,000 subject days in the olestra group and 33,000 olestra-eating days.

Finally, the active surveillance. Different sites around the country have been chosen, about 3,000 individuals are included. This study will continue for the next three years. It includes blood draws done to measure a number of parameters especially serum levels of fat-soluble vitamins and carotenoids.

One year of that has been completed in Indianapolis starting with a cross-section of 1,069 adults prior to olestra introduction, and 947 new recruits a year later. 402 non-pregnant adults were recruited from the first sample as a cohort to be tested again after one year.

[Slide.]

Just to reiterate the charge and the questions for you again. GI effects, this is what we are asking you to focus on. Based on new data or other information, are there any significant unanticipated GI effects captured in the passive surveillance reporting or in the post-marketing studies that could be attributed to the ingestion of olestra and that are adverse to health?

[Slide.]

With respect to nutrients, do the new data from the first year of active surveillance or any other newly available data show that consumption of savory snacks containing olestra has a significant adverse effect on health due to interference with absorption of fat-soluble vitamins or other lipophilic substances?

[Slide.]

Finally, on labeling, in light of the new data and information concerning consumption of olestra, should the label of olestra-containing products be changed in any way? If so, what factual information, if any, regarding the

consequences of consuming olestra-containing products should be disclosed on the product label?

[Slide.]

The committee is being asked to evaluate whether the newly-available data and information regarding olestra raise significant public health concerns or other findings that were not anticipated at the time of the agency's January 1996 decision.

That is the length and breadth of my comments. We are about to begin two and a half days of in-depth discussions on the data developed on olestra since approval, and we will also devote considerable time discussing the labeling of products containing olestra.

FDA would like to thank you for your willingness to serve the agency in this way. We truly appreciate all the help that you have given us in the past and the help you are about to provide us with.

At this time, I am happy to try to answer any questions that you may have.

Questions of Clarification

DR. BRANDT: Are there questions from the committee? Dr. Feinleib.

DR. FEINLEIB: I am Manning Feinleib. I am a newcomer to the committee. The second charge on active surveillance contains the phrase whether or not olestra has

a significant adverse effect on health. The words "significant adverse effect on health" seems to be different from the "no harm" phrase that was used previously.

Could you explain that?

DR. RULIS: Let's point the word out here, so we are clear about it. Let's read the whole thing, too, just for the record: Do the new data from the first year of active surveillance or any other newly available data show that consumption of savory snacks containing olestra has a significant adverse effect on health due to interference with absorption of fat-soluble vitamins or other lipophilic substances?

Significant here is an adjective, and its interpretation is going to depend on each individual's views. We are interested in your views about it. I think you have focused on the word, and I hope everyone has focused on the word, and I would hope in the discussions that take place here, you raise whether or not you think an effect is, in fact, significant, and give your opinions about that, because that is part of what we want to hear.

I think there is probably some potential for redundancy. If there is an adverse effect on health, then, by its very nature, one could argue that is significant, and I think we should discuss that openly, we should listen to your views on that.

I think the word is here to remind you that there is a possibility that effects, even though some may say they are adverse and they do affect health, may not be significant, and I think that we need to get your views on that.

One of the ways I try to think about this is with respect to macroingredients, as opposed to the toxicological framework in which we normally review food additives, we are looking at that relative to a baseline of zero. We are comparing what we see in animals to zero effect.

For macroingredients we are comparing what we see to a baseline of food intake, people eating a varied diet, selecting among a tremendously wide range of foods, having, if you watch the commercials in the evening news programs, a wide variety of gastrointestinal complaints all the time, about everything, gas and bloating, and upset stomachs, and that baseline is what we have as part of life.

So, part of your job I think in working with this word significant is to think about that baseline as we discuss the effects that olestra is associated with in both the GI effects and with respect to nutrients.

Now, on the nutrient question, of course, there are well-accepted definitions for important nutrients versus ones there are still debates about. Vitamins are generally accepted by the nutritional community as being essential.

We will have further discussion I am sure about the nature of carotenoids. There is a wide variety of opinion about that still here.

Again, the word significant here I think needs to be brought up in light of that, as well.

So, that is a long answer. I guess I am challenging you back to please use the word and discuss what you think about what it means.

DR. BRANDT: Other questions? Yes, sir. Dr. Lamm.

DR. LAMM: In some of the previous papers, you have used the phrase "public health significance" as if you are distinguishing that from "clinical significance." With respect to the question that was just above that, before us, are you referring there specifically to public health significance in contrast to clinical significance?

DR. RULIS: We are referring to public health significance. Now, someone could argue I suppose that clinical significance presages public health significance, and that is a subject for debate, and I think we can talk about that.

DR. BRANDT: Other questions, comments? Dr. Benedict.

DR. BENEDICT: This is more a comment, and it has to do with in the briefing book, it was addressed that we

will not include drugs as lipophilic substances for purposes of our discussion. I note that in the charge and in some of your remarks, it still just says fat-soluble vitamins or lipophilic substances.

I thought perhaps we should clarify that we are not going to deal with drugs, or are we?

DR. RULIS: I am going to let the chairman I guess adjudicate that partly.

DR. BRANDT: Thanks a lot.

DR. RULIS: Let me try to start it off. I think the question of interaction of olestra with prescription medicines and drug bioavailability was discussed in the previous advisory committee meeting.

I can't imagine it won't come up in our discussion, but to the extent that that discussion is a rehash of previous discussions, I think our chairman will probably cut it off. To the extent that it has pertinence to what we are trying to get at here, he may allow it, but that is why I defer to him.

DR. BRANDT: You can bring it up, Dr. Benedict, should you choose to do so, and we will see. I will remind all of you that contrary to the past, I do not have the opportunity to cut off your microphones like I have had in the past.

Other questions, comments, discussion? Everybody

on this committee, members and experts, invited experts satisfied that they know what we are going to be doing for the next two and a half days?

[No response.]

DR. BRANDT: Okay. We are early. I don't think you took advantage of your opportunity to use three or four words instead of one, but rather than try to disrupt the continuity of the next series of presentations, I am going to go ahead and say we are going to take a 15-minute break, but wait a minute. A couple of important issues.

One. For members of the committee, break room is meeting room D right down the hall. The plumbing facilities, assuming they are working, is to the left as you go outside the door. There is one for each gender.

We will return according to my watch at 9:35, and those of you who are old members know that we will start at 9:35 by my watch.

[Recess.]

DR. BRANDT: We are ready to start if everybody can sit down.

Dr. Rulis, I am told had a slip of the tongue in his presentation, and you want to correct the record, please.

DR. RULIS: Yes. You want to remind me of my slip?

DR. LARSEN: Sucralose versus sucrose.

DR. RULIS: Yes, I am sorry. It might be an interesting molecule, but that is not what we have here. it is sucrose and not sucralose. You know, when you spend your life thinking about food additives, they are rolling around in your brain all the time. I am sorry about that.

DR. BRANDT: No problem.

We are ready to begin. Representatives from Procter & Gamble are here with us for the next hour or so. Dr. Keith Treibwasser, who is Director of Olestra Regulatory and Clinical Development, and Dr. Zorich, Medical Director, same outfit. They have been here with us before. We welcome you back.

Dr. Treibwasser, the floor is yours.

Results from Passive Surveillance Reports and Special GI Studies

Procter & Gamble Presentations

DR. TREIBWASSER: Thank you, Chairman Brandt.

I want to thank the Food Advisory Committee for the opportunity to be here today and to present the new data that Procter & Gamble has obtained on olestra since it was approved for use in savory snacks in January of 1996.

[Slide.]

Since approval, Procter & Gamble has conducted four placebo-controlled or clinical studies to determine

just exactly what consumers experience when they eat olestra snacks. These studies involved more than 4,400 subjects. We applied placebo controls and randomized clinical approaches to study real life snacking. We did this so we could determine exactly which responses, if any, could be attributed to olestra snacks.

[Slide.]

These new studies show that olestra snacking does not cause diarrhea or increased abdominal cramping. They show that few, if any, additional GI symptoms can be attributed to olestra snacks and that any such symptoms that do occur have no impact on the daily lives of those consumers.

These data have been submitted to the FDA, and they will form the basis for what we will review over the next two and a half days.

[Slide.]

In addition, we are conducting two types of post-marketing surveillance. In the first type, the more traditional form of surveillance, we collect and analyze information from consumers who call olestra's toll-free lines reporting adverse GI symptoms which they associate with consuming olestra snacks. These reports are all reviewed by health professionals on our Medical Affairs staff. These reports are reviewed by a five-member external

advisory panel, and all of this information is submitted quarterly to FDA.

Nearly 100 of these callers have been tested under placebo-controlled conditions to determine if their responses could be repeated. They could not.

[Slide.]

For the second type of surveillance, the investigators from the Fred Hutchinson Cancer Research Center are actively monitoring the food and snack intake patterns of over 6,000 people nationwide. They are also monitoring the blood, vitamin, and carotenoid levels of those people.

You will see the first data from this study tomorrow. Even though it is preliminary, the results from the first year at the sentinel site are very reassuring.

In aggregate, we believe this new data provides us with even greater certainty that olestra is safe.

Now, I would like to share with you the schedule of presentations and what is going to be covered in those over the next two and a half days.

[Slide.]

First of all, this morning, I am going to provide a little more background. Then, Dr. Zorich, the Director of our Medical Affairs staff, will review the controlled clinical trials that we have conducted to further our

understanding of the GI effects of olestra, specifically when it is consumed as savory snacks.

Next, we will review our data from the post-marketing surveillance programs. Dr. Zorich will introduce this and review the system that we use for the collection and analysis of these consumer reports.

Then, Dr. Judith Jones, formerly with the FDA surveillance group, and now with the Degge Group, will discuss some of the constraints which we are presented with in the analysis of passive surveillance data.

Finally, Dr. Robert Sandler, Professor of Medicine and Epidemiology at the University of North Carolina at Chapel Hill, will provide an analysis of the consumer reports which P&G has received over the last two years. Dr. Sandler is Chair of the five-member review panel that looks at all of these reports.

He will describe in detail the types and numbers of reports which we have received, and he will present the results of the five-member review panel's analysis of this data.

Following Dr. Sandler, we will hear from three other individuals who are not shown on this slide. First, we will hear from Ms. Teri Butler, a Columbus resident, who is someone who called us and reported an adverse GI complaint, and then participated in our re-challenge study.

Second, we will hear from Dr. Juling McClung, Chief of Pediatric Gastroenterology at Ohio State University, who will report on the clinical experience in Columbus, Ohio, during the olestra test markets.

Finally, we will hear from Dr. Robert Drotman, of Frito-Lay, who will present Frito-Lay's analysis of their test market and national expansion experiences.

[Slide.]

Tomorrow, Dr. John Peters will present a summary of our analysis of the recent literature regarding the chronic health effects of carotenoids. He will also provide an introduction to the active post-marketing surveillance programs.

Tomorrow morning we will also hear from two individuals not shown on this slide, Dr. Gil Omenn, of the University of Michigan, and Dr. Allen Ho, from Pittsburgh, who will talk about their perspective on the relationship of carotenoids in chronic disease.

After Dr. Peters, the investigators from the Fred Hutchinson Cancer Research Center will present a review of the design of the active surveillance program and the results from the first year of surveillance at the sentinel site in Indianapolis.

Then, two more individuals not shown on this slide will speak. Dr. Tom Ciulla, from Indianapolis, and Dr.

JoAnn Curran-Celentano, from the University of New Hampshire, will review the results of their recent report which we have just completed, where they have looked at the relationship between various dietary factors and lifestyle factors including olestra intake and the level of carotenoid pigments of the eye.

Finally, on Wednesday, Dr. Greg Allgood and Lisa Papa will present an analysis of the new GI data and the implications which we believe that has for the information label which currently appears on olestra snacks.

Before I go any further, I would like to review what olestra is and why we feel it is important. Dr. Rulis has already shown you the chemical structure of olestra. I am going to provide a bit more of a layman's point of view of what it is.

[Slide.]

It is a no-calorie cooking oil. It is made from sugar and vegetable oil which is combined in a way to make a bigger molecule. This molecule is so big that it isn't absorbed or digested, and therefore it passes through the GI tract unchanged. Therefore, it provides no calories and no fat.

It has the same cooking properties as fat, so when it is used to prepare savory snacks, it provides snacks that have the same taste and texture as regular, full-fat snacks,

but without the fat calories.

If you indulge me for a minute, I am going to say a little bit about why we feel this is important. I understand it is not the purpose of this committee to talk about benefits, but if you will indulge me, I am going to say just a word about it.

We think it is important because fat intake in this country is still too high today. High dietary fat increases the risk of obesity, heart disease, and some cancers. Obesity continues to increase and looms as a major public health issue of the 21st Century. Fifty-four percent of adults in this country are overweight, 25 percent of children are obese, up from 15 percent just 10 years ago.

The striking increase in obesity in children is truly frightening because it appears that obesity in youth predicts obesity as an adult. High-fat, calorie-dense foods contribute to the development of obesity, because the body doesn't regulate calorie intake from these foods as well as it does from foods that are lower in fat and calorie density. This leads to overeating, one of the main contributing causes of obesity.

Fat-modified foods, like olestra foods, can play a role, a tool in helping people reduce fat and calorie intake. These foods with fewer calories and good taste that people will accept may play a key role alongside with

increased physical activity, in preventing the development of obesity in the first place.

[Slide.]

Olestra snacks can provide a tool, a healthier choice for occasions when people want to eat a savory snack. Ten grams of fat is reduced to zero, and importantly, calories are cut in half. This 10-gram reduction represents one-eighth of the daily fat intake of the average person.

[Slide.]

We, and others, have studied how fat-reduced foods, including olestra foods, how people respond when these foods are put into their diets, and I just show here a number of publications, and some of the olestra publications are quite recent. I just want to talk about two examples, the last two, the two most recent ones here.

The study with Debra Miller and Barbara Rolls was a 10-day study in potato chip eaters. It showed that most people did not eat more olestra chips when they were provided the opportunity, and all participants reduced fat and calorie intake when eating the olestra chips.

In another study, the last one on the list here, conducted by Jim Hill at the University of Colorado, and just published last week in the American Journal of Clinical Nutrition, daily fat intake was reduced by 23 grams and calorie intake by 188 grams when olestra was used to replace

one-third of the dietary fat in normal and obese men and women.

In all of these slides that I have shown, there is one overwhelming conclusion. Foods with olestra can and do help people reduce fat and calorie intake. Olestra adds a new option for making reasonable food choices.

Now, I would like to spend just a few minutes and go back and review the basis for FDA's approval of olestra. These were described in detail by Dr. Rulis, and they were described in detail by the Federal Register document signed by Dr. David Kessler when olestra was approved on January 24th of 1996.

[Slide.]

After a thorough review of the data, FDA concluded that olestra was not absorbed or metabolized, wasn't toxic, carcinogenic, genotoxic, or teratogenic.

[Slide.]

FDA concluded that olestra does not affect water-soluble vitamins and minerals, such as vitamin B12, folate, calcium, iron, or zinc. It was further concluded that any olestra effects on the absorption of the fat-soluble vitamins A, E, D, and K could be compensated by the addition of those vitamins to the olestra foods, and the olestra regulation spells out specific levels, as Dr. Rulis showed, for the addition of those vitamins.

[Slide.]

With respect to carotenoids, after careful review of the literature in this area, including consultation with the NIH, the FDA concluded that it was not necessary to add carotenoids to olestra-containing foods to compensate for any effect of olestra on the absorption of carotenoids from foods eaten with the olestra snacks.

FDA acknowledged that the epidemiologic evidence shows an association between diets rich in fruits and vegetables and reduced risk of chronic disease, however, it is unclear whether that effect is attributable to the carotenoids themselves.

FDA further noted that the effect of olestra on carotenoids may well be within the normal variation due to diet and other factors which influence bioavailability. In other words, olestra was no different from any other dietary factors that influence carotenoid status on a day to day basis.

[Slide.]

At the time FDA approved olestra, it concluded that olestra may cause GI effects due to the fact that it is not absorbed and it will be present in the stool. This conclusion was based on studies where olestra was consumed every day, at every meal, for eight weeks, for 168 consecutive meals.

FDA concluded that the observations in these studies did not present any evidence to suggest adverse health consequences. Further, they concluded that olestra did not cause diarrhea, and that there was no significant evidence of water loss, dehydration, or electrolyte imbalance.

FDA concluded that the effects observed in the available data were not a safety concern, even among subpopulations, such as children and the elderly.

[Slide.]

As Dr. Rulis said, FDA further concluded that olestra foods should bear a label disclosing several facts that it considered pertinent at the time based on the data that was available.

FDA clearly stated that this label was an information label, not a warning label, and it was not being required on the products to ensure safe use. This was an interim label, and FDA requested comments on the need for the label, the adequacy of its content, the choice of words used, and the configuration of the label.

P&G and others have submitted data and comments on this interim label, and on Wednesday, you will hear an analysis by P&G of our interpretation of that interim label in light of all the new data which is now available.

[Slide.]

In summary, as Alan has already said, FDA concluded that olestra was safe for use in savory snacks. The agency required an interim label and post-marketing surveillance, and they said that they would reconvene this committee in 30 months to review the results of those post-marketing studies, and that is what we are here to do, to review the results of the post-marketing studies.

Before we go into the data, I do want to briefly cover a couple of other key events which followed the approval of olestra.

[Slide.]

In February of 1996, following the approval of olestra, Procter & Gamble initiated the construction of a plant which would provide adequate olestra for national snack manufacturers. This plant was completed in January of 1998.

During the construction of the plant, Procter & Gamble manufactured olestra in a pilot plant facility. In April of 1996, the first test markets were started by the Frito-Lay Company in Grand Junction, Colorado, Cedar Rapids, Iowa, and Eau Claire, Wisconsin.

In October of '96, Procter & Gamble launched its first test market of fat-free Pringles in Columbus, Ohio, and in February of 1997, Frito-Lay, Procter & Gamble, and Nabisco test-marketed products in Indianapolis, Indiana.

In February of 1998, with a national scale supply of olestra available, and successful test market results in hand, the national expansion of olestra snacks was begun. Frito-Lay has led the expansion of olestra snacks nationwide with the introduction of their products.

Frito-Lay reports that the consumer response to these products has been extremely positive.

[Slide.]

So, in summary, I would just like to point out that the consumer response to olestra snacks is enthusiastic. Frito-Lay reports that they have sold over 70 million bags of these products containing over 400 million servings in just the last several months.

Our new clinical study data show that olestra snacking does not produce any meaningful increases in GI symptoms especially no increases in diarrhea and cramping. These data have been very useful in interpreting the significance of the 800 number calls we have received.

The active surveillance program, which Procter & Gamble committed to conduct, and is now being conducted by the investigators at the Fred Hutchinson Cancer Research Center, the first year's results are reassuring.

As you will see over the next two and a half days, all of this data continues to confirm that olestra is safe.

I would now like to turn the podium over to Dr.

Nora Zorich. Dr. Zorich is the Director of our Medical Affairs staff on olestra. Dr. Zorich has also managed the worldwide drug surveillance activities for Procter & Gamble, and she has managed our olestra surveillance activities, as well as the GI clinical program which you will hear about today.

Dr. Zorich.

DR. ZORICH: Thank you.

Good morning. Actually, I am very grateful for the opportunity to present the data that we have been collecting since the last time we met about two and a half years ago. As you heard, we have been pretty busy, we continued to collect data -- I hope that is going to be fixed --

[Pause.]

DR. ZORICH: I think with that nice, smooth start, let me start over by saying that I really welcome an opportunity to be here and share the data that we have been collecting over the last two and a half years. We have been pretty busy, we have been continuing to collect a lot of information about olestra since that time.

[Slide.]

These are basically the three studies that we are going to be covering this morning. The first study looks specifically at objective measures of stool composition and

then the next two are really where I want to focus a lot of my discussion today, because in contrast to the data that was submitted prior to approval, which these were nutritional studies by design, they were not designed nor meant to address what would be the GI experiences in people who are eating as intended with snack foods.

These two studies were designed to better understand GI symptoms with snacking, and there is a single, what we call an acute consumption study, single, unlimited snacking, and then a six-week basically chronic, longer term, unlimited snacking study.

[Slide.]

The findings from these studies you will see show that olestra consumption results and predictable effects on the stool, and olestra snacking, the intended use of the products does not produce any meaningful change in GI symptoms.

[Slide.]

Now, were we surprised? The answer is no. At the time of approval, of course, we had a very good understanding of the effect of olestra when people would be eating it. In addition, we had a lot of animal data, data in three species, lifetime studies demonstrated that olestra had no negative impact on the GI mucosa, there was no injury, specifically, no inflammation.

We had done studies to verify that olestra itself was not going to be fermented in the body, was not broken down in the bowel by the microflora, and we had also conducted studies in humans to demonstrate that eating olestra had no negative impact on the colonic microflora themselves.

We also did two studies in man, and studies have also been published by Unilever demonstrating that olestra has no negative or adverse consequence on GI transit, and importantly, several studies in animal and in human demonstrated that olestra has no negative impact on macronutrient absorption, in other words, there is no malabsorption of carbohydrate, protein, or fat when people are eating olestra.

[Slide.]

Our conclusion at the time, and what you heard me say, was that olestra passes through the GI tract unchanged with no harmful GI effects. Basically, it's inert.

[Slide.]

So, with that as a backdrop, let's look at the first study that we conducted to extend our understanding of olestra.

[Slide.]

If you assume that olestra is inert, as I just told you it is, then, if you look at what happens to the

stool when people are eating olestra, you would predict that it would increase the stool weight. You eat a given amount, it will appear in the stool, and that the amount of stool weight that you see should be proportional to how much people ate.

We did not anticipate any meaningful change in stool water output because olestra, as I just explained to you, the mechanisms by which additional stool water are added to our result from consuming a product or there is injury, those mechanisms we had clearly addressed, and there was no evidence that stool water would be increased.

The only other possible effect could be an osmotic effect, and we addressed that in this study. We also believed that because olestra will add to the stool bulk, it could change the viscosity of the stool and you would see that probably after several days of consumption considering that normal GI transit can be anywhere from one to three days.

Now, because olestra adds to the bulk of the stool, we anticipated that there could be an effect on bowel movement frequency, but that effect would be in the normal range. So, we worked with Dr. Ralph Giannella. He is at the University of Cincinnati, and he is an expert in disease, diseases of the bowel, in particular, diarrhea, and we asked him to work with us in the design, execution, and

analysis of the study I am about to show you. Unfortunately, Dr. Giannella is in Europe right now, but he did present this data just last month at the annual meeting of the American Gastroenterologic Association, and the data has been submitted for publication.

[Slide.]

Now, the objective of the study was to look at the objective measures of stool. We looked at the number of daily bowel movements in this group of people, total daily stool output. We also importantly looked at stool, water, and electrolyte content.

Now, why are we looking at these objective measures? I know there is a couple of gastroenterologists on the panel. For those of you who are not familiar with this area, these objective measures are the ones that clinicians use to make an assessment of whether or not alterations in stool are such that there is a possible negative health impact. So, we wanted to specifically focus on these objective measures.

In addition to that, we wanted to measure stool viscosity because we thought with feeding two different doses of olestra, we should see a dose-dependent stool softening if our prediction about olestra is correct.

Now, as I mentioned, Dr. Giannella just presented this last month, and his conclusions at the time were that

olestra does not result in any negative consequence in any one of these objective measures, in fact, the effects were quite predicted.

[Slide.]

Now, the study was randomized and double-blinded, with parallel groups, but in addition to a placebo group, people eating conventional potato chips, we also introduced a positive control, and the positive control used was sorbitol.

You may be familiar with sorbitol. Sorbitol is one of a family of sugar alcohols used as sweeteners. Sorbitol, along with the other sugar alcohols, have well-described osmotic effects that result in predictable changes in increased stool output and increased water in the stool.

Now, subjects were housed for 12 days, and we monitored all the laboratories, so each bowel movement could be collected and then each bowel movement was analyzed for weight, stool water and electrolyte, and in addition to that, we also were monitoring BM frequency, and then we monitored the viscosity of the stool.

Now, we included 66 subjects, and we enrolled a broad range of adults, and had good distribution among both genders.

[Slide.]

Let's talk for a minute more about what people

were eating. During the study, the first six days, it was an acclimation and baseline period, so we collect data from these people to understand what their normal bowel habits and stool water content was like. During this period, they ate an ounce and a half of plain sugared candy in the morning and 5 ounces of potato chips in the afternoon.

I am going to leave the mike, but hopefully, you will be able to hear me.

DR. BRANDT: You can't leave the mike because you don't get recorded, so use one of those table mikes.

DR. ZORICH: Thank you. Good suggestion.

This is basically 5 ounces of potato chips that they ate in the afternoon every day, and an ounce and a half of sorbitol candy. Again, the placebo groups, these are conventional potato chips and regular sugared candy.

Now, during the treatment period, people in the placebo group continued to eat the same products that they were eating during the baseline period. The people in the 20-gram-a-day, one dose of olestra, they ate placebo candy in the morning, and in the afternoon, half of the chips they ate were made with olestra, and the other half were conventional chips.

The 40-gram-a-day olestra group, they are eating the placebo candy in the morning, and all the chips that they ate each day, on six consecutive days, were made with

olestra.

Clearly, the sorbitol group, they are eating the sorbitol candy in the morning and conventional chips in the afternoon.

The one thing I do want to mention about the sorbitol -- luckily, I have got a backup in case I spill -- these are "Smarties," and I am not exactly sure who makes them, but I am sure they wouldn't want their name mentioned anyway. This is an ounce and a half of these candies.

Now, sorbitol-containing products are required by regulation to have an information statement about GI symptoms if the amount that people are likely to ingest is 50 grams or greater. The amount that we used here, 40 grams, and the amount that you see here, this would not require an information label if this were sold as packaged.

[Slide.]

This is the first objective measure. We looked at total stool output. Let me first take you through -- these slides will look similar -- the placebo group is shown in white, the olestra groups are shown in green, and the red demonstrates the sorbitol group.

Here, we are looking at the same data during the baseline period for these same participants, the same subjects, so each one of these hatched bars shows you the baseline period for the same group of people.

Here, we are looking at stool output in grams per day. All of the analyses I have done here are relative to the placebo group, I think are probably the most conservative analysis. What you can see is the total stool output does increase when people are eating olestra, and sorbitol increases quite a bit more.

For a perspective, I have added now a bar at 20 grams a day for this group and 40 grams a day for the olestra group, and what you can see is that relative to the baseline period for the same people, the additional stool output is mostly accounted for here by the additional weight of the inert olestra, just as you would anticipate.

[Slide.]

Now, we are looking at the frequency of bowel movements, another objective measure, and again we monitored all bowel movements so we have this number precisely. Here, placebo, olestra in the green, and the red, and the corresponding baseline period in hatch.

What you can see is that relative to the placebo group, you had about not really a doubling, but more bowel movement frequency, about 1 1/4 here compared to 2 at 40 grams a day.

But now if you look again at the baseline period for both groups, you can see that people eating 2 1/2 ounces of olestra chips a day basically did not have a change in

their bowel movement frequency relative to what their experience was prior to being in the treatment period, and at 40 grams a day, they go from about 1 1/2 to 2 bowel movements, so it is about an increment of a half a bowel movement a day.

[Slide.]

Here, we are looking at stool water output, and you can see that there are changes in stool water which are pretty modest with the exception of the sorbitol, and again, relative to the placebo group, what you see actually has more desiccated stool, there is about just under an ounce to about an ounce and a half difference from placebo.

Again relative to the baseline period, the people in the 20-gram-a-day group, they are excreting about two teaspoons more water a day, and relative to the 40-gram group, this is about 2 1/2 tablespoons more water a day on average. Contrast that to the sorbitol group, with the known osmotic effect, it showed up here nicely with about 11 ounces more of water each day in the stool.

[Slide.]

The important thing is whether those incremental changes in water resulted in watery bowel movements, and I show you that data here. You can see that most of the bowel movements actually with the sorbitol group were watery bowel movements as you might imagine from the data I just showed

you, and we did not see watery bowel movements in any of the olestra groups. There is one bowel movement in baseline and one at the 40, so there is no evidence of watery bowel movements on olestra.

[Slide.]

Now, importantly, we looked at the stool viscosity on each day of the study. I am going to take you through this because it is not something that people probably think a lot of, but you can actually measure the viscosity of the stool, and this is a peak force measurement.

I am presenting it here on a log scale, but what you do is you take a sample of the stool and then a probe is driven into the sample, and you can actually look at the force that it takes to displace the stool in this apparatus. So, it is a measurement of force to take the probe and drive it into the sample stool.

When you do that using the Stevens texture analyzer and getting these numbers, you can see numbers around 3 on the log scale represent firm stool. Numbers between 3 and 2 1/2, these are softer stools. Between 2 1/2 and 2 these are looser stools, and as the numbers decrease, you have more and more watery stools as you get closer to 1.

Now, remember that the first six days, people are all eating the placebo products. You can see during that period they all basically had firm stools. Then, day 7 is

the first day that people are eating the test products.

As you can see, with sorbitol, there is almost an immediate response, and that is because the sorbitol has an osmotic effect, so there is this addition of water into the stool, and it passes rapidly through the bowel.

With olestra, we saw, as we predicted, a dose-dependent softening which was accompanied by a lag here of getting into one, two, and, in this case, perhaps three days before you saw the dose-dependent softening.

Now, at the 20-gram group, you might say that that is a softening. Some of this difference here, or course, is exacerbated by the fact that the placebo people eating lots of chips and candy are actually having more desiccated, firmer stools, but I do think that you can support that there is a difference here in the 40-gram group. It levels off after the second and third day of dosing. I think that that lag period is just as we would expect from normal transit.

[Slide.]

Now, why do we see that dose-dependent -- actually, this is a slide that I have taken the liberty of reproducing from Dr. Joanne Lupton's review that was shared with the committee two and a half years ago, and it's not new, but it's worth repeating, is that if you look in our study, during the baseline period, the average stool weight

was about 140 grams.

So if you are eating 40 grams now of olestra a day, you are adding another 40 grams to 140-gram mass, so about 30 percent of the stool is now actually going to be olestra.

The 20-gram-a-day group, they are adding about 20 grams to 140 grams to a mass, so about 15 percent of the stool is actually olestra. So, it is not surprising, using a very sensitive thing like the Stevens texture analyzer that you do see dose-dependent changes in the stool consistency.

[Slide.]

So, from this study, we concluded that olestra consumption results in predictable changes in the stool parameters that are consistent with normal physiologic processes. We didn't see any meaningful increases in the stool water output, total stool output, or the number of bowel movements people had. Consequently, we can say that olestra does not cause diarrhea.

[Slide.]

I am going to return to this morning's outline, and I want to now bridge to what I think are the most important studies that we will show you from the perspective of GI. These are the studies that we conducted to understand what would be the consequences of eating snacks

under more typical or even unlimited snacking conditions, but snacking conditions.

Now, the first study was a single eating or acute consumption study. At the time that I conducted this study, I was really looking at what would happen when you just gave somebody a large bag of chips and said go ahead, and what exactly would or would not be attributable to those snacks.

It turns out that as we look back, now that we have the 800-line data, it is even more important to have this study as a backdrop because, as you will see, the majority of calls to Frito-Lay and Procter & Gamble and to CSPI have been from people who have said they have eaten the product once. So, let's now look at that study.

[Slide.]

We are trying to look at a single snacking experience, so the objective was we wanted to determine the effect when people would eat the snacks as they normally would and then look at the GI effects that would be measured.

What we found is there was no difference in the type of symptoms people reported, how often they reported, and importantly, we found no difference in the severity of the symptoms that people report.

Now, Dr. Laurence Cheskin unfortunately couldn't be here today, he will be at the meetings tomorrow, he is

actually in a very unique position to be studying olestra with us, and approached us because he was very interested in olestra, because he is a gastroenterologist, but he also manages the Hopkins Weight Management Center.

[Slide.]

As was mentioned by Dr. Rulis, this study was just published in January in JAMA. The study was randomized and double-blind with a placebo control. Again, these people are eating conventional, full-fat potato chips.

Now, we gave the people a 13-ounce bag. That is one of those jumbo bags -- and I am going to stay at the podium for this one -- but basically, this is what it looked like when people came to the site, and they were given this bag along with the study case report forms in a shopping bag, and the same reaction. I was at the sites, and people had the same reaction because they thought we were probably going to give them a little sample, but this is what they got.

The study was tightly controlled for compliance, and we wanted to ensure that because even though the study was conducted in a somewhat unusual setting, in a movie theater, that was the best way to ensure that the study was well controlled, and we could have people at ease eating the snacks as they normally would.

So, we monitored the theaters and we did not

permit any sharing of product. In fact, people were asked to sit a seat apart, and then we had theater monitors in all the time. Dr. Cheskin and I personally went into every theater every time we had participants there, and assured that there was compliance, and there was actually very good compliance, even the teenagers who were in the study watching Space Jam complied with our study.

Now, in addition to the 13-ounce bag of chips, everyone was supplied a 32-ounce drink, but no other food was available. We closed down the theaters. It was only open to the study participants, so there aren't other people there not in the study.

Now, people were called back two to four days, and the reason we selected that window, as you just heard from our previous study, we wanted to allow for a sufficient amount of time for olestra to transit the GI system, but not for so long that people wouldn't be able to recall. As Dr. Rulis mentioned, actually, 90 percent of the people were called back within the window specified in the protocol.

In addition, though, just to ensure that we didn't miss anyone wanting to call us, everyone had an 800 line that they could call anytime day or night to get to the study staff.

[Slide.]

Now, the study was large. We had 1,092

participants who completed, and you can see that we were able to recruit some teens and people over 65 apparently aren't as interested in going to the movies, but we did have some people, and we did have a good balance on gender.

[Slide.]

Now, this is how much people ate of that bag you just saw. We knew how much people ate because we weighed the bag prior to the study, and then we stood by the doorways and as they came out, we took their bag back, and there was only one spill in the entire 1,100 people participating. So, we knew exactly how much people ate by weight.

You can see from this graph. This is the 25th percentile of consumption, and this, the 75th percentile. The median here is shown in the black bar, and the lines coming from the box show you the full range of consumption. Median consumption is about 2 1/2 to 3, a little higher on the placebo, and the 75th percentile is 4 ounces.

As you can see, that means about 100 people are eating more than 4 ounces in this study. In fact, only one person was actually able to eat the whole bag, although others tried.

[Slide.]

The percent of people having symptoms is shown on this slide, so I have percent of subjects. I am showing you

here only the five most commonly reported symptoms, but we allowed people to use whatever words they wanted, and captured all verbatims, so that we can know specifically if there were any unique symptoms reported in the people in the olestra group, and there were not. There were about 20 verbatims that were used, and they were all, as you are seeing here, equally reported by both treatment groups.

One thing I would like to point out here is that you see 16 percent of the people on olestra and 18 percent on placebo, are we saying that 18 percent of these people had symptoms because they ate full-fat chips? I am not saying that because the study would not support that statement, nor do I need to say that. I think the more important thing is that this 18 percent undoubtedly reflects the high background rate of symptom reporting in the general population.

[Slide.]

Importantly, did people have symptoms more? No. In fact, it was higher in the placebo group, but these are not different statistically. We wanted to also know were the symptoms different in any other way. So, we asked people to rate their symptoms, and we saw that there were not differences in the rating of symptoms. In fact, there was only one woman who said she needed to see her physician for GI symptoms she experienced, and that was somebody who

was actually in the triglyceride group.

Now, I want to tell you that we also looked at whether the symptoms had a different onset or a different duration, and looking at all these parameters, we were not able to distinguish differences in the kinds of symptoms, reset, duration, or the severity.

[Slide.]

I want to tell you about I think one of the more remarkable calls that we had during the study, and this was from a mother of a 13-year-old male who had been at our study, in fact, watched Space Jam, and he ate about 10.2 ounces of chips during the study.

If I haven't said this before, I think it is worth your knowing that that bag contains about 110 grams of either olestra or triglyceride. That is how much fat is in that size of chips.

So, he ate a pretty good amount of chips, and the mom called us the next day on the 800 line, and she said he had had kind of a rough night, some abdominal upset, but he went to school because he wasn't doing too bad, but at school he had diarrhea and cramping, and he wanted to come home because he had soiled himself.

Well, we took that information and then later on when we proceeded to close the data set, lock the data, we saw that the boy actually had been in the full-fat chips,

and the reason I bring up this particular experience in this subject is that this is an excellent demonstration of why controlled studies are necessary.

Had we not been doing a controlled study without a placebo leg, if the same event could have occurred, of course, it could have, it was just random that it occurred, we would have attributed this perhaps to our product, but in fact, this is an event that simply is occurring. Whether it is because of how much he ate of the chips, I am not going to make that causal assessment, but clearly, his experience had nothing to do with olestra.

[Slide.]

We also looked at whether or not people who ate more in general had more symptoms, and what we found is here I am showing chip consumption in 2-ounce increments, and overall, there is no good pattern between describing symptoms and the amount people ate.

You can see that there is more symptom reporting in this very upper end consumption, but importantly, that is equally distributed between olestra and the full-fat chips.

[Slide.]

So, we concluded from this first look at how people eat snacks, and this a single eating incident, which is very often just the way people do snack unlimited amounts on a single occasion now and then, that eating olestra

snacks will not result in increases in type frequency or severity in this circumstance and in this study.

[Slide.]

Now, we have just reviewed one type of design to look at unlimited snacking, and I want to move on to our six-week study where we allowed people to eat snacks in their home as often as they chose to, and in addition to eating snacks, we also monitored their GI symptoms. The results actually were very comparable.

We wanted to monitor symptoms in a setting where we would create basically a population of households eating lots of olestra snacks. How do you accomplish that? We accomplished it through several different means.

The first thing is we recruited people who self-identified themselves as liking to eat snacks often. They had to have been purchasing snacks at least four times in the last month. It was the minimum criteria for participation by the households.

Then, we asked them, are you willing to eat olestra, there has been some controversy, and are you willing personally to eat olestra and to feed it to your family members. They had to say yes, they would, they weren't concerned.

Then, we gave them basically unlimited free snacks to take into their home, incorporate into their diet the way

that they normally would. So, everyone in the household had to sign up for the study.

[Slide.]

Now, what we found is that most consumers actually did not experience any change in terms of GI symptoms or GI effects, and importantly, the subjects who did note differences reported no negative impact on their daily lives.

Now, Dr. Robert Sandler, who is the investigator for the study, he is a Professor of Medicine and Epidemiology at UNC, he actually is here, and you will be hearing from him because he is also the chairman of our post-marketing surveillance committee. So, Dr. Sandler is here, and he has just presented this data, in fact, at the annual meeting of the American Gastroenterologic Association last month in New Orleans, and we have submitted this study for publication.

[Slide.]

Again, it was a randomized study with a placebo control, and the placebo people are eating full-fat chips, and it was a parallel design. Now, in addition to keeping track of how much people ate, we also kept track of a variety of other measures.

How did we accomplish that? Within each household we designated a household contact who had to be an adult.

This person was the person responsible to come to the site each week for six weeks. This person also assured that the diaries are being completed, and if there are small children in the household, this person was responsible for assisting the children in the completion of their diaries.

In addition to meeting this household contact, we also had all family members come in on the very first visit to, of course, give their informed consent, and also we just wanted to verify household membership. So, we did meet every single person in this study at the study site.

Now, we collected symptoms, and addition to collecting symptoms, importantly, we asked people to tell us whenever they had symptoms whether the symptoms had any impact, and beyond that we also collected any use of medications, if they were going to a physician, if there were hospitalizations or any other important event occurring in the household.

Now, we carefully double-blinded this study. I am going to take a few minutes to tell you how we did that.

[Slide.]

The household contact came to the site, and this is what they saw. Basically, you would not be able to distinguish these packages from what is on the shelves right now. The only way that within the study we could distinguish what was going into a household was the bar

code, but neither the participants in the study nor anyone at the site or executing the study had the decode to the bar code until after the data was locked, so if you are in the study, and you are a household randomized to olestra, when you go to the site and you see this on a shelf, you can check off give me whatever products you like, and when you took these products home, inside those bags are olestra chips.

If you are in the control group, you come to the site, you look at the same shelf. It looks exactly the same, you can't tell the difference. When you take these products home, what is inside the bag is triglyceride chips.

Now, we also gave people the option of selecting regular potato chips and regular marketed products, and we did that so they could have an experience as if they were shopping, being able to select from each one, and then not being forced to eat one or the other, and still getting free product. In this way, if they are switching, we can also tell.

Now, we allowed people to select eight of these per week, eight bags or canisters of Pringles, going from about 6 ounces to 9 ounces in each bag. Now for your perspective, if you look at data that has been published by the Snack Food Manufacturers of America, the Snack Food Manufacturers say that the average household who takes home

snacks take home two bags per month, and the 90th percentile or the very heaviest snacking households take home about two bags in a week.

So, when I said that we deliberately tried to create a population of heavy snackers, we did this by essentially giving people four times more than what the Snack Food Manufacturers call a heavy snacking household, and 16 times more than the average snacking household.

[Slide.]

Let's look at the participants in the study. One of the goals of this study was to include a substantial number of children, and we were able to accomplish that, and we did that by recruiting households who had children, and we met our goal. You can see children age 2 to 12.

The other aim of the study was to get in a substantial number of people on the other end of the age spectrum, and again we did that by recruiting families who had a broad range of ages within their households. You can see that we did have good representation of people over age 65.

We had 3,181 evaluable subjects in over 1,000 households. Importantly, there were no exclusions based on the person's past medical history, their current medical history, or any medication use. So, in every sense, this is an all-comers study, and we also included everyone in the

household, so even if there were people in the household with medical problems, they were included and the snacks were available to them if they wanted to eat them.

I am going to show you how much people ate.

[Slide.]

This is a breakout of the number of people, and here I am showing you the cumulative consumption of chips in ounces over the course of the six weeks. What you can see is that there is a broad range of consumption fairly comparable between the two groups except a little bit more eating of the triglyceride snacks in the very highest group. Let me talk about those people in just a minute.

You can see most of the people here, 90 percent of the people in the study are eating 70 ounces or less with the median being just around 30 ounces over the course of the six weeks. I think it is also worth mentioning that virtually everyone in the study ate olestra-labeled products. There were only about 15 people who did not, so we had excellent compliance with our study.

This group, this upper 10 percent of eating, these are the upper 10 percent in the study in terms of their consumption, they ate actually over a very broad range, from 70 ounces up to 250 ounces over the course of six weeks. The majority of the people even in this group, though, are eating between 70 and about 125 ounces. There are just a

few outliers in here at the very, very upper end of consumption.

[Slide.]

Now, that shows you how much they ate over the course of the study. How much did any one eat on a given day? I have averages here. For any one day of the study, the median eaters were eating about an ounce and a half, and that is true for teens, adults, and elderly, pretty comparable between the groups, children eating a little bit less, just as you would expect them to based on body weight, and the 90th percentile, this is that upper 10 percent of the group, based on how much they are eating, they are eating more. They are eating between 2 1/2 and 3 ounces a day, fairly comparable, and a little bit more eating here on the control compared to the olestra.

We also saw very comparable between gender.

[Slide.]

Now, how much is that relative to what people are eating right now? I told you that we supplied them more product than people typically eat. Did that translate into actually more eating than what people typically eat? We believe yes.

Probably the best database that looks at food consumption in the U.S. is MRCA, and the FDA, in fact, relies on them quite a bit for their menu census data, and

the reason is that MRCA goes to the trouble of collecting menu census rather than recall, and these data are geographically and demographically balanced across the U.S., so it is probably one of the best databases that we have.

If you look at MRCA, and you say right now how many ounces of snacks are people eating in the general population in the United States, what I have done is I have taken the MRCA data and I am looking at it for six weeks, so that we can do an apples to apples comparison in our study, which was six weeks long.

Right now in the U.S., MRCA would say that the average person eating savory snacks is eating 15 ounces across nine days in a six-week period. The upper 90th percentile of snacking, these are people who are eating 31 ounces across 21 days over a six-week period. So, the heavy snackers are eating basically every other day, 21 out of 42.

DR. BRANDT: You have five more minutes, Dr. Zorich.

DR. ZORICH: Thank you.

What you see is if you just take the ounces and the number of days, that is about an ounce and a half a day. If you look at our study, our 50th percentile snacker was eating 28 ounces across 20 days, and our 90th percentile, these are people that started at 70 and went up in terms of the ounces, over 35 days or almost every day of the 42-day

period. You can see that we were able to simulate an environment where our 50th percentile snacker actually looks more like the 90th percentile snacker from MRCA.

You recall that this was a deliberate effort on our part, so understand how much they were eating, what kind of symptoms were they reporting.

First, we are going to look at the percent of subjects reporting symptoms at least once over the course of the study, and what you can see is that about 40 percent of these people reported GI symptoms over a six-week period regardless of what treatment group they are in. This again we believe is probably just showing the background level of GI symptom reporting. There are not statistical differences here except that nausea was statistically less common in people eating olestra snacks than triglyceride.

[Slide.]

One of the goals of the study was to look at the extremes of age. We saw no difference in symptom reporting by children or in people over 65 years of age.

[Slide.]

Now we are looking at the percent of subjects reporting symptoms by a dose. As you saw from MRCA, and the way we presented this data, we think in terms of the 50th and 90th percentile of consumption, and so we broke out these data in these 10-ounce increments because that gives

you kind of a realistic look at just how much people were eating, and what you can see is both for placebo and olestra, there is no good clear connection between symptom reporting and how much people were eating, suggesting that for a majority of these people, these are independent events.

There are two statistical differences on this graph at the 30- to 40-ounce breakout, and then you see on this upper end group, these people are reporting symptoms more often. There is a greater delta here. This is partially exacerbated by the fact that the placebo group here is the lowest placebo. It is actually quite a bit lower than the average placebo rate.

[Slide.]

So far we have just been looking at symptom reporting at least once over the course of the six-week study, but it is fair to ask, well, what about people who reported symptoms more than once, and so we looked at that and I am going to show you that on the next couple of slides.

[Slide.]

We looked at the number of symptom days, and you can see that it is quite comparable for olestra and control. Particularly, I want to point out, for looser stools and cramping, there were no differences in symptom days, and

there is only one statistical difference here, more frequent bowel movements, the magnitude of which is about one-day difference, 2.8 in control versus 3.7 days of reporting more frequent bowel movements in the olestra groups.

Now, this finding was primarily attributable to people who are eating the most, and because of that, I want to show you that data from the people who were in this upper 10 percentile. For your perspective, these are people who are eating at least 10 bags.

DR. BRANDT: One minute.

[Slide.]

What you can see is that there are not statistical differences here, but there are numeric differences in how often more frequent bowel movements and looser stools are being reported. This amounts to about three more days out of 42, and this isn't unexpected based on what we know from the first study I showed you.

Basically, at this level of consumption, these people are eating product on most of the days of the study at high level. It is not surprising that they had effects that are equivalent with our stool viscosity changes.

The important thing is that we could understand whether or not these effects had any impact on the people, and what we found was if you look at the impact rating overall, for all subjects, there is no overall difference in

how often people describe their symptoms as having no effect, slight, missed sometime during the day or missed all day, if you look at the percent of symptom days. That is for the overall group. We think that asking people this way is a more sensitive way of understanding whether or not there is impact.

DR. BRANDT: Your time has expired. Sorry.

DR. ZORICH: Could I have a few more since we had that fumbling at the beginning?

DR. BRANDT: I gave you time for that fumbling around, but what do you need?

DR. ZORICH: Two minutes.

DR. BRANDT: Two minutes you have got.

DR. ZORICH: Thank you. I appreciate it.

If you look at the impact reporting for people in this upper 10 percentile, you see the same thing, with most of these being reported as did not affect, and no differences otherwise.

Beyond just this self-assessment of symptoms, we had other data that I explained. We knew if people were taking medications or going to the doctor, and what we can see is that there is no more medication used, and particularly I thought people would want to know about anti-diarrheals, and they were not used more often.

There were no additional physician visits because

of GI symptoms. There is only one dropped from the study for GI, a woman with unexplained abdominal pain, and she was in the triglyceride group.

[Slide.]

Probably the more important thing you can say is these people knew they were in a study to monitor GI symptoms. Every day they filled out diaries, they were being asked all these questions. It is improbable that anyone in the study didn't wonder if they had symptoms if it was because of these chips.

So, an important question is did they keep eating the chips. What you can see, as I have shown you here, in both the total amount eaten and the number of days, that it is virtually the same, if they did or did not report GI symptoms, if they kept eating the product.

[Slide.]

So, what we saw in this study is that there actually was about 40 percent of the people reporting symptoms. That was regardless of what treatment group they were in. The vast majority noted no changes in digestive symptoms when they were eating olestra snacks.

Importantly, even in the people that there were small differences, there is no indication of any negative impact of these symptoms on their lives, and I would like to point out that there was no evidence of any serious effect

that could be reasonably associated with olestra in this study.

[Slide.]

So, we concluded that from both these studies, the single eating and the additional study that we did with unlimited snacking over six weeks, that eating olestra snacks caused no meaningful changes in GI symptoms.

Thank you for the additional time.

DR. BRANDT: You came out with one second to spare.

Questions of Clarification

We are now open for discussion by the committee. Are there questions, comments, whatever? Ms. Richardson.

MS. RICHARDSON: Yes. In talking about the symptoms that people had that had eaten the chips, you indicated that the age range was from 18 to 74?

DR. ZORICH: In the first study?

MS. RICHARDSON: In the first study.

DR. ZORICH: Yes, in the first study, on the stool composition, they were adults. They were housed in the metabolic ward for 12 days. The second study, we included teens, and in the third study we started at age two.

MS. RICHARDSON: In the first study, of those who complained of GI symptoms, did there appear to be more symptoms in any certain age range?

DR. ZORICH: Actually not, no. We have not seen in any of these studies, when we have looked across age range, a collection of symptoms in a given age range.

MS. RICHARDSON: Thank you.

DR. BRANDT: Dr. Fennema.

DR. FENNEMA: Did you make any attempt to determine the effect of olestra on persons which normally had frequent bowel movements per day versus those that had very few bowel movements per day?

DR. ZORICH: We did not specifically enroll people with a distribution of bowel symptoms in the study on stool. We did have a range in that group, but it was between people not having a bowel movement and maybe three a day. Actually, in the baseline period, we had someone with four bowel movements in a day.

However, in the other studies, in the studies where we looked at snacking, we did not exclude anyone with any history of frequent bowel movements, and particularly you may be aware of a disorder called irritable bowel. We looked at the data. There were people in the study who had described themselves as having irritable bowel syndrome, and we looked at symptom reporting within those individuals, and didn't find an increase.

DR. FENNEMA: Thank you.

DR. BRANDT: Dr. Hubbard.

DR. HUBBARD: During your stool composition study, during the baseline period, were they also consuming the chips and candy at that point, or was there any difference between what they were consuming during the baseline period and from the placebo group?

DR. ZORICH: Yes. During the baseline period, in fact, these people didn't know they were in a baseline and then treatment. Every day looked probably from their perspective, unfortunately, the same. They had to eat the candy in the morning, but it was sugared candy, regular sugar, and they had to eat potato chips in the afternoon. So, yes, they were eating those two types of food throughout all 12 days.

DR. HUBBARD: The baseline period, as well?

DR. ZORICH: Yes, every day.

DR. HUBBARD: And when you said morning and afternoon consumption, was it throughout the morning and throughout the afternoon?

DR. ZORICH: No.

DR. HUBBARD: Or at one sitting basically?

DR. ZORICH: They were given an hour to eat this, and they were given actually two afternoon breaks, one at about 3:00 and one at 4:30, but they had to finish it all within those periods.

DR. HUBBARD: And the differences that you showed

between the olestra groups and the placebo group, the statistical significant difference was both with during the treatment period, not compared to baseline, is that correct?

DR. ZORICH: Yes, only during the treatment period. The remainder of their diet was American Heart Association Step 1.

DR. HUBBARD: But would I be correct that if you compared it back to baseline, that there would probably not be a significant difference?

DR. ZORICH: No, the groups were well balanced. They were not different from each other.

DR. HUBBARD: I mean the olestra treatment group back to baseline groups --

DR. ZORICH: They are not different.

DR. BRANDT: Dr. Lamm.

DR. LAMM: In your acute consumption study, you demonstrated that there was no dose-response relationship for symptoms overall. Was there a dose-response relationship for any particular symptom?

DR. ZORICH: No. Actually, we looked at that and did not find a dose-dependent response for any individual symptom.

DR. LAMM: Were there any suggestions of trends?

DR. ZORICH: Our statistician is here.

Did you hear the question, Tom?

DR. FILLOON: My name is Tom Filloon. I am with Procter & Gamble Company, statistician.

The issue is we have done dose-response plots, and when you plot smooth curve fits to the data, you don't see any obvious trends in the data. There is a couple of data points here and there, but it is not clear whether those are random noise in the data and you see random points across both treatment groups.

So to the extent of in the high dose groups, there is only a couple of observations out there, there is no way to determine whether there is any trends. So, it would be an eyeball test. To your point of can you differentiate those trends, there is no statistically significant trends, and then it is a differentiation of what do you see in the data.

DR. BRANDT: Dr. Benedict.

DR. BENEDICT: Just a couple of brief things. Did any of your subjects report hives?

DR. ZORICH: I would like to say that in addition to not seeing hives or allergic response in any of these studies, I have been working on this project since 1991. My experience is probably over 10,000 study participants, and I can say no to that in my entire experience on olestra.

DR. BENEDICT: In the metabolic ward study, did you note any increase in liquid intake over the course of

the study?

DR. ZORICH: We didn't actually monitor input and output. They had free access to -- we didn't monitor input, we did, obviously, the output -- they had free access to fluid available to them, so they regulated their own fluid balance.

DR. BENEDICT: So, there is no way to know whether they compensated for the slight increase of water output, but one would assume that they did?

DR. ZORICH: These people were absolutely fine and healthy, and there was no -- I mean we did physical exams and chem 20's on them before and after, and there was no evidence at all of any either their health status or by the chemical measurements of their blood.

DR. BENEDICT: And, finally, the household study included some people who might logically be taking some fat-soluble drugs, coumadin, et cetera, and might be monitored over the course of the study just accidently. Did you notice any certainly just trends for changes in blood levels, did that get reported to you at all?

DR. ZORICH: There were people on a variety of prescription products, and we had no reports or any indication of any lack of efficacy or problem with their products. We did monitor all their physician visits, so I would say no, there was no indication of any problem.

DR. BENEDICT: Just to make sure that I understood you correctly, you actually looked at the numbers?

DR. ZORICH: No, I did not look at the numbers. What we had data on is whether or not their physician had told them there was an issue or a problem.

DR. BENEDICT: Thank you.

DR. BRANDT: Dr. Blackburn.

DR. BLACKBURN: I would like to ask Dr. Zorich or the statistician, in the acute consumption study, what were your power computations, what were your chances of detecting a relative difference if it was there, and what assumptions were the power computations based on?

DR. ZORICH: The power prior to the participation in the study was based on symptoms being prevalent at about a 10 to 15 percent rate in the background, and then we sized the study initially to look for a 5 percent delta. We did not have as many people participate as we had hoped. We were initially planning for 1,700.

The important thing I think is that, looking at the observed data with the fact that actually, in olestra, it was 2 percent lower than the triglyceride group. This speaks to the fact that with the observed data, and our ability to discriminate with the actual results we had, the chance that we could have had more than a 5 percent difference, I think is about 1 in 1,000. If you look with

the confidence interval that we had this data, that we can say with assurance, about a 1 in 20 assurance, 95 percent, that it could not have actually been olestra, 2 percent higher than triglyceride and got the observed results that we had.

So, we think that the study actually is still quite powerful even though we didn't get the numbers we had hoped for because of the observed effect.

DR. BLACKBURN: And your estimated dosage and response to that dosage that went into this?

DR. ZORICH: Yes, we thought people would eat about 2 ounces on average, 2 to 3, based upon the data from the MRCA, and they did, in fact, so we were confident that this actually did a nice job of looking at the overall population and what a normal distribution looks like.

DR. BRANDT: Dr. Feinleib.

DR. FEINLEIB: Since olestra was developed primarily to enable people who are concerned about their diets and overweight to have more access to savory snacks, did you do any analyses about consumption and symptoms by body weight index?

DR. ZORICH: In these studies, we did have information on BMI, but did not follow the BMI through the study. We were really focused on the GI symptoms, however, prior to this set of studies, prior to approval, we did many

studies to specifically look at people who were hypercholesterolemic, obese, Type 2 diabetics, and looked at these people specifically and did follow their GI symptom reporting.

DR. FEINLEIB: Since obesity is often associated with hypertension, and people with hypertension are often advised to lower their salt intake, encouraging them to have these savory snacks or salty snacks might have an adverse effect upon their blood pressure. Was this studied?

DR. ZORICH: We did include hypertensives if they were selecting the snacks. I would say that we are not encouraging people who are on salt restriction to eat more salt. If people decided that they were going to eat these snacks, we did not restrict them, but it would not be our intent to ask them to eat salty snacks if they were on a salt-restricted diet.

DR. BRANDT: Dr. Chassy.

DR. CHASSY: I was, in addressing the acute study, consumption study, concerned about calling back and getting a number 16 to 18 percent reporting occurrences. I don't know anything about what you would expect, and you just made reference to a 10 or 12 percent number.

Could you tell us a little bit more about what you would expect to see if you just called people up and asked what incidence of symptoms like this are?

DR. ZORICH: Actually, let me in a nutshell say that these numbers are very right on with what we expected, and let me ask you, if you wouldn't mind, to defer. Dr. Sandler actually conducted a very large telephone study, which I think illustrates exactly the kind of information that you wanted. He will be presenting that in the afternoon.

DR. CHASSY: Okay. In the second study, how did you handle the issue of people consuming savory snacks outside the household? What was your rationale on that?

DR. ZORICH: People have asked us that question, and I think the way that we did it was several-fold. First, we gave them so much free that it is hard to imagine they would have spent their hard-earned money, but they could have, but we really tried to just give them as much as they possibly wanted.

The second way that we did take care of that problem is that we gave them the option of the regular snacks, so that it would be just like going to the store, so they would see everything that they could possibly want for their household right in front of them, so they wouldn't be tempted to shop otherwise.

DR. CHASSY: I guess following up on that, did you ever plot the data of consumption in a timewise fashion to see whether -- on the placebo group or on the olestra group

-- whether consumption fell off with time?

DR. ZORICH: Yes, we did. Of course, that was one parameter of interest, and what I can tell you is that on any given day, day to day, there is a remarkable consistency with about 50 percent of the people in the study, on any given day of the study, eating the product, the olestra-labeled product, and then if you look on a week-by-week basis, you always have about 85 percent of the people each week eating the products, and it is very consistent through the course of the six weeks.

DR. BRANDT: Dr. Byers.

DR. BYERS: A question about the 90th percentile in the outpatient feeding study. You said that the intake was 2 1/2 to 3 grams a day was the 90th percentile value. Did you monitor how that was consumed, what proportion of those chips were consumed with meals?

DR. ZORICH: It was 2 1/2 to 3 ounces a day.

DR. BYERS: I am sorry, yes.

DR. ZORICH: No, we did not. We did not keep track of when in the day they consumed the product.

DR. BYERS: So, you did not monitor how the chips were consumed in the outpatient study?

DR. ZORICH: I think that there is going to be data specifically from our active surveillance program that will address that question.

DR. BRANDT: Dr. Clancy.

DR. CLANCY: A couple of things going back to your saying that your power assumption was 10 to 15 percent background symptoms. Can you say what the incidence of symptoms was in your home study at zero? You have got a category of zero to 10. Could you give us the percentage of incidence of symptoms at zero, not zero to 10, or you can't break it down any farther than that?

DR. ZORICH: There were only 15 people who didn't eat, so I would say it is a very small number, but I mean we could look at those people. I would predict that it would be comparable to background rate, which would be 35 to 40 percent over a month.

DR. CLANCY: That would be interesting to look at because those numbers look like they are a little bit higher than what you predicted for your power assumption.

DR. ZORICH: Those numbers from the six-week study are accumulative over six weeks versus my power assumption was based on a single talking to somebody, so I think that is why you see the 15 to 40.

DR. CLANCY: That is useful to have you clarify that. The second thing is since you predicted a dose response, why didn't you get it, why isn't there any dose response in these studies since you are predicting a dose response? Did something miraculously happen to the olestra?

DR. ZORICH: I think the difference between studies where you can see a clear dose response, the key difference is that in those studies, you actually have to have a mandatory consumption, and not only do you have to have a mandatory consumption of the snacks, you have to have a mandatory consumption of the diet, and every study where we allow people to eat snacks and the rest of their diet ad lib, then, you get into what we have here.

You do not see the dose response, and it has to do probably with basically people's own food selections and how people balance through the day, but you don't see the dose response unless you fix the diet and you fix the amount of olestra.

DR. CLANCY: Do you have any information about that?

DR. ZORICH: Yes. I think that what we would predict is that somewhere where people were closer to this more mandatory consumption we would see it. I think that what I tried to show here is that even at this upper range, it is not statistically significant, but there was a suggestion that those people perhaps we are seeing a more predictive effect, but it was not statistically different.

DR. BRANDT: Dr. Harlander.

DR. HARLANDER: My question was asked previously. Thank you.

DR. BRANDT: Okay. Dr. Hubbard.

DR. HUBBARD: I will ask you for your analysis of something that has probably been said in other ways, but with time or duration of exposure, do you see any change in reporting of symptoms?

DR. ZORICH: These studies, the longest of which was six weeks, prior to approval, the longest study we had was five months, and in that study, we did not see any difference in GI symptom reporting at the beginning to the end of the study, and in the shorter studies, we have certainly not seen anything.

DR. HUBBARD: Again, in your stool composition study, did you do any type of balance studies during that particular effort, as well?

DR. ZORICH: Balance for?

DR. HUBBARD: Macronutrients or other nutrients?

DR. ZORICH: No. Actually, the data that was mentioned by Dr. Rulis in pigs, very clearly addresses mass balance.

DR. BRANDT: Dr. Chassy.

DR. CHASSY: The suggestion was made that people would calorie compensate and eat more olestra chips because of the lost metabolizable fat. Your data seem to indicate that is not the case. Does it have sufficient power to justify that conclusion?

DR. ZORICH: There have been specific studies that have been conducted to look at this, and I think Dr. John Peters, who runs our nutrition group, probably would be the best person to answer your question.

DR. BRANDT: And he is coming up later, isn't he? Why don't you just address it when it comes up in your presentation, would you?

DR. PETERS: Fine. I will give you the data then. The answer is there doesn't appear to be any excess compensation for replacement of regular fat snacks with olestra snacks.

DR. BRANDT: But you will give us the data whenever you talk again, whenever that is.

Dr. Applebaum.

DR. APPLEBAUM: If we could, could we go back to that slide, I think it was maybe 10 slides ago, 7 to 10, where you showed significant difference. This is in the six-week consumption study where there are two points where statistical significance are seen, one between the 70 and the 250. I am assuming because of time constraints you went very quickly over that. Could you go over this one a little bit more?

DR. ZORICH: Yes.

[Slide.]

What this looked at was the percent of people

reporting over the course of the study from the people eating the smallest amount to the largest amount, and we have broken out the groups by 10-ounce increments, so you are looking at people who ate the smallest amounts and here, 20 to 30, 40 to 50, until you get to this group, and that is not a 10-ounce increment. I just pooled the people, the upper 10 percentile of the population. It is a very broad range as you can see.

Just looking at this slide, there are only two groups that had statistical differences, this 30 to 40 group, and this group at the higher end. The point I was trying to make -- and you are right, I think that is when I got my first warning bell -- is that you see the levels kind of up and down, there is no clear association, and I did want to point out the two statistical differences, particularly it was of interest to us that this was the lowest placebo rate happened to be in that group.

Was that sufficient?

DR. APPLEBAUM: I guess what I need is better clarification in terms of your interpretation as to why there is difference.

DR. ZORICH: Yes, I can do that from here.

[Slide.]

Why there is difference I think is accounted for right here. There is a statistical increase here in the

number of times people reported more frequent bowel movements, and this seems like a small difference, and it is a small difference, about one day, but in all the participants in the study, I think that this effect accounts for the difference in the percent of people reporting symptoms. That is why I showed this data.

DR. APPLEBAUM: Thank you.

DR. BRANDT: Dr. Lamm, one more question.

DR. LAMM: I am still a bit confused in your initial study design on the chronic study, the six-week consumption, what the role was of the bags with the regular product in it, and that were labeled such, and I am a bit confused with when people came in, were people on olestra throughout the whole six weeks, or if everything was blinded, how would you have it that when somebody came in for the follow-up visit, that they were only shown bags that, in fact, contained olestra?

DR. ZORICH: Yes, I can handle that, and, in fact, you are going to give me an opportunity to go on and on about my studies, which I never mind.

This was actually a terrific job by the group of people that work with me in my data management group. We had set up at the site -- remember I said the bar codes were over-labeled -- and we randomized the households, so there were certain bar codes for olestra households and other bar

codes for the control households.

If you have been to Service Merchandise, you look at the things and then you check off on a sheet give me two of these and one of that, and then a runner went back from that room to the room where we had four different shelves, A, B, C, D, and they went to the right designation.

Then, we had someone sitting there with the same kind of scanner that you use at the grocery store, a laser scanner, and they checked before we dispensed it, they checked the bar code, and then the computer had the randomization, so we could verify that what went into their shopping bag was, in fact, the right one. You are right, otherwise, how could you know.

So, that is how we accomplished that, and, yes, people were, once you were on a treatment group, that is throughout the course of the study.

Now, to answer your other question, the reason I think was brought up here just a minute ago, we did not want people to feel that they needed to go to the grocery store and buy chips, and since the average household has members that choose to eat low-fat foods, fat-free foods, and other members of the household may, in fact, not choose to eat those foods, we didn't want the household contact to go out and bring those other kinds of foods in, and we wouldn't know how much or when they were doing that.

So, we just offered them free of charge. It wasn't integral to the study design, but it was a method of keeping them from going out to buy other snacks, and importantly, it allowed us to know were people eating the olestra products and then two weeks later stop, and they are only now choosing the free regular, and so it was another indicator of what I call the overall acceptance by the participants of the products, and we didn't see households stopping choosing the products.

As I said, 85 percent of the households continued week to week, continued to select the olestra-labeled products.

DR. LAMM: While we aren't dealing with the issues of benefits, you talked about having the BMI. Did you look at weight differences over the time and find anything?

DR. ZORICH: We didn't look at the exit weight difference, and we talked about that at length and decided that we were really focusing on the GI questions, and so we did not.

DR. BRANDT: Dr. Underwood. Last question.

DR. UNDERWOOD: In your studies that included children down to two years of age, can you tell us what the level of consumption was in the younger age group versus the adult?

DR. ZORICH: I do. I have a specific backup slide

that I can share with you to look specifically at children.

[Slide.]

Specifically, you can see the children. This one shows it better. This shows you both, so we don't have to go back and forth between the two slides. It shows you the number of eating days and the total amount eaten, so the amount eaten per day for the children in both groups, both by median and 90th percentile.

What you found actually was very good consumption, that these families, in fact, did let their children eat the olestra-labeled products, and the children ate them pretty frequently.

I have also included here, because you are probably also curious, that the children did very well in the study, and even as they were eating these snacks often, there is no difference in GI symptom reporting, and, in fact, no difference in the impact of the symptoms in the children.

DR. BRANDT: Dr. Treibwasser, if we were to go on and let Dr. Zorich make her next presentation, what kind of time are we talking about, passive surveillance?

DR. ZORICH: Two hours.

DR. TREIBWASSER: It is the better part of 80 minutes if we go into the whole thing.

DR. LARSEN: As I recall, you said that we could

split that presentation, and Dr. Zorich and Dr. Jones could make theirs before lunch if we had the time. That is the issue I think we were raising.

DR. TREIBWASSER: Yes, we could do that.

DR. BRANDT: How long will that take is what I am trying to ask you.

DR. TREIBWASSER: Twenty-five, 30 minutes, not more than that.

DR. BRANDT: Let's go. I am going to set this at 30 minutes.

DR. TREIBWASSER: We will see how right I was.

DR. BRANDT: You will find out.

DR. ZORICH: I was going to say good morning, but I will hold back.

DR. BRANDT: Don't say anything about lunch because I am already hungry. Go ahead.

[Slide.]

DR. ZORICH: We have just seen the data now from the controlled clinical studies that we are looking at people eating snacks, the way people eat snacks compared to when they were eating full-fat snacks.

Now, we are going to look at our post-marketing surveillance program. We have tried to put together a comprehensive look at the data on the calls that have come in over the 800 lines, and I am also, after lunch I think,

going to talk about some special testing that we did with some of these consumers who had called us.

As you are aware, at the time of approval, P&G agreed to conduct passive post-marketing surveillance. Now, we report this data from the consumers on a quarterly basis, and we have filed eight quarterly reports since the time of approval.

[Slide.]

I think what we are going to do is hear a little bit from me on our overall program, and then we will allow Dr. Judith Jones to give her background of the fundamentals of surveillance.

Then, we will probably stop there. Do you agree?

DR. BRANDT: Yes.

DR. ZORICH: I will put this back up when we come back, and take us through the rest of the agenda at that time.

DR. BRANDT: Thank you.

DR. ZORICH: So, let me go ahead then. Actually, we will go right into Dr. Jones' presentation. Dr. Jones formerly was with the FDA surveillance group, and is now the president of a consultancy firm in Washington which specializes in research in epidemiology and safety surveillance. She is also an adjunct professor here in Washington at Georgetown and GW.

We have asked her to talk to the committee and give you a little background on the purpose, as well as the strengths and limitations, of our post-marketing surveillance system.

Dr. Jones.

DR. JONES: Thank you, Dr. Brandt, ladies and gentlemen. For about the past 20 years, I have had the opportunity to focus on the area of post-marketing surveillance, and Procter & Gamble asked me to provide some background just to place the passive surveillance -- which we are going to be talking about quite a bit this afternoon -- into some context of this whole area.

[Slide.]

Now, passive surveillance, of course, has been a major method, particularly in other consumer products, particularly drugs and biologics and devices, for gathering information on the entire population of what might be happening, and basically, it is predicated on setting up various monitoring systems that can collect reports from physicians, other practitioners, and consumers, and those interested in any problems with the products.

This is followed by an ability to collect specific information, and in the case of olestra, this was actually done where targeted information was collected, an ability to follow up with either the consumer or the physician or the

reporter to make inquiries about specific concerns that weren't collected on the initial contact, and then tabulate these in a database to allow an analysis of this information.

[Slide.]

Because of the importance of the events and the reporting of those events in the data that we are going to be hearing about this afternoon, I would like to talk a little bit about what this event is and what it means in the context of the information that will be presented.

It is important to realize that the event that occurs can be caused by a variety of different things ranging from drugs, certainly underlying diseases, various kinds of foods, and environmental factors, and other factors, and a certain proportion of those events are, in fact, reported in any given system.

[Slide.]

Once an event occurs, it is either noticed or not noticed, and there are various things that will determine whether, in fact, it is even noticed. A lot of it has to do with the clinical nature of the event. Obviously, the more dramatic the event, the more likely it is to be noticed. Conversely, the less dramatic, that is, a mild abdominal discomfort, may or may not be noticed if a person is in a very busy meeting, et cetera.

The observer knowledge and bias has a great deal to do with whether it is noticed. In clinical practice, obviously, the specialty will determine that. An ophthalmologist will not be likely to notice GI events or symptoms, but a gastroenterologist would. So, there is a high degree of variation depending upon the event and the observer as to whether the event is even noticed.

[Slide.]

Furthermore, given that there are several possible causes for any event, the likelihood of attribution of this event to any of these particular causes relates to a number of different factors, some of which are listed here.

Obviously, the timing of the event, if it occurs within an hour or two after exposure to any of these possible causes, will have a lot to do with whether it is attributed to one of those causes or not.

The nature of the event and actually the observer knowledge and belief about what that event is due to will have a great deal of effect on its attribution, and obviously, a various knowledge and bias of what the event might be due to will again have a great deal to do with the attribution that occurs.

[Slide.]

Finally, whether or not it is reported -- and a high proportion are not reported, some are reported -- will

be related to the ease of reporting, and obviously, a 1-800 number facilitates this, and other knowledge of reporting mechanism, that is, information on the package label and other advertisement, and to some extent, the dramatic nature or severity or inconvenience may well motivate people to report to a greater extent.

Now, what does all of this mean? Well, one thing is that any given event is only in some cases detected and attributed and reported.

[Slide.]

Accordingly, because of these many factors that are affecting the ultimate step of reporting, the number of reports does not reliably relate in any case to the incident events in populations.

[Slide.]

The second message that relates to this has to do with the fact that in addition to not reflecting true incidence, which can only be determined in controlled studies where exposure and events are collected in a structured way, there are a number of biases that operate on spontaneous reports, particularly recent information, publicity, and overlooking accompanying conditions or foods that a person may be exposed to.

However, this system is very important and useful because it provides signals of what may be occurring in

actual use of a product that can be tested in formal studies, and again to emphasize the fact that it does cover the entire country. So, we really have a coverage of the 260- or 270 million people who might potentially be exposed to any particular product. That is an important baseline, safety surveillance.

[Slide.]

Furthermore, these signals can be analyzed to develop hypotheses, and in most cases, one can analyze them in a variety of ways including by reporter, by subgroup, that is, particularly looking at the children and the elderly, as has been raised earlier. Certainly in this particular case by reported symptom type and subtype, again, by dose and type of product, as well as latency of the impact to determine whether it is biologically plausible.

Now, again, because this is a national surveillance system, and one of the questions that was raised in the charge to the committee is looking at public health, the advantage is that the power of the system is considerable and it does allow one to look at rare events, and that is one of the major values of an overall passive surveillance system. These events can, in fact, be analyzed in a standardized way by using a standard method or algorithm, which Dr. Sandler will be describing this afternoon.

Now, in analyzing these, it is obvious that we are dealing with events that are reported for various reasons that may not be food associated, or, in fact, may often be food-associated changes, that is, changes in color or odor of urine and fractures, but the majority of events that we are really talking about are, in fact, both drug, food, or disease-associated events, and therefore must be differentiated in some other way, and nausea, vomiting, and diarrhea are obviously fully confounded.

[Slide.]

The method that Dr. Sandler will be talking about is derived from the standard methodology that is used for assessing causality in single cases, and it has been in use for approximately 20 years with various different methods, primarily assessing drugs, but it is applicable here.

That is, it is based on timing, that is, was the exposure before the event or not, on challenge, that is, did the event go away when the exposure was removed, on re-challenge, that is, did the event occur when the alleged exposure was reintroduced -- and you will hear more about that this afternoon -- and furthermore confounding, that is, are there alternative explanations based on underlying diseases or other exposure, and also addressing the issue of biological plausibility, either dose mechanism or, in some cases, prior reports, although that is probably the softest

criterion.

[Slide.]

With this evaluation one can in a surveillance system -- and you will hear this described this afternoon -- plot some trends to look at type and dose, time of onset in both the total and all populations, and particularly look at biological plausibility.

Now, the purpose of this whole exercise is not to make conclusions about this data because, as I indicated, it is not incident data, but rather determine hypotheses testable in structured clinical trials or formal epidemiologic studies where you have exposure and events collected in a standardized fashion.

[Slide.]

How does this fit in the overall system of post-marketing surveillance? Well, essentially, at the time of approval, you have a system that is the passive surveillance system, and there will be ongoing spontaneous reports, which will be described, which are evaluated for safety, and you will hear more about this, this afternoon, with a particular focus on public health importance.

All of that data is essentially non-quantitative, however, this data can generate hypotheses which can be evaluated in quantitative methods including the randomized controlled trials which you heard about just a few minutes

ago, and additionally, a re-challenge study directly linked to this particular surveillance system and the observational population studies. All of these must occur over time to actually understand the product in the context of use.

That is the end of my remarks. Thank you, Dr. Brandt.

DR. BRANDT: Thank you very much. I appreciate it.

Dr. Zorich, do you have other things to say? You have got 16 minutes and 24 seconds left.

DR. ZORICH: Thank you very much for this time.

Now I would like to go ahead and start talking about our post-marketing surveillance system. Over the last two and a half years, since approval, olestra has been test-marketed in several cities across the U.S.

This has provided us with an excellent opportunity to establish our post-marketing surveillance system, and at the same time it was an opportunity to understand overall consumer acceptance about the snacks, so I am going to preface my discussion about the 800 line calls with just giving you a few minutes of background on just how often many consumer companies like Procter & Gamble hear from people.

[Slide.]

You may be surprised to know that last year alone,

we received 2 1/2 million phone calls, and our food and beverage sector, that part of the company that sells the Pringles and Olean, we received about 400,000 phone calls last year.

Now, I want to ask you to consider, for an example, how often we hear from people on a product, a popular product where there is no controversy. Our regular Pringles last year, we received 26,000 phone calls. Most of those actually were not complimentary. Very few of them, actually, 1 percent, were compliments, but that is typical what you hear from people.

[Slide.]

By contrast, let's look at our test marketing of fat-free Pringles in the first two years. You can see that about 80 percent of the calls, in fact, over 80 percent here, are information and testimonials.

For us at Procter & Gamble, this level of calls, 26 percent of these calls being testimonials, is unprecedented. We simply don't hear from that many happy consumers, and we do very carefully collect data on symptoms.

We take these calls very seriously, but I think it is important for you to know and have the perspective that relative to the total number of calls, the symptom calls are less than 10 percent.

[Slide.]

To ensure that we do capture the information on these calls, we have established with Frito-Lay and Nabisco that they will, in addition to the way that we do, we have an 800 line on all of our products, so for us hearing from consumers is our normal day-to-day routine.

We worked with Frito-Lay and Nabisco to ensure that they will have an 800 line specifically on their Olean products that would direct people specifically to operators who were going to then triage that call appropriately.

Now, during the test markets -- now, we have maintained this for the important calls and national -- when a call comes in to Frito-Lay -- there have been very few calls to Nabisco -- when a call comes to Frito-Lay, it is immediately transferred to my group at Procter & Gamble, and then we collect the data, and we handle the call.

So, the data I am going to take you through today, and the data that Bob Sandler will share with you, actually contains all the data on Olean, not just Procter & Gamble's Pringles products.

All of us at Procter & Gamble who work in the Medical Affairs group actually have extensive experience in safety surveillance, and we are physicians, clinical pharmacists, and nurses, who then follow up, take the information, and follow up as necessary with consumers. I

should say that the calls have been from consumers, not from health care professionals.

We use standardized formats to ensure accurate data collection, and put all of this information into a large database. We then submit all this data to the FDA every three months on the day, and we also send them the electronic data, so that they have full access to all this information.

Now, because we understand the importance of help in looking at this very complex data, we have established a five-member external panel of experts who have expertise in epidemiology, safety surveillance, gastroenterology, and pediatric gastroenterology, and they have met with us periodically. We have met now five times and they have looked at all of the data with us. They also submit their conclusions to the FDA directly.

[Slide.]

This is the five-member panel. You have already met Dr. Jones. Dr. Dennis Ahnen is a gastroenterologist at the University of Colorado, and he has extensive expertise in population surveillance. Dr. Steve Czinn is a pediatric gastroenterologist. He is at Case Western and Rainbow Babies in Cleveland. Dr. James Freston is at the University of Connecticut and the immediate past chair of the American Gastroenterologic Association. Dr. Robert Sandler is

Professor of Medicine and Epidemiology, and you will be hearing from him I guess immediately after lunch.

All of our expert panel members are going to be here with the exception of Dr. Ahnen.

[Slide.]

Before we talk about the post-marketing surveillance data, I think it is important for you to have some idea of what it was like in the test markets while this product was being -- the last two and a half years -- while it was being test marketed.

CSPI sponsored 10 press conferences and formal protests within the test markets. There was also an anti-olestra television commercial that was shown in the test markets, and there were anti-olestra newspaper advertisements.

CSPI even hired an airplane to fly anti-olestra messages behind on a banner over the Ohio State games in Columbus. So, the people in the test markets were inundated with local coverage, and unfortunately, most of this coverage focused on the potential negative, very serious consequences of eating products made with Pringles.

[Slide.]

Here is an example of the newspaper advertisement which was actually put out under the guise of a public health advisory. This was not shared, nor was it known by

the State Board of Health that this was going out, and it said, "Did you get sick after eating the products? Call in."

[Slide.]

I wanted to show you just a few clippings from the local papers to let you see what kind of coverage then came out of this kind of media activity.

I also have -- it is only 30 seconds -- so I will show you the television commercial that was shown all on the test products in the test markets.

[Video played.]

Now, the reason that I thought it was important for you to have this perspective is that I believe that altogether this kind of media coverage probably affected the surveillance program both in the number of calls and importantly, the types of symptoms that people reported when they did make a call to us.

[Slide.]

We are going to look at the 800 calls that were received over time, and I have got them broken out here for the three test markets, the initial cities, Columbus, and then Greater Indiana.

Basically, we saw the same pattern each time. When the snacks were introduced into the test market, there was a lot of interest, and there was also a lot of media

coverage, as I explained. I have shown you here with asterisks when the press conferences and protests occurred, and you could see that within about a week of when those occurred, there are spikes in the call volume.

Then, as the media interest subsides, the rates go down. Now, if I had three different slides, I could show you for each one of the test markets that it goes up, and then it goes down, if you were to just look at those cities.

For Ohio, the rates go up and then come down, and for Indiana, this is shown nicely because it goes up and then it comes down with no further calls coming in. But, of course, the logical question is, well, did people keep eating the product.

[Slide.]

I am showing this here for Pringles. We had the sales data, Pringles being our brand, and this is Columbus, and you can see here are the calls coming in and the initial introduction of the product with the attendant negative media coverage, and then media attention subsides, calls subside, and I have shown you here in green, cumulative reports in those markets for symptom calls, and I have also shown you now, cumulative sales in the same market going well beyond a million cans of Pringles being sold without any increase in the calls coming in.

At this point, we are going to ask Dr. Sandler, as

soon as we get back from lunch, to address a question that came in, I believe two came in from the committee just how often did we expect people to be reporting symptoms in our clinical studies and what is the general background prevalence of GI symptom reporting in the community at large, and so I will end now.

I will take specific questions if you would like me to.

DR. BRANDT: No, we are going to delay questions until we come back. You used, Dr. Treibwasser used 25 minutes of your 80, so when you come back, you have got whatever the difference is between 80 minus 25. Anyway, it is 55 minutes, so we are in good shape.

We will now adjourn for lunch. According to my watch it is 20 minutes to 12:00. We will reassemble promptly at 20 minutes to 1:00.

[Whereupon, at 11:40 a.m., the proceedings were recessed, to be resumed at 12:40 p.m.]

AFTERNOON SESSION

[12:40 p.m.]

DR. BRANDT: It is time to get started. I have a couple of quick announcements. Dr. Wang wants a picture of all of the graduating members of this committee. She is a self-proclaimed member of our alumni association, and also collect your first year dues at the same time.

DR. WANG: At the break.

DR. BRANDT: Second is Dr. Larsen has passed out a whole stack of other stuff for you in case you didn't have anything to do this evening, you can read it all. That will take care of that.

Any other things? I am letting P&G give their whole story on passive surveillance, and we will throw the whole thing open for questions, so if you have questions coming to mind, write them down unless your memory is considerably better than mine.

Dr. Treibwasser, I have the timer set at 55 minutes, so let's go.

DR. ZORICH: Good afternoon. Welcome back. I just want to take us very briefly through the agenda for the rest of Procter & Gamble's formal presentations for today.

[Slide.]

We are now going to hear from Dr. Robert Sandler. He is going to spend time telling us about the survey that I

mentioned, and then he will go over the 800 line calls and the analysis from the five-member panel.

I will be back to talk to you about the special study we did to specifically re-challenge people who had called the 800 line. Then, we are going to hear from three people who are not on this slide. We will hear from Ms. Teri Butler, consumer in the Columbus area, who participated in our study. Dr. Juling McClung, who is a pediatric gastroenterologist out of Columbus, and Dr. Robert Drotman from Frito-Lay, who will talk about Frito-Lay's experience in the test in national markets.

Dr. Sandler.

DR. SANDLER: Thank you.

[Slide.]

I am Robert Sandler. I am a Professor of Medicine and Clinical Professor of Epidemiology at the University of North Carolina at Chapel Hill. I am a gastroenterologist with an interest in epidemiology.

For the past 20 years, I have been doing epidemiology studies on common digestive conditions, such as heartburn, constipation, and diarrhea, and the work that I have been doing as a consultant for Procter & Gamble on digestive effects is really a logical extension of my research interests.

[Slide.]

I am here this afternoon to talk about two activities that I have been involved in. The first is a national survey that we conducted of digestive complaints in the United States, and the second activity is the work of the Post-Marketing Surveillance Advisory Committee.

Now, it is the work of the Post-Marketing Committee that actually provides the motivation for this national survey. When the members of our committee began to review reports, it became very apparent to us that the sorts of reports that we were seeing of adverse events were exactly the sorts of things that we, as clinicians, were seeing in our every-day practice.

It looked like this might be representing the background rates of these conditions, but when we looked in the literature, we were surprised to discover that, in fact, there were no accurate prevalence estimates for how common these conditions were in the general population.

So, we therefore urged Procter & Gamble to sponsor a national survey that would provide us with some baseline information and it would serve as a context in which to interpret these passive reports.

[Slide.]

The survey that we conducted, we call the U.S. National Survey of Digestive Complaints. This survey was conducted by the research firm Innovative Medical Research,

which is an independent research company that is based in Towson, Maryland.

This company was started by Walter Stewart, who is an epidemiologist on the faculty of the Johns Hopkins University School of Public Health, and Innovative Medical has done a number of studies over the year, specializing in population-based surveys in clinical trials.

This particular work was recently presented at the annual meeting of the Gastroenterological Association, and the abstract has appeared in the Journal of Gastroenterology, and a manuscript is being prepared.

[Slide.]

The specific aim of this survey was to determine the prevalence and impact of digestive complaints in the United States, and the symptoms we were interested in looking at were abdominal pain or discomfort, abdominal distention or bloating, and loose stools or diarrhea.

[Slide.]

This was a nationwide cross-sectional household telephone survey, and it was done before olestra chips were available nationwide. In order to be eligible for this study, an individual had to be between the ages of 18 and 75, a permanent resident of the household telephoned, and conversant in English.

We made up to 10 attempts to reach each household.

There were 4,908 households contacted, 1,114 were not eligible, 2,684, or 71 percent participated. This is an excellent participation rate, and 2,510 completed the entire interview, and they formed the basis for this report.

[Slide.]

We asked respondents about digestive symptoms, specifically, pain, bloating, and loose stools during the month prior to their interview, and for each symptom we asked them the frequency and duration of the symptom. We asked them about the severity of the symptom using a 10-point anchored scale that I will describe in a minute.

We asked if the symptom reduced their daily activity level from zero to 100 percent, and for any symptom they might have experienced, we asked if they visited a physician or took medications.

Now, because the most recent symptom might be recalled most accurately, we asked people about the characteristics of their most recent symptom, recognizing that the most recent symptom might not necessarily be either the most severe or representative.

I will just briefly mention that when we looked at the features of the most recent symptom, they were identical to the overall symptoms.

Finally, we asked people about digestive symptoms that they might have experienced after eating certain foods,

such as beans, onions, and spicy foods that are widely regarded to cause digestive complaints.

[Slide.]

In addition, we conducted a formal reliability study. We recontacted a systematic random sample every eleventh phone number. There was 88.1 percent participation in the second interview. The interval between the first and second interview was 10 to 25 days with a median of 13 days, and there was excellent agreement between the responses on the first interview and the second interview. The level of agreement was 81 percent for pain, 91 percent for bloating, and 79 percent for diarrhea.

Remember that the second interview may have been anywhere between 10 and 25 days after the first interview, and if an individual had infrequent symptoms, they might have given different answers on the first interview and the second interview, so this level of agreement is really very excellent.

[Slide.]

These are the demographic characteristics of the 2,510 survey participants - 41 percent were between the ages of 18 and 39, 36 percent were from 40 to 59, and 23 percent were over the age of 60; 38 percent were men, 80 percent were white, and 56 percent were married.

[Slide.]

The overall study findings are shown here. This shows the prevalence of GI symptoms in the past month, and you can see that 40.5 percent of individuals that we surveyed had one of these individual symptoms during the course of the month; 21.8 percent reported pain, 15.9 percent bloating, and 26.9 percent had diarrhea.

[Slide.]

This slide looks at the prevalence of GI symptoms in the past month by sex, and you can see that women were more likely to report a digestive symptom. This was particularly notable for bloating, which was about twice as common in women than it was in men.

We specifically asked women to exclude bloating associated with menstrual periods, and diarrhea was equally common in men and women.

[Slide.]

Now, the previous slide that I have been showing you showed the proportion of people who had a digestive symptom during the previous month. People could have had symptoms on more than one day, so we therefore asked people how many times during the previous month they had a symptom, and you can see that the green bars are one time a month, and the majority of people actually had a symptom on more than one day per month, particularly for pain and bloating. So, not only are symptoms common, but they occur repeatedly

during the course of a month.

[Slide.]

This slide looks at the average severity of symptoms in the past month, and this was on a 10-point scale for pain and bloating. This was an anchored scale with zero being no pain or bloating, and 10 being the most severe pain or bloating that people have ever had.

For diarrhea, the scale went from zero, which was a hard stool, to 10, a watery stool, and then we categorized their responses in the following way. A score from zero to 3 was categorized as mild, 4 to 6 was moderate, and 7 to 10 was severe.

You can see that for bloating and pain, more than 70 percent of people rated their symptoms as of moderate or severe intensity. For diarrhea, 90 percent of people had symptoms rated in the moderate or severe categories.

So, not only are symptoms common, but every-day symptoms in the community are perceived as moderate or severe in intensity by the people who experienced them.

[Slide.]

We also asked people about how much their daily activities were reduced when they experienced these symptoms, and this was on a 100-point scale. The green bar suggests no activity limitation, and you can see that when people had these symptoms, the majority of them had some

activity limitation.

In addition, focusing on the gray bars, about 15 percent of people thought that their activities were reduced by half when they experienced these symptoms.

[Slide.]

Next, we asked people if they consulted a physician or took a medication for their symptoms in the past month, and between 9 and 19 percent of people with symptoms consulted physicians, and between 40 and 60 percent of people took medications, generally over-the-counter medications for these symptoms.

[Slide.]

Finally, we asked people whether they ate and experienced digestive symptoms from food that are widely regarded to cause digest symptoms, and the foods we looked at were beans, onions, and spicy foods, and you can see that approximately 80 percent of people reported that they ate those foods, and of the people who ate the foods, approximately 20 percent experienced digestive symptoms after eating those foods.

Interestingly, although they experienced symptoms, approximately 80 percent of people continued to eat those foods even though they experienced symptoms.

[Slide.]

So, what do we conclude from this study? We

conclude that digestive complaints including pain, bloating, and loose stools are common. More than 40 percent of respondents report one or more. 71 percent perceived their symptoms as moderate to severe in intensity, more than 50 percent had some activity limitation, 9 to 19 percent consult physicians, and 43 to 60 percent take medications.

Because symptoms are common and because they occur a number of times during the month, it is not surprising to notice that of those people who have symptoms, 21 to 24 percent have symptoms in the previous 24 hours. If those people at an olestra chip and then experienced symptoms, it might be logical for them to attribute those symptoms to eating those chips, when, in fact, it may simply be coincidence.

[Slide.]

Finally, we discovered that a number of foods, such as beans, onions, and spicy foods commonly produce digestive complaints, but people eat them anyway.

[Slide.]

Now, I mentioned that we conducted this study to provide some accurate prevalence information about a common condition, and it turns out that while we were conducting our study, the CDC was also conducting a study on diarrheal illness.

Now, this report was recently presented at the

International Conference on Emerging Infections Diseases presented in Atlanta, Georgia, in March. I have seen the abstract from this paper, but I haven't seen the paper or talked to the authors, but I thought the information was so important that I would share it with the committee.

[Slide.]

Again, this was a study that was done before olestra was available nationwide. This was a population-based telephone survey of 9,000 randomly selected people in five states. Eleven percent reported a diarrheal illness in 28 days prior. I don't know how they defined diarrheal illness. This number is lower than our number. Our number was 26 percent, but we asked about both diarrhea and loose stools, and when you ask people about individual symptoms, it is generally a more sensitive measure.

The important part, however, I think is the information that follows. Of those people who had a diarrheal illness, 7.5 percent of those with diarrhea visited physicians, and carrying that back to the population, that means that there were 9,921 people per 100,000 person years of observation.

That means for every 100,000 people, 9,900 visited physicians for diarrhea during the year. In addition, of those who had diarrhea, 6.6 percent of those people were hospitalized. That is an estimate of 600 per 100,000 person

years.

So, the CDC estimates 340 million episodes of acute diarrheal illness occur in the United States each year and are a major burden to the population and health care system. 340 million episodes of acute diarrhea occur in the United States every year. None of those are due to olestra because this survey was done before olestra was available.

[Slide.]

What are the implications of our study and the CDC study? Because episodic digestive complaints are common, it would be very difficult to assign a specific cause in an individual instance.

Now, I am going to move next to talk about the passive surveillance system. I am going to talk about the activities of the Post-Marketing Surveillance Committee where we reviewed spontaneous reports, but as I do that, I hope you will keep in mind the information from our survey and the CDC survey which show that these conditions are very common in the general population.

[Slide.]

I will begin my discussion of the activities of the Post-Marketing Surveillance Advisory Committee by reminding you of the membership. This is a group of senior clinician scientists who represent a number of different disciplines including adult and pediatric gastroenterology,

epidemiology, pharmacology, and regulatory affairs.

[Slide.]

The mission statement for our committee is the following. The mission of the Olestra Post-Marketing Surveillance Advisory Committee is to provide independent review of the adverse experiences associated with olestra consumption and to make recommendations about the safety of olestra.

[Slide.]

The methods that were used by this committee are shown in this slide, and I would like to spend a few minutes going over this because I think it is very important that you understand the process that we used.

We took a very conscientious and thorough approach to these reports, and I would like to describe that process to you. The first thing we looked at were individual reports of adverse experiences that are collected and assembled by Procter & Gamble. These are the phone calls that come in to the toll-free number.

Procter & Gamble collects information on what sort of chips they ate, how much they ate, how long it took before they developed symptoms, how long the symptoms lasted, and whatnot. There were over 1,300 of those reports and every member of our committee read every single one of those reports.

In addition, we divided all of those reports and assigned certain ones to individuals for their special scrutiny. So, all of us read all of the reports, and certain of us read certain of the reports in greater detail, and whenever anyone had any concerns about a specific report, it was discussed by the committee.

In addition to the individual reports, we asked Procter & Gamble to provide us with a series of charts and tables and graphs and statistical arrays that could organize that data to help us possibly spot some trends, and I am going to show you some of those tables.

Now, the second thing we did is we looked at detailed narrative reports of individuals who sought medical attention due to adverse experiences. These are people who went to a medical provider, an emergency room at a hospital for an alleged adverse event, and we paid particular attention to these because by virtue of the fact of going to seek medical help, these people may, in fact, have had a serious adverse event, and we paid particular attention to those.

In order to deal with those, we developed, after some discussion with Judith Jones, an algorithm that I will describe in more detail later, but at this point I will simply mention that the purpose of the algorithm was to provide us a tool that would permit us to have an explicit

and systematic way to look at these reports rather than coming to some sort of global subjective judgment.

Finally, we looked at individual and aggregate data from re-challenge testing. In our view, this re-challenge testing is extremely important for the following reason, and that is, these individual reports are simply anecdotes, they are like case reports, and the problem with case reports is they don't permit us to draw conclusions about cause and effect.

What they are useful for is to help us generate hypotheses. Those hypotheses need to be tested in a more formal fashion. This re-challenge testing does that. It takes people who have self-selected themselves as possibly sensitive to olestra, and then enrolls them in a scientific randomized, controlled trial. So, for that reason, we found the re-challenge testing to be very persuasive.

[Slide.]

Let me discuss some of the individual reports. I am going to show you a series of tables that we used to help us organize the data, and I would begin by pointing out that while organizing the data in this way helps us to spot trends, by virtue of the data, it is very difficult to draw any conclusions necessarily about cause and effect. This is numerator data.

But on this slide, I have shown the age and gender

of individuals who reported an adverse event, and we asked for this table because we were concerned that young people and older people might be experiencing adverse events, but as you can see, the numbers of young people and old people who report adverse events is quite low. Most of the reports come from women.

You will recall from the national survey that we conducted that women are more likely to experience an adverse event than men are.

[Slide.]

This slide looks at the most frequently reported symptoms, and you can see that the most frequently reported symptoms, coded by COSTART term, which you can't see because it is behind the projector here, is diarrhea, abdominal cramping, and flatulence.

These are precisely the same symptoms that we found to be very common in the national survey, and these are also the symptoms that were the targets of media activity. So, it is not surprising, I think, to find that these are the most commonly reported symptoms.

[Slide.]

This slide shows the amount of olestra snacks that were consumed among individuals who reported symptoms, and I have organized the data by the percent of total callers in the cumulative percent.

You can see that 40 percent of people who reported symptoms at less than 1 ounce of chips, 65 percent of people ate less than 2 ounces, in control studies, intake at this level generally did not produce any symptoms.

Only 5 percent of people at more than 6 ounces of chips, so most people who had these adverse events didn't eat very many chips.

[Slide.]

This slide looks at the number of days that olestra snacks were consumed in individuals who reported symptoms. 77 percent of people only ate the chips on one day, 88 percent of people ate the chips on one or two days. In the control studies again, people often had to eat these chips repeatedly before we saw any changes, so it is a little surprising that people ate chips so infrequently.

[Slide.]

This looks at the time to onset of symptoms, and it shows, for example, that people who reported diarrhea, 41 percent of them developed diarrhea in less than six hours. Again, from the stool composition study, you saw data to suggest that there wasn't any change in the stool characteristics until people had eaten these chips for a couple of days. 54 percent of people who reported abdominal cramping, again developed cramping quite quickly, within less than six hours.

[Slide.]

This slide looks at the duration of the reported symptoms, and I would focus your attention on this row of the table. Only about 30 percent of people had symptoms for greater than 24 hours, suggesting that whatever symptoms they had were generally brief and self-limited.

[Slide.]

Our committee was particularly interested in looking at dose, because if there were a dose-response relationship, that might suggest there was something going on. We reasoned that if olestra was causing an adverse event, the people who ate a lot of it might, in fact, experience different kinds of symptoms than people who ate only a little bit of it.

Having said that, I would caution you that you need to interpret a figure such as this cautiously, first of all, because it represents numerator data, and secondly, because the number of people who ate more than 6 ounces was only 5 percent of the people, so the numbers on this end of the figure are small, and the estimates are unstable.

[Slide.]

Looking at this information, our committee concluded that the types of symptoms that people experienced across a range of doses was quite similar.

We also looked to see if there were differences in

symptom severity by the amount of chips eaten. Again, you can see that across a broad range of doses, the severity of symptoms were quite similar. One might expect that is olestra were causing symptoms, the people who ate the most of it might have the most severe symptoms, but that is not what we observed.

[Slide.]

Finally, again, looking to see whether young people or older people were more likely to have adverse events, we see that the severity of the symptoms was again quite similar across a broad range of ages.

[Slide.]

The information that I shared with you just now had to do with people who called up the 800 number and reported adverse events. I would next like to talk about those individuals who sought medical attention, and during the test market phase of the post-marketing surveillance, there were 1,316 test market calls, 86 percent of people sought medical attention, 55 went to a doctor's office, 25 to an emergency room, and 6 went to a hospital. This is 7 percent of 1,316 test market calls.

You will recall from the national survey that people we found reported that 15 percent of them sought medical attention for digestive symptoms, which would suggest that, in fact, the 7 percent may actually be lower

than what we see in terms of background.

[Slide.]

In order to deal with these reports, as I mentioned, our committee developed an algorithm, and the algorithm was designed to evaluate documented physician visits, but, in fact, although we tried to document these visits by getting medical information from medical providers, we were only able to get that information in 30 percent of cases.

Nonetheless, we evaluated the reports whether we got the physician's records or not. The purpose of this algorithm was to try to create a tool that would permit us to carefully review the reports of people who sought medical attention.

Our goal was to come up with a systematic explicit and hopefully reproducible way to deal with these reports, and the elements that went into that algorithm included some of the following. For instance, we looked at timing, was the exposure before the event. If someone had diarrhea before they ate the chips, it would be hard to blame the chips for the diarrhea.

Disappearance, did the event disappear within some reasonable period after discontinuation of the exposure. Plausibility, are the dose and mechanism biologically plausible.

Our committee had a lot of trouble with biological plausibility because we don't understand everything about biology, but in certain cases, I think we could make a determination about this.

For example, if someone ate olestra chips and had rash on both hands, it would be likely that that was a systematic allergic event caused by olestra. We didn't think that would be biologically plausible. In general, biological plausibility did not figure prominently in our decisionmaking.

Alternatives, was there a strong alternative explanation for the symptoms. For example, if a husband and wife and two children had nausea, vomiting, fever, and diarrhea, we would conclude that it was probably some sort of infectious illness rather than olestra that was responsible.

Finally, re-challenge, did the illness recur with reintroduction of exposure.

So, we applied this algorithm in each of the cases, and used that algorithm to decide whether we thought as a committee that the event was probable, possible, or unlikely.

In addition, we decided whether that symptom was serious using FDA Med Watch criteria. After doing that, we found that there were no cases that our committee thought

were probably related to olestra, and we found no cases that we thought were serious using FDA criteria.

[Slide.]

In summary, we found no trend of increased symptoms with increasing dose. We found no trend of increased severity with increasing dose, no differences in severity by age group or gender, and we concluded that serious reactions are unlikely to be caused by olestra.

In summary, our committee found no reason to question the FDA's decision to conclude that olestra was safe to be marketed in savory snacks.

[Slide.]

This slide shows what has happened nationally. What I have been showing you now is, by and large, the test market experience. Since olestra was released nationally, this is the volume of calls that were received, and you can see that those calls peaked in about week 6 and have gradually decreased over time.

We don't have information available to us on how many people are eating these chips, but it is logical to conclude that over this time, the number of people eating chips has continued to increase while the number of people reporting adverse events has continued to decrease.

In addition, when we looked at the sorts of reports that were being received since olestra was available

nationally, the types of symptoms that people were reporting were exactly the same as the ones that we saw during the test market phase.

[Slide.]

So, in summary, we feel that the high background rates of digestive symptoms require that we use caution in interpreting these 800 lines calls. The vast majority of reports are likely to be measuring the background rate of digestive effects, and not symptoms that are caused by olestra. There were no reports of serious adverse reactions which are likely due to eating olestra, and there is no evidence from these data that olestra is harmful.

[Slide.]

Next you will hear from Dr. Zorich about rechallange testing. Rechallange testing was something, again, that our committee looked at. The reason we were interested in this is because the high background rates of symptoms make causal inference very difficult.

You will probably hear from some consumers today who have reported serious digestive symptoms after eating olestra. I would maintain that it is very difficult in this individual situation when the background rates are so high to attribute those symptoms to eating olestra chips.

One way to formalize that process and to impose some science would be to do formal rechallange testing which

provides a methodologically sound approach. What it does is take self-identified sensitive individuals. These are people who have phoned in and said that they had an adverse effect after eating these chips, and enrolls those people in a double-blind controlled trial.

So, instead of looking at anecdotes, we are able to use scientific methods to evaluate whether those symptoms are, in fact, due to olestra. In addition, the retesting that Dr. Zorich will tell you about also had consistent monitoring for adverse effects. So, after people ate the chips, they were questioned to see if they had any symptoms.

So that is the end of my conclusions and then I will have Dr. Zorich tell you about retesting.

DR. ZORICH: Thank you, Dr. Sandler, for that presentation of the 800 line data.

[Slide.]

Now we are going to talk about the study that Dr. Sandler mentioned and that specifically is a study we conducted to look at whether the 800 line callers were somehow uniquely intolerant of eating olestra snacks. As Dr. Sandler mentioned, and as the discussion earlier today, we pointed out that we were hearing from people who had been eating the product maybe just one time, and one to two ounces of product, and they were describing moderate to severe symptoms.

Based on our data from our controlled studies, this was unexpected. So we were faced with asking ourselves could these people who are calling us actually be somehow unique. Are they sensitive or intolerant of eating olestra or are they, perhaps, having typical background GI symptoms that are prevalent in the population.

So we designed this study to answer that question and we found that they weren't. They were not intolerant to eating olestra. This study has been published in a peer-reviewed journal.

[Slide.]

The study was designed, as Dr. Sandler mentioned, in a double-blind, placebo-controlled environment to test these people who had called the 800 line. We invited everyone during the first year of test marketing. At that time, there were about 1,100 people who had called in with GI symptoms.

We asked each of them, or as many as we could contact, if they would consider enrolling in this study. Then we designed the study to be representative of a typical 800-line caller's consumption experience; that is, people eating the product once on a single day and eating, on average, two ounces of chips.

As you saw from Dr. Sandler's presentation, actually 40 percent of people had only eaten an ounce or

less and very few people had eaten larger amounts, full bags. So we had the people eat olestra snacks twice and then they ate full-fat snacks twice. They did that in a random sequence over the four weeks of the study.

They came to a site. We set up sites in each one of the test cities to make it as convenient as possible for the participants to be in the study. They came to the site one day a week and then we called them back three to five days later. Again, of course, they were back at the site a week later.

But, in addition, we always provided people with a study 800 line that they could call and report any symptoms they wanted to in real time. All of that data was included in the analysis.

[Slide.]

What I am going to show you now is a series of slides that compares the demographics and other characteristics about callers who participated in the study versus the overall population. So each one of these slides shows the cohort of people in the study and compares that to the overall group of people who had called during that first year of test market.

As we have mentioned, a majority are female and a majority are adults. Very few children or people over 65 had called.

[Slide.]

The symptoms that they reported--here, these are verbatims rather than COSTART terms that you saw from Dr. Sandler. Most of the people here are reporting abdominal cramping and diarrhea whether they are in the whole test market, very well represented in our cohort of participants.

[Slide.]

In fact, most of these people had eaten two ounces or less, both in the total group and in our participants in the study with very few people eating six ounces or more.

[Slide.]

This is probably the most important aspect that I want to share with you when comparing the people in the study compared to the people who had called, the total population of callers. If we had enrolled in the study only people who had mild symptoms and that was not representative of the entire group, it wouldn't be a well-designed study.

But we were, in fact, able to recruit people into the study who originally described their symptoms--and here I am just showing you the two most common symptoms, diarrhea and abdominal cramping--who had originally described their symptoms, self-assessment, as moderate and severe.

In fact, you will see that there is a remarkable consistency between how often people are describing these symptoms as moderate or severe up to 70 percent of the time

when you look back at the GI survey data conducted by Dr. Sandler and Innovative Medical.

So these people had the same type of symptoms and the same severity prior to their participation in our study.

[Slide.]

When they are in the study, if you look, now at the percent of subjects recording a symptom, comparing the weeks when they had been eating full-fat snacks to the weeks they had been eating olestra snacks, you see that, actually, there is no difference in any GI symptom or any one of the individual GI symptoms that they reported.

[Slide.]

In fact, even though up to 40 percent of these people had initially described on the telephone a self-assessed symptom as severe, when we entered them into the study in a controlled study, we actually found very few people now used the word "severe" and, in fact, no one described their symptoms as severe in the weeks that they were eating the olestra snacks.

So you can see there actually are no differences here but, in fact, there are no people describing severe symptoms even among this group of 100 people who had initially called, and 40 percent of them said they had severe symptoms.

[Slide.]

Now, this slide is a little busy but I want to take the time to take you through it because I think it pretty much summarizes the actual objective of the study, what we were hoping to understand.

This shows you, in the one, two, three or four weeks of the study, what people were eating in that week when they reported symptoms and the percent of people reporting symptoms during that week. You can see that about 70 percent of the people in the study said they had symptoms at least once. Said another way, 31 percent had no symptoms over course of the four weeks.

Then you have 41 percent of the people having symptoms on one week of the study. It is equally divided between a placebo week or an olestra week. Then you have got 20 percent of the people having symptoms two times, again well-divided, two weeks on full fat, two weeks eating olestra, or a week eating full fat or a week eating olestra. Then very few people actually had symptoms all three or all four of the weeks.

Now, in this population, GI symptom reporting actually turned out to be higher than the average population. If you recall, 70 percent of these people are saying they are having symptoms during this month rather than 40. So the actual chance that someone was reporting symptoms on a week-to-week basis was about 25 percent.

If you assume that the background of reporting is 25 percent and then you have four chances to make your report, what would you expect to get on random chance alone if symptom reporting is not connected to what people are eating.

I am going to show you that here in the far right column. This is expected by random chance alone, the percent. As you can see, it is a remarkable similarity to what we actually found when we tested these people who had initially called to tell us that they had symptoms when they ate the snacks.

[Slide.]

So we concluded that these particular consumers we were enrolling who were a good representation of the overall population of callers actually did not turn out to be intolerant to eating the olestra snacks and that it was, perhaps, more likely that these reports were just measuring GI symptoms in the population at large.

I think that brings us to the conclusion of the formal presentation by Proctor and Gamble for today. We have, this morning, gone through placebo-controlled studies and in the morning, and also in the afternoon, covered our postmarketing surveillance activities including an understanding of the background prevalence of GI symptoms and the 800-line callers and rechallange of those groups.

[Slide.]

Our data show that olestra does not cause diarrhea. On the basis of objective measurements of stool, stool water content, total stool output and bowel movement frequency, we have no evidence that olestra, even when eaten at five ounces for six consecutive days, would cause diarrhea.

[Slide.]

Olestra snacking, as we saw from our two studies that simulated high and/or unlimited snacking in a single and extended eating studies, we saw no meaningful changes in GI symptoms.

[Slide.]

We did see, throughout our studies with the background placebo rates and by the survey that Dr. Sandler shared with us, that GI symptoms occur frequently in the general population.

[Slide.]

And, from our formal rechallange testing as well as the careful analysis by our five-member panel, we are able to conclude that the 800 line calls do not raise a safety concern.

[Slide.]

Now I would like to introduce Ms. Terry Butler from Columbus.

MS. BUTLER: Hi. My name is Terry Butler. I am from Dublin, Ohio which is a suburb of Columbus. I am a teacher with the Bradford School in Columbus and I am the mother of three children, ages 20, 13 and 11. I am here today voluntarily because I would like to share my experiences with you with olestra and also tell you about my participation in a follow-up study.

I was not paid to be here but Proctor and Gamble was very accommodating in paying for my travel expenses.

Back in the fall of 1996, my family and I were going to watch the Ohio State/Notre Dame football game on t.v. and my son was having friends over. So I ran to the store to grab some chips and dips and things like this. While I was there, I noticed the big display of the new fat-free Pringles. I decided to try some.

So I grabbed a can of the regular fat-free Pringles and a can of the sour-cream-and-onion fat-free Pringles. I took them home. They were very well received. In fact, everyone commented about how delicious they were. We polished off the cans in no time flat and everyone said, "Oh, gosh, they don't taste like the yucky diet chips that you are used to buying, Mom."

So we were really pleased with them. But, later on that night, not everyone that was there, but my youngest son, my daughter and I all experienced some very severe

cramping and diarrhea. Well, immediately I attributed our problems to the chips because it is the only thing that we hadn't normally eaten. It was the only new thing that we had tried.

Our symptoms lasted about less than 24 hours, my kids, and mine was just a little bit over 24 hours. But being a concerned consumer, I saw the number to call Proctor and Gamble and decided that I would tell them about what happened.

So I called. And they were very concerned, very nice. They made some follow-up calls to see how we were doing. They called me later on and asked me to participate in the follow-up study that Dr. Zorich has just talked about.

Well, I really wanted to participate because, like I said, my family enjoyed the chips and I decided I wanted to see if it was the olestra that I had a problem with or maybe something else. So the research study was very comprehensive. Every Tuesday at 2 o'clock I would go in and eat 2 ounces of chips under the supervision of a researcher.

One thing I might common is that 2 ounces of chips is quite a bit. It doesn't sound like a lot but a 6-inch bowl overflowing, it would take me 20 minutes to consume the chips while I was reading a magazine. And this is like eating them constantly.

Before Proctor and Gamble even told me the results, I realized that it was not the olestra that I was having a problem with because I had no symptoms whatsoever during the actual research. I did find out at the end of the study that, yes, I had consumed two bags of olestra chips and I was delighted to know that it wasn't the olestra that I was having a problem with.

I try to give my children healthy snacks. As a concerned mother, I give them fruits, vegetables. But a lot of times, like me, they want something salty and crunchy. And so now, besides pretzels, I can actually give them something that will satisfy them because we have a very busy schedule. My kids play a lot of sports and a lot of times dinner is not until really late.

Now I know that they have something healthy that they can snack on besides the fruits and vegetables that I provide for them. But I really have total confidence, as a mother, in giving my children these olestra snacks and I think it is a great alternative.

Thank you.

DR. McCLUNG: Good afternoon. I am Juling McClung, Mr. Chairman, members of the committee. I am professor of pediatrics at the Ohio State University and Columbus Children's Hospital and I also serve as the Chief of Pediatric Gastroenterology. I appreciate the opportunity

to extend some of my thoughts. I am a volunteer reporter.

With the public announcements that we were to expect an epidemic of diarrhea in the Columbus area, I was particularly interested, and my entire research career has been spent on, studying substances that either soften or harden stools and particularly the interactions of dietary fiber.

We have a medical environment that allows me to see what is going on very well. The Children's Hospital emergency room is the largest emergency room in Central Ohio and my particular practice sees over 90 percent of all GI referrals.

Using this network and our close contact with community pediatricians, I can report the following. No patients have been referred to our pediatric gastroenterology service for problems with olestra. Inquiries made into several large practices in town, none of those practitioners had had reports in their day-to-day practice.

A quick survey of some of our emergency room doctors, including the chief of the ER, nobody had seen or heard of a problem. Now, with the high profile of the warning, I was really fairly surprised at this paucity of reports, so I went a couple of steps further. I contacted the Central Ohio Poison Control Center which has a number of

very high-profile lines in the Columbus area. Anybody who is having a problem can call there, they will help the family triage the problem.

They received a number of generic question phone calls but no phone calls asking what to do because the person was experiencing some type of symptoms.

As one last measure to expand this somewhat informal survey, I checked with the billing coordinators for the two largest emergency rooms in Columbus. They would have had to have brought up unique codes to have coded for anything like this. They had not done that.

Now, simply stated, the introduction of olestra did not show up on the medical radar screen in Central Ohio. There was no epidemic of any sort. Obviously, on this sort of an informal survey, I could have missed an individual case that was coded differently but considering the extremely high profile in the media, it is unlikely that, at least the individuals that I contacted, wouldn't have been aware of the problem and reported on it.

My second comment is from my perspective as a fiberologist. Most of the discussions on olestra have centered on its physical, chemical properties. That is well and good but from a symptomatic medical point of view, I think in the setting of gastrointestinal physiology, we should think of olestra as a modified dietary substance that

goes through the gastrointestinal tract unchanged.

The Fiber Symposium has now lumped this increasingly ubiquitous group of products into what they call the liquid and semi-soft group of fibers. Interestingly enough, when they do this, the side effects of this whole group of compounds are exactly the same as our most cherished group of food substances, the solid fibers.

If you look at the literature of people who binge on fiber, they get extra-soft stools. If you look at the people who eat way too much olestra, they are going to get soft stools. Simply stated, people who eat large quantities of any stool-softening substance will experience that effect.

In conclusion, I was not able to find direct or indirect evidence of medical complications from olestra during its introduction and subsequent sale in the Columbus area. If significant digestive effects are reported in the future, I would expect them to be in this same generic category that we have come to know of as effects of fiber.

Finally, as an individual who feels responsible for public health, I find it increasingly difficult to get important medical messages out to the community when they are being inundated by incorrect information. I think it is important, for the record, to be safe. From my perspective, this is a safe and wholesome product.

Thank you for your time.

DR. DROTMAN: Good afternoon, members of the Food Advisory Committee. I am Dr. Robert Drotman from Frito-Lay.

[Slide.]

Frito-Lay is the world's largest manufacturer of olestra savory snack products and Frito-Lay has collected GI reports from consumers in both the largest test market to date in Indiana. We are also the only company currently in national production of olestra products.

[Slide.]

Today what I am going to focus on is our 800 number, our collection of GI reports as they relate to sales. As was mentioned earlier, our GI reports are collected through a unique 800 number which is found on every bag of Wow product chips, which is olestra chips.

This 800 line is answered by specially trained operators and all GI reports are recorded and data is transferred to Proctor and Gamble on a daily basis. Routine reports are transferred immediately for follow up.

[Slide.]

Very quick information about the two types of markets I am going to talk about today, the Indiana test market. Products were introduced in February of this year. This test market was continued for one year. It contained several brands and flavors of potato chips and tortilla

chips. It was sold through the multiple retain channels you are used to, supermarkets, warehouse clubs, et cetera.

In this market over the one-year test period, we sold about 2.5 million bags of chips.

[Slide.]

Our national product rollout just began in February of this year. We were in complete national distribution by March 30. This has two brands and one flavor of potato chips and one brand of tortilla chips sold in multiple retail channels just as it was in the Indiana test market. We sold about 78-and-a-quarter million bags so far.

[Slide.]

Now, I am going to turn back to the test market. I am going to bounce back and forth between both the test market and the national market. The cumulative GI report frequency through week 16 and the test market was about 305 people with GI reports per million bags sold.

I have through week 16 so this is going to be directly comparable to the national market. The greatest majority of the reports occurred in the first 11 weeks and they dropped off significantly after this period of time. On the bottom line, I would just like to draw your attention to the average calls per week in the second half of the test market. We actually had less than one call per week with

the GI report.

[Slide.]

For the national launch, consumer response has been overwhelmingly positive so far. The GI reporting is significantly lower than it was in the test market and through week 16, it has only been about 71 people reporting per million units or per million bags sold relating to the 305 in the test market.

GI reports represent a small percentage of all or our 800 calls, about 3 percent, and compliments are outnumbering GI reports about 10 to 1. About 30 percent of the calls are compliments.

[Slide.]

This demonstrates the number of calls we got. This is the number of calls plotted against the test-market week. As I mentioned earlier, you can see there are two phases here, phase 1 which occurs through 11 weeks. We had an average of about 43 persons calling per week and we had about 83 percent of our calls.

From week 12 through week 51, we only had about three calls per week. We believe the first phase, or the first 11 weeks, was due to high media activity.

[Slide.]

The next slide relates the sales with the GI reports. You see there is no relationship. Sales continued

after week 11, approximately week 11 or 13, at a strong and steady rate and GI reports tail off significantly. Actually, in the last eight weeks of our test market, we got no reports despite the fact that sales were steady.

[Slide.]

This just compares the Indiana test market report rate with the report rate from our national market. As you can see again, you have that large spike within the first 11 weeks of the test market and then it is coming down to approximately what the national market is.

You can see there is a significant difference in the two reporting rates in test versus national market.

[Slide.]

Just some quick data for you. We estimate that about 37 million people have eating this product so far. We have sold, again, about 78-and-a-quarter million bags. It represents almost half a billion servings. Total GI reports out of that are about 5,500, 5,600 GI reports. We have had about 177,000 total 1-800 calls.

[Slide.]

To give you an idea of how the GI reports related to the rest of the phone calls we have gotten, we classify "other" as about 51 percent. That is the purple portion of the pie. That includes things like product information, what product is this in. We get a lot of questions like

that.

You see the red part, which is the compliments, which is about actually 30 percent of the phone calls. And GI reports represented about 3 percent which is about ten-fold less than the compliments we are getting.

[Slide.]

Finally, I would like to say that consumer response to olestra products is positive and test-market and GI reports dropped off significantly after week 11. And for national induction, GI report rate, so far, has been significantly lower than the Indiana test market.

Sorry to go so fast, but I wanted to make it in seven minutes. Thank you.

DR. BRANDT: Actually, you made it in five minutes. You have two whole minute left if you want to use it. Dr. Zorich, Dr. Treibwasser, do you want to wind up? You have got two minutes.

DR. TREIBWASSER: That completes our presentation. We will not use the two minutes. We will take questions.

DR. BRANDT: Thank you very much. Appreciate it.

Questions of Clarification

DR. BRANDT: We are now open for committee discussion of all of the material presented by Proctor and Gamble. Anyone have a question?

DR. BENEDICT: I guess this question is for Dr.

Sandler. In an effort to be fully confident, in my own mind, which doesn't mean much, I realize, globally, of the strength of your survey, the telephone survey, my question, which is going to be poorly formulated, will be something along the lines of the people who answer the phone and agree to do this study, are they people who have jobs and work during the day?

Are they people who mostly stay at home? Are they mostly retired folks? Are they people who might pay more attention to their bowel habits than, perhaps, other people?

DR. SANDLER: That is very good question. That was well-formulated. Let me tell you a little bit about the survey techniques. These are commonly used, random-digit-dialing, techniques that specify that the calls be arranged on weekdays, weekends, evenings and throughout the week so that we capture a full range of people.

Secondly, because the response rate was quite high--it was 71 percent which is actually quite high for this kind of method--I think we can be reasonably confident that these are more or less representative. Now, we don't know anything about the people who don't respond so, perhaps, in fact, these estimates may be off a little bit.

We carefully begin the survey with some questions that have nothing to do with bowel function. We do that because we thought that people wouldn't talk about bowel

function on the phone. We were very surprised and, in fact, from this survey and from some other surveys that we have done that have included even more intimate details, people are quite willing to talk about this.

So I am reasonably confident and I am also confident in the estimates in the fact that the responses to the first survey and the second survey were very similar.

DR. FUKAGAWA: I just had a quick question. Do you compensate your volunteers for participating in any of the studies, Dr. Zorich?

DR. ZORICH: Yes. We always do and we always negotiate what is considered to be the appropriate and fair compensation through the IRB. All the studies have had full IRB approval.

DR. CLANCY: Another question for Dr. Sandler. You have presented both your study and the CDC study about background GI complaints but I just want to be clear about this. You are not saying that the people who might have been responding, calling a hot line or something, around olestra are, by definition, the same people that you are gathering background--it could, in fact, be that people could respond to olestra when they don't normally respond to, say, things like beans or onions or spicy foods, or have you been able to correlate that?

DR. SANDLER: I guess what I am saying is that

these symptoms, pain and cramps and diarrhea, are very common in the community. 40 percent of people that we surveyed had one of those symptoms during 30 days.

I am not saying that those are the people who get called in. That would be impossible to say that. It would also be impossible to say that someone who called in did, in fact, experience a side effect with olestra. Perhaps they did but, by the nature of the passive surveillance system, you can't attribute that event to that cause.

That is why I think that we need to pay attention to the scientific studies when scientific studies are done in a controlled fashion in the home simulating normal eating experience. We just don't see it.

DR. CLANCY: This is a general policy question. 60 percent of people in a month don't experience any kind of gastrointestinal symptoms is also what you are saying so we have to be pretty careful about looking at background data in general as we look at various studies.

DR. SANDLER: I think that is true.

MS. RICHARDSON: What was the time period between the initial call to the 800 line and then the follow up?

DR. ZORICH: Actually, that varied by test market. These test markets, perhaps--this all goes by so fast, but they were separated in time. The rechallange study did not start until after we were already into the first set of test

markets because it was only after the calls started coming in that we were motivated to conduct a study to address it.

So, for the first test markets, there was, perhaps, of the order of 1 to 2 months before the person was asked to come back in. By the time we were in Columbus and Indiana where we actually had the majority of the participants, the sites were up and running. So the amount of time became smaller and smaller and, for many people, it was even on the same day.

Once the site is up and running, we could enroll people as they were calling in.

MS. RICHARDSON: Did any of these callers indicate whether or not, in that interim period, that they had tried another olestra product and had any other symptoms?

DR. ZORICH: Actually, most of these callers, I would say, in fact, stated they had not tried it again based upon their initial experience. So it would have been rare, of course, that they would have had that and that would have confounded, of course, our analysis.

But, no, they did not.

DR. WANG: I didn't see the slides too well on the two slides that you have, the duration, the onset of the diarrhea symptoms. Will you be able to show that to us? The reason I am asking this question is I am rather concerned about--

DR. BRANDT: Who are you asking the question to, which slide?

DR. WANG: Dr. Sandler. The two sets of studies comparing the survey that CDC did on population base, if my understanding is right, the purpose of that study is to show underreporting of food-borne illness information data; right?

DR. SANDLER: That is a preference of Foodnet. But the point is they surveyed 9,000 people and they said, how often did people have diarrhea in a month and 11 percent of people did. I think that, if I can sort of follow up on that, a lot of people have diarrhea in a month and we don't know why it is. Probably a lot of it is food-borne infectious illness which we are not talking about today.

Some of it is probably irritable-bowel syndrome. Probably some of it is non-food-borne enteric viruses. And some of it we probably can't explain. But, based on what I have seen, I don't think it is due to olestra.

DR. WANG: Was there any follow up on the frequency of the diarrhea, each person--I mean, when you are comparing these data, you said it was a six-hour onset and they recover within 24 hours.

DR. SANDLER: That is slide 52.

[Slide.]

DR. BRANDT: Is that what you are interested in?

DR. WANG: Yes. The duration. How about the one before where you have the onset. Do you have one before that?

[Slide.]

DR. SANDLER: I guess the point I made when I showed this, if I can clarify, is that people who experience diarrhea, they did it very quickly after eating this product. The question is did the product cause the diarrhea or was it coincidence and, because it was such a short interval, people remembered eating the chips and attributed the diarrhea to the chips.

Based on the controlled studies, you didn't see any changes in people's stool consistency after six hours. In addition, remember that most of the people who ate chips and experienced diarrhea in six hours didn't eat very many chips. By and large, they ate less than 2 ounces. So I think that this is probably coincidence and not cause and effect.

DR. WANG: Thank you.

DR. CLYDESDALE: Dr. Zorich, on the rechallange study, I don't think I am quite clear on how you selected the subjects and how that number were selected out of the total numbers.

DR. ZORICH: We did not select the subjects. They were self-selected. We asked everyone who had called either

Frito-Lay or Proctor and Gamble during the first year of test market. Whenever, we had a phone number that was valid for that person and we can call them back, which was the majority of people, we asked them if they would be willing to participate in the study and then we had a prepared text to kind of take them through to let them know what we wanted them to do.

Of that group of people, actually 98, agreed to participate in four test-market sites, actually five test-market sites.

DR. BRANDT: Dr. Potter, who is from CDC, by the way.

DR. POTTER: Dr. Sandler and Dr. Wang both mentioned the CDC Foodnet survey. In that, the definition of diarrhea was three or more loose stools in a 24-hour period and that came out to 1.4 episodes per year. In one of the Foodnet sites, the State of Minnesota, they asked for an unqualified diarrhea, or diarrhea of all definitions, and it came out 1.8 episodes per year. I think all of the Foodnet sites were outside your test-market areas.

DR. HARLANDER: Can I ask a question of Terry?

DR. BRANDT: You may, indeed. You can ask a question of anybody that has presented.

DR. HARLANDER: Terry, I am wondering when you purchased the chips, were you alerted by the label on the

chips or were you aware of possible GI symptoms based on negative publicity that you might have seen in your area or read in the newspaper, or what caused you to make the association with the chips?

MS. BUTLER: I bought the chips, I think the first week they came out in Columbus. I had not read any negative publicity at all about the chips. I just thought they sounded like--fat-free; it sounded wonderful. I purchased the chips and just made the association because that was the only thing I ate that day that was different from--that I hadn't normally eaten.

So I had no preconceived notions about the chips before I ate them.

DR. FEINLEIB: One of the symptoms we are concerned about is fecal incontinence. How many times was that reported in either the national or the regional surveillance?

DR. SANDLER: I would begin by pointing out that, just for background, in 1986, we published a study where we interviewed 1,000 college studies and hospital employees. 5.5 percent reported fecal incontinence when they had diarrhea, the point being when normal people have diarrhea, sometimes they have fecal incontinence.

I don't have it at the tip of my fingers how many people reported fecal incontinence, but I don't remember--I

don't know the numbers.

DR. ZORICH: Actually, in spite of the concern that has been raise about this, that has been reported exceedingly rarely and is in the category of one of the rarest reports.

DR. FEINLEIB: The second question. I think you said something like 80 percent of the people have symptoms after eating onions, spices, and things like that, continue to use those products. Do you have any information on those who reported symptoms related to olestra, what proportion of those continued to use the olestra chips?

DR. SANDLER: I guess that presupposes that you believe the symptoms are caused by olestra chips. I think it presumes that the people that are experiencing symptoms are really having it due to olestra chips.

What I can tell you is that, for example, in the home-consumption study, the six-week study, people in the olestra arm who had symptoms kept eating olestra chips. So that is probably the only information we have on repeating eating in people who are really getting olestra chips.

DR. BYERS: Just a quick question on the protocol for the rechallange study. These were all done fasting; is that correct?

DR. ZORICH: No.

DR. BYERS: What was the protocol, then? Were

they allowed to come in at any time of day?

DR. ZORICH: We schedule the timing so that it would be in the afternoon or early evening to work around people's work schedules and there was, in fact--we did not give them any instructions to change their diet. They did know that they had to eat chips, 2 ounces.

So the way that we tried to compensate for the otherwise not controlling of their environment was to have them come in on the same day of the week at the same time, thinking that all things being relatively the same for most people's routines, that if you came in Tuesday at 2:00, that would be a typical day.

We avoided the weekends, of course.

DR. BYERS: Let me correct my question. I didn't mean fasting as in a.m. fasting. But this was basically between meals and this was the only food consumed.

DR. ZORICH: Other than a soft drink.

DR. LAMM: Dr. Zorich, you mentioned that individuals were paid. What was the dollar amount that you paid for various types of participation?

DR. ZORICH: Actually, in the feeder test, there was no dollar amount. These people received a free movie pass to the same theater. In the home-consumption test, for participation of the full family, they were given $50 per individual in the family for all six weeks. In the

rechallange, study, it was $150. The IRB thought that was fair because they had to drive to a site four times and then they had to spend time on the telephone several times in the week.

DR. LAMM: Thank you. Second question for Dr. Sandler. In your national survey, it was limited to English-speaking households. Has there been any particular attempt to take a look particularly at the Hispanic population?

DR. SANDLER: There has not been a special attempt to look at the Hispanic population. I would comment that we did look at African-Americans and their responses were identical in every way to whites. But we did not look at Hispanics.

DR. LAMM: Thank you.

MS. RICHARDSON: I have a question for Dr. Zorich. Ms. Butler indicated that when she purchased her chips that she was also purchasing dips. Did there seem to be any correlation between whether or not people just ate chips cold or that they were dipping them into onion and clam dip?

DR. BRANDT: I think what she said was she was picking up a variety of Pringles potato chips, didn't she say? You got something mixed in with or something? Sour-cream and onion variety; yes.

DR. ZORICH: We have not specifically looked at a

combination of chip and dips, but we have done a variety of studies which cover everything between snacking scenarios and coconsumption with the diet. So we do have a range of data on different kinds of eating patterns but not specifically dips.

MS. RICHARDSON: Second question. With the people who call in to the 800 number, having several friends who always contact manufacturers about whatever product it is, do these people, then, receive, like, coupons and things?

DR. ZORICH: I would say that Frito-Lay--Dr. Drotman? When there is a call to Frito-Lay, do you send a coupon?

DR. ZORICH: And also for Pringles? He said it depends on the situation. They do not always coupon. I would say that the same is true for Pringles. They do not always coupon. The telephone operator is given a series of instructions and they can decide whether the person actually would be not enthusiastic about receiving a coupon and then we wouldn't send.

MS. RICHARDSON: The last question is for Ms. Butler. In talking about your call to the 800 number, you indicated that you looked at the label and then made the call. When you purchased the chips, did you look at the label before you purchased them after you got them home and you started to eat them, or was this where you had to go

through the trash and retrieve it and look at the label?

MS. BUTLER: No; I didn't even notice the label when I bought them. Like I said, I hadn't heard any negative publicity and I didn't see any reason to look at the label. It was, like, a fat-free chip that I was interested in trying and it was after our symptoms started that I decided, "Well, maybe I want to call the company," just being a concerned consumer.

That is when I did--I think I did dig through the trash and find the can, and I saw the number.

MS. RICHARDSON: Did you find the label prominent and user-friendly?

MS. BUTLER: Yes. I thought it was a good label.

DR. APPLEBAUM: I have several questions on the volunteers for the rechallange study. Were you surprised, or can you inform me whether 10 percent agreeing to participate--is that a good number, or do you consider that a low number?

DR. ZORICH: Actually, the data that we have is that actually that is a good number. The source of that data actually is talking to the people at Nutrisweet. For instance, when they had concerns about headache, their formal rechallange program included 40 people.

DR. APPLEBAUM: Then, in regards to the text where you say the others could not be contacted, or refused to

participate, can you provide some more information on "could not be contacted?" They just didn't answer the phone? It was a wrong phone number?

DR. ZORICH: Yes; a wide variety and often we would attempt three follow-up calls. We could just be getting answering machines so we always left our number and asked people to call us back. Sometimes they did. So that was another reason that they couldn't have been contacted.

DR. APPLEBAUM: Last, but not least, in the case of Ms. Butler's family where you had not only herself both others in her family allegedly impacted, were there members of her family, or did you go to one family representative only?

DR. ZORICH: No. Actually, we were interested in enrolling everyone so there were no exclusions. The only exclusion would have been, and it is not an exclusion. That is the wrong word. We had generally run cohorts through the study site in time and so we would have asked other family members to participate in the next round of study because we didn't want the confounding of people, then, reporting in the same weeks.

So everyone could have participated from the study, just at a different time.

DR. ASKEW: This is for Dr. Zorich. Have you, in any of your earlier studies or your later studies identified

an individual that is olestra-intolerant, that olestra will, every time, cause abdominal cramping, bloating, GI distress?

DR. ZORICH: No.

DR. BRANDT: We are now going to turn to our friend, Dr. Larsen, and his administrative announcements.

DR. LARSEN: I just have one brief announcement, that the waiver for Dr. Hubbard has been approved by the agency. So once he signs the waiver, he will have full participation in the meeting.

DR. BRANDT: Will you sign that waiver pretty quick. Thank you very much. I appreciate that.

DR. BLACKBURN: I just had a brief little comment for the benefit of Steve Benedict and Dr. Sandler, perhaps. When I went to medical school they called people who were particularly observant of and conversant with their excretory functions "stool gazers." It was shortly after medical school that I learned the name of the grandfather of the society of stool gazers who was Johnathan Swift. He wrote a wonder tract with the title, Human Ordure.

I not long ago got a photocopy of that from the Library of Congress. It is a thoroughgoing scientific treatise, also a treatise in mythology, the mythology having to do with the form that it took on the ground.

It was a very rich and fertile field for epidemiology at that time because, of course, there were no

indoor toilets. I learned subsequently that the father of modern SG was, of course, Dennis Burkett. He spent a great deal of time, and I hope some of you have seen his marvelous lecture, observing things in Central Africa in the early period of his career.

He had a particularly delightful description of the difference between his missionary colleagues who had rabbitlike excretion versus the local natives who had herbivorous ones. He is the only person I ever met who called himself a fiberologist until Dr. McClung this afternoon. I would like to talk to Dr. McClung about that. Dennis had a body-mass index of 10.

That is my comment.

DR. BRANDT: We appreciate your bringing intellectualism back to the committee. We can always count on you. Stool gazing is not what we called them when I was in medical school, but the name was something else.

Center for Science in the Public Interest presentation. You will have 50 minutes, Dr. Jacobson. Use them as you see fit. I am now setting the timer.

CSPI PRESENTATION

DR. JACOBSON: Thank you very much, Dr. Brandt. I appreciate the opportunity that the FDA has given to us to be here this afternoon.

Olestra has been the subject of a number of

studies of its ability to cause gastrointestinal symptoms. While the controlled studies appear well-done, it is regrettable that not on study was conducted with significant independence from the manufacturer.

That said, we turn to a review of some of the research including information that CSPI has collected. I would like to begin with a brief discussion of two key words; harm and diarrhea. At the 1995 Food Advisory Committee meeting on olestra, then-Commissioner David Kessler noted that if olestra just modified the consistency of someone's stool, he wouldn't care.

But, "If someone is going to the bathroom all day and there is really an effect on someone's life, then that certainly can be--I think one could argue, that is harm." We concur with his reasonable definition.

It appears that some FDA officials believe anything less than permanent medical harm does not constitute harm. One official said, "Even the worst isolated cases reported anecdotally through CSPI don't meet the clinical definition of 'serious.'"

Using a very strict definition of harm, would one likely adopt a very different policy recommendation than if using Dr. Kessler's definition. We believe that consumers don't expect even mild cramps, increased frequency of bowel movements or any other adverse symptoms as a result of

eating snacks.

In some cases, olestra appears to cause such severe, though not permanent, symptoms that they totally disrupt people's daily routines. Sometimes those incidents lead to safety risks that could result in serious injury or death.

The second definitional issue concerns diarrhea. In some discussions, both the FDA and P&G insist on distinguishing between diarrhea and loose stools. In other places, but not on the special olestra label, FDA acknowledges that olestra causes diarrhea. When it approved olestra, the FDA made the common-sense argument that, "The difference between loose stools and diarrhea-like stools may not have always been clear to the study subjects and may be simply variable manifestations of the same effect."

In other words, what some people labeled loose stools could actually be diarrhea and vice-versa.

Then there is the effort by FDA and P&G to disregard any form of diarrhea other than so-called medical diarrhea. Although diarrhea involving loss of fluids and electrolytes is clearly clinically important, there is no reason, arbitrarily, to dismiss all other reports of diarrhea as insignificant or irrelevant to a person's choice of potato chips.

Moreover, as we will discuss shortly, at least one

P&G clinical trial, the small but important fecal-parameters rechallange study, demonstrates that medically significant diarrhea does occur in olestra consumers.

It is worth considering various experts' definitions of diarrhea. Dorland's Medical Dictionary defines diarrhea as, "abnormal frequency and liquidity of fecal discharges." The CDC defines it as, "three or more loose stools in a 24-hour period." NCI has a grading system with grade 1 diarrhea being an increase of two to three stools per day over pre-drug treatment. Grade 2 is an increase of four to six stools per day, or nocturnal stools or moderate cramping. Grade 3 is an increase of seven to nine stools per day or incontinence or severe cramping, and so on.

In some of P&G's studies, diarrhea was defined as the frequent passage of watery stools that are difficult to control. Hundreds, although possibly thousands, now, of people have told P&G or CSPI that experienced frequent watery bowel movements with hours of eating olestra. Several people reported that they went to the emergency room and were given IV fluids to prevent dehydration.

Obviously, none of those individuals or their doctors could document water or electrolyte losses, but we ignore their observations and diagnoses at our peril. What they experienced was clearly different from a simple change

in stool consistency. The committee should conclude that olestra causes diarrhea.

At its 1995 meeting on olestra, there was minimal discussion of severe effects caused by diarrhea. One key study was not discussed at all and others were discussed but not with regard to olestra. I would like to introduce CSPI's Director of Toxicology, Dr. Mark Brown, to discuss some of the studies showing that olestra causes severe GI symptoms.

DR. BROWN: Thanks, Mike. I have some nice slides for you which I will share with you in a moment. But, before that, I would like to talk about some of the data from all available studies that address this issue of the severity of gastrointestinal disturbances in both the average consumer of olestra and the possibility that there may be some especially sensitive consumers of olestra who show more severe effects.

As you heard, most subjects in P&G's clinical studies report only mild to moderate symptoms. But, in some cases, subjects report more severe episodes of gastrointestinal disturbances. For example, in FDA's analysis of Proctor and Gamble's two eight-week clinical trials which have been alluded to several times as the key studies that address the whole issue of GI effects of olestra, the FDA reported in the Federal Register notice

which was in your briefing booklets, and I quote, "Although most symptoms were reported as mild on average, the petitioner," P&G, "stated that at least one symptom described as severe was reported by some subjects.

Our analysis of this data that has appeared in the Federal Register notice indicates that it was a statistically significant increase. This is table 1 under tab FDA of your briefing books.

Secondly, Mike alluded to another study which I don't think that this committee has considered yet. This is an analysis by one of FDA's medical officers of an earlier consumer rechallange study that was conducted in 1989 given the somewhat unlikely title, Measurement of Selected Fecal Parameters.

This analysis found that there was an increase in the incidence of diarrhea reported as severe with increasing olestra consumed over the seven-day treatment period. Our analysis of this data is shown in table 2 under tab F of your briefing books.

The study is unique. This earlier rechallange study, the 1989 rechallange study is unique for several reasons which I would just like to briefly go over. It is unique because it is the only study that involved a rigid preliminary prescreening process of subjects in an effort to identify individuals who might be especially sensitive to

olestra.

No other study has used such a rigid prescreening process. So, specifically, 52 person who believed that they were affected by olestra were prescreened. Perhaps some of them weren't really experiencing effects from olestra. So they rechallenged those. Out of that, they found approximately 35 percent or 18 subjects, only a handful, who appeared to be reproducibly affected by consuming olestra.

Secondly, that study was unique because it involved consumption of olestra for seven consecutive days instead of just one or two widely separated days, as in some of the other rechallange studies or acute studies that we have heard about this morning.

FDA's medical officer further reported that in these the rigorously prescreened subjects of this study that subjects who consumed 20 grams a day of olestra over the seven-day period experienced mean daily stool weights that exceeded the stool weights during the placebo phase of the study. It happened to be a crossover study.

This suggests, obviously, that these individuals were experiencing the increased water and possibly electrolyte loss that are the hallmarks of clinical diarrhea.

The FDA, in its own analysis of this study that appeared in the Federal Register, also noted that there was

an increased weight of stools and subjects reporting diarrhea when eating 20 grams a day of olestra that could not be accounted for by just the presence of the olestra in the stool.

Other evidence shows that many of the subjects who report these types of GI symptoms experience seriously inconvenient effects from consuming olestra. In their two eight-week clinical trials, P&G stated, in their own conclusions about the trials, and I am quoting, "Six subjects, in either the 20-gram-per-day olestra group or the 32-gram-per-day olestra groups, temporarily stopped eating olestra foods because of their GI symptoms."

They also stated that, "Two subjects in the 32-gram-per-day group were temporarily removed from the study. One of them was given Imodium for diarrhea. The subject in the 20-gram-per-day group was temporarily removed from the study but not given Imodium."

My point is that these subjects, which amounted to six out of approximately 115 subjects who were on this diet, or about 5 percent, surely these subjects, if they were here today, would tell us that these symptoms had some meaning to them, that they were not without meaning, that they were, at least, inconvenient.

The data from these two eight-week clinical trials tell us that the average consumer of olestra can expect to

sometimes experience seriously inconvenient or, to use the word that we heard earlier, this morning, "meaningful GI symptoms."

As has been noted, both P&G and CSPI have received numerous anecdotal accounts and also in the postmarket surveillance data from olestra consumers some of whom describe severe GI effects, including emergency room visits. Taken together, these results seem to us to be consistent with the conclusion that olestra consumption can sometimes cause severe adverse GI effects in at least some individuals.

The rates of the most severe GI effects may be under 10 percent. We don't know. We haven't really seen any data that would address specific rates. But the point is that is severe effects are 1 percent or lower, no reasonable clinical trial or, indeed, any postmarket surveillance is going to be able to easily detect a 1 percent of a tenth-of-a-percent rate of severe GI effects.

Therefore, the postmarket surveillance study or the anecdotal reports or case reports, although they can't prove that the effects are really associated with olestra, they may be our only ability to have any insight into the most severe effects that olestra can cause in at least a few individuals.

Thank you.

DR. JACOBSON: I would like to continue now by discussing virtually the only independent data on GI symptoms, data that CSPI has collected in two different ways. First, beginning in April 1996, CSPI has invited consumers who believed that they were affected by olestra to contact us by telephone or E-mail.

CSPI had received about 1900 adverse-reaction reports including 600 since Wow chips went national in February. As of late May, Proctor and Gamble had received about 7,000 reports. That include Frito-Lay. Because most people don't report symptoms, those 9,000 or so reports represent only a small fraction of the total number of people who believe they were affected by olestra.

We recognize that the symptoms reported cannot be proven to have been caused by olestra and sometimes might be purely coincidental. Normally, one would treat such consumer reports with skepticism and conduct controlled studies to determine whether the symptoms could be caused by the suspected agent.

In this case, however, controlled studies were conducted before the consumer reports were receive. The consumers are reporting the same kinds of effects seen in those studies. The reports indicate that the symptoms found in the studies do, in fact, also occur in real consumers. Many of these reports provide insight into how real people

are affected in their daily lives especially by severe symptoms.

For instance, at least 37 people told P&G or CSPI that they had to go to the emergency room. Hundreds more said they called or visited a doctor. People have undergone colonoscopies, ultrasound, X-rays, blood, urine and stool analyses. Patients were prescribed a wide range of drugs and one man needed two injections of morphine to relieve the pain of cramps.

Some of the doctors attributed the symptoms to olestra. Three teachers had to run out of their classrooms to get to the bathroom in time leaving their students unsupervised. Numerous women said that their cramps were as severe as labor pain during childbirth.

Several consumers defecated in their clothing at word. Others defecated in their clothing at home, while shopping or in their car or in the middle of the night. Several business people missed important meetings. One woman was driving to the hospital because of cramps that she attributed to olestra. On the way, she experienced another cramp and was almost in an accident.

Several other people told us that they had to drive at unsafe speeds to get to a toilet in time. Several people, including two healthcare professionals, reported having blood in their stools. One young physician reported

experiencing severe diarrhea followed by thrombosed hemorrhoids.

One person had a gall-bladder attack and subsequent surgery with the physician attributing the gall-bladder in part to olestra. Obviously, such symptoms engender great concern in consumers, but they were not discussed by the Food Advisory Committee.

To give you a better sense of the misery that olestra appears to cause, I would like to introduce Tracy Blume from Moorsville, North Carolina, to describe her run-in with some potato chips.

MS. BLUME: Nice segue of run-in. My name is Tracy Blume and I am flight attendant for U.S. Airways. While I was over at a friend's house, I had occasion to try a handful of the potato and nacho chips made with olestra. Within one hour, I experienced mild stomach cramping. Within 24 hours, I was in acute abdominal distress accompanied by diarrhea that followed within 36 hours.

Aspirin, Advil, Accid AR, Mylanta and Pepto-Bismol offered no relief nor did soaking in a hot tub or alternating a heating pad with ice packs. I was unable to get any relief from the constant, intense pain that racked my body leaving me frightened and exhausted.

I sought medical assistance within 72 hours of eating the olestra chips. It was Easter Sunday and the

doctor on call at my doctor's office was not my primary-care physician. He thought my problems might be ulcer-related even though I have no history of gastrointestinal problems. His suggestion to take Accid-AR and Mylanta did nothing.

On Monday morning, I found myself at an urgent-care facility. The doctor there thought I was suffering from gallstones. She put me on a clear liquid diet and scheduled an ultrasound. On Tuesday, the ultrasound revealed no gallstones, tumors or otherwise. On Thursday, I was finally able to see my primary-care physician. His diagnosis was olestra poisoning after ruling out food poisoning and other causes.

My colon had been aggravated and was in spasm from my body's adverse reaction to the olestra chips. He prescribed the antispasmodic Levbid and my symptoms began to ease. I was on a clear liquid diet for a full week following that.

I have never experienced anything like this before in my life and find it highly unlikely that its occurrence shortly after eating the olestra chips was merely coincidental. It is unbelievable to me that the FDA has approved olestra for human consumption knowing full well that it has the potential for severe reactions in some people.

The symptoms I experienced were nowhere near

"normal" everyday aches and pains as Proctor and Gamble would have us believe. I was deathly ill for a full week, lost time from work, ran up hundreds of dollars in medical bills trying to find out the cause of my pain and diarrhea and was unbelievably frightened not knowing what was wrong with me when all the over-the-counter medications for abdominal pains and diarrhea were ineffective.

Our government has an obligation to protect the public's food supply. Warning labels alone are not sufficient for any product made with olestra. I feel the FDA has been hasty in its approval of olestra's use for public consumption and I strongly encourage the FDA to take a strong stand to protect the people of America by taking this product off the market.

As a flight attendant, I am very concerned about the health and welfare of flight crews who may suffer and adverse reaction to olestra while on a trip or in flight. One person reacting as severely as I did is too many. Thousands is unconscionable.

Please do the right thing and do it now.

Thank you.

DR. JACOBSON: Thank you very much, Tracy, for coming up to Virginia.

If there were just a handful of undocumented reports, they could be dismissed as just coincidence. But

here we have thousands with a sizeable percentage of people reporting severe symptoms. Virtually all of the symptoms are consistent with the effects seen in P&G's clinical trials.

Some of the symptoms, such as fecal incontinence in healthy adults, yellow stools and vomiting up of oily material are uniquely characteristic of olestra's properties. In some cases, physicians diagnosed their patients' symptoms as being caused by olestra.

In some cases, people have tested themselves. One physician titrated herself down from about a half an ounce to a quarter ounce and reexperienced symptoms every single time. While P&G dismisses all the anecdotal reports, it simply begs credulity to attribute them all to causes other than olestra. You can bet that if there were no such reports, P&G would be claiming that the lack of reports reflects olestra's safety.

[Slide.]

We have analyzed a sample of 875 reports, mostly from Indiana. People affected range in age from five months to 89 years. 8 percent of people were children under ten, including 2 percent under the age of three. 11 percent were over 60 and 1 percent over 80. These people included 34 nurses, a physician, a machinist, a fire fighter, an airline pilot, an air-traffic controller and a roofer.

Olestra was consumed 75 percent of the time as a snack, 25 with meals. 11 percent of the callers said that they had a preexisting GI condition such as ulcers, colitis and so on. On 5 percent of the people who called CSPI said they also called P&G.

[Slide.]

Abdominal cramps, diarrhea and loose stools were the most common symptoms with about 80 percent of the callers affected by each. Vomiting was not a symptom in our questionnaire for most of this sample, but about 10 percent of the callers listed that symptom both voluntarily and after we added it.

Fecal incontinence and hives, which were never in our questionnaire were each reported by just under 1 percent. 92 out of the 875 reports indicated that people were inconvenienced, mostly at work or while driving. 28 said they missed work or school.

We examined a series of 250 consecutive reports to estimate rates of severe symptoms. 14 percent of those reports included a severe symptom with cramps, diarrhea and gas being the three most common. Six people volunteered that they thought they were going to die. Three said they were doubled over with pain and one pregnant woman thought she was experiencing preterm labor.

9 percent of the people said they sought medical

advice. Four people, a half of 1 percent, went to the emergency room and 50 out of 875 people said a medication was used to alleviate their symptoms. More recently, since it has gone national, we are getting a much higher percentage of the reports to us represent severe symptoms.

In a sample of 100 reports from Indiana, we estimated the interval between consumption of chips and onset of symptoms. About one-half of the callers said that their symptoms occurred within eight hours of consumption. Another 40 percent said their symptoms started between 8 and 24 hours after consumption and five people said symptoms started 24 hours or more later.

In those 100 reports, 86 indicated the duration of symptoms. 19 people said two hours or less--that is 22 percent. 30 percent of the people said three to 18 hours. And 23 percent said their symptoms lasted two to three days. 2 percent of the people said symptoms lasted a week or more.

The amount of chips that people who experience symptoms consumed was generally quite ordinary. In a sample of 92 people for whom we could estimate the amount consumed, 34 consumed less than half an ounce and another 28 between one-half and one ounce. Only five people consumed 4 to 6.5 ounces. And our data are quite similar to what P&G found.

In the seven weeks or so in which CSPI was

publicizing its toll-free number in Indianapolis, we received four reports of people who went to the emergency room. Considering that Indianapolis represents less than one-two-hundredth of the U.S. population, it is likely that olestra products have already sent at least hundreds of people to the emergency room assuming that olestra was the cause in those situations.

Because not everyone who went to the emergency room contacted CSPI or P&G, for that matter, that number may even be in the thousands. Judging from the reports we have received, gastrointestinal symptoms caused by olestra add an extra and unnecessary burden to America's healthcare system.

The second type of study that CSPI conducted was a random telephone survey of Indianapolis consumers to get some sense of the prevalence of symptoms attributed to olestra. The survey was conducted by a major survey research firm and included 543 consumers with 204 who had olestra.

On average, the respondents ate regular chips an average of eight-and-a-half times in eight weeks, or 73 percent more often than people who ate olestra chips, who ate them about five times in eight weeks. 15 out of the 204 olestra eaters, or 7.4 percent, said they experienced adverse gastrointestinal effects.

[Slide.]

Not one of the 351 people eating conventional chips, almost twice as many times, associated any GI effects with eating those chips. It would appear that, given occasional exposure, about 1.5 percent of the people would experience adverse effects per exposure. 1.5 percent is 7.4 percent divided by the 4.9 exposures to olestra.

It is worth noting that not one of the 15 people who reported GI symptoms said they called either P&G or CSPI to report their symptoms. Obviously, some of the people who said they experienced a symptom due to olestra could have misattributed the cause. Likewise, some people may have experienced GI symptoms but did not realize that olestra was the cause.

While P&G has said that CSPI's t.v. messages misled people into thinking olestra was unsafe, our telephone survey found that five times as many people saw ads for Olean or olestra-containing products which may have misled people into thinking the products were safe.

I would like to highlight several of the inadequacies of the passive surveillance process. The FDA allowed companies to print the olestra notice on the front of the package but all three companies that use olestra print it on the back. The FDA allowed companies to include a toll-free number in the notice, but none did so.

Also, some people told us that when they called

the manufacturer, they got a busy signal or a recorded message or were disconnected. One person said that Frito-Lay's telephone operator even denied that olestra could cause the severe symptoms that she wanted to report, and one person told us that the operator refused to accept is report because he didn't have the Wow chip package.

All of those factors help companies make spurious claims about how few complaints they have received. Of course, one reason for the declining number of complaints with time is the declining sales of the chips with time in Indianapolis and other test markets.

Now, let me turn the microphone back to Mark Brown for our critique of P&G's recent clinical studies.

DR. BROWN: I am going to talk about our analysis of some of the recent postmarketing studies that we have heard about earlier today. First, I think that the recent postmarket studies really have to be understood, and they can really only be understood in the context of the earlier P&G studies that were presented to the Food Advisory Committee back in 1995.

Especially, I want to draw your attention to the two eight-week clinical trials that were alluded to earlier that were conducted in 1992 and 1993 in which subjects were fed 0, 8, 20 or 32 grams per day of olestra in their meals.

In reviewing those studies following the last Food

Advisory Committee meeting, the FDA made several important points that were reported in the Federal Register notice that we mentioned. First, and I am quoting from the Federal Register notice, "The FDA found, in general, whether the data from the two studies were analyzed separately or together, the differences in the incidence of GI symptoms between the control group, on one hand, and the 20 or 32 gram per day olestra groups were statistically significant."

Secondly, "The FDA's analysis of the data from two eight-week clinical studies show that there was a dose-response effect for olestra with respect to two endpoints; reported diarrhea/loose stools, and fecal urgency."

Third, again quoting, "The mean number of diarrheal bowel movements per subject reporting any diarrhea increased with increasing olestra consumption." Let me just reiterate that. The FDA, looking at those eight-week clinical trials found that there was a dose-response effect for three critical endpoints; diarrhea, loose stools, fecal urgency.

Secondly, for those subjects that reported any diarrhea, the number of incidences of diarrhea increased with increasing olestra dose.

The FDA concluded, based in large part on those studies, I believe, that, "FDA believes it is important that

consumers know that the GI symptoms they are experiencing may be due to the consumption of olestra."

We agree with FDA's conclusions. We think that these studies are, in effect, the gold standard by which further studies, more recent studies, need to be evaluated. Where we disagree with the FDA is with their conclusion that these demonstrated adverse GI effects are consistent with a finding that there is a reasonable certainty of no harm from eating olestra.

[Slide.]

We got a hold of some of the data from these two eight-week clinical trials and we did some of our own analysis which I would like to share with you now.

This data shows a daily rate for reports of diarrhea, loose stools or fecal urgency, the three key endpoints that the FDA noted were the crucial endpoints to look at in these studies and it shows it in subjects eating, in this case 0, the control, or in this case 8 grams per day, of olestra.

What this shows is the data for individual subjects. This is three-digit subject codes here for almost 20 subjects along the vertical axis over the weeks of the study, up to week 8 and two weeks following, when the study finished and olestra consumption stopped.

So you can see, for instance, in this group, the

no olestra, the control, that one yellow box indicates that on that particular day, that particular subject reported one or more of those three symptoms; diarrhea, loose stools or fecal urgency. This subject reported it for almost a week plus a day over the second and third week of the study, for example.

If you add up all the subject age over this whole study for all subjects, all eight weeks of the study, you have 1,008 days. Out of those, there were 14 days in which a subject reported one or more of those three symptoms for an average daily rate of 1.4 percent.

If we look at the low-dose group, 8 grams a day olestra, which is about three-quarters of an ounce of olestra, again, summarizing, over the eight weeks of the study, for all the subjects, all subject days, there were 1,176 days, subject days, for this group of which there were 37 days in which a subject reported one of those three symptoms for an average daily rate of 3.2 percent.

That means, on the average day, 3.2 percent of those subjects were reporting one or more of those three key symptoms. If you do a simple no-brainer chi-square test, is statistically significant at the 0.01 level.

[Slide.]

The next slide shows the same analysis comparing, again, the same control, this time to the group consuming

20 grams of olestra a day, about 2 ounces of chips. You can see, again, summarizing over all subject days, there were 1,176 days. We have 362 days in which a subject reported one of the three key symptoms; diarrhea, loose stools or fecal urgency for an average daily rate of 30.8 percent. A simply chi-square test, this is a very significant difference.

Now, I don't think that this committee has seen this data which came from the 1992 and 1993 studies. I don't think they have seen it presented exactly this way. The way it has been presented in the Federal Register notice is in the percent of subjects that experienced this symptom at least once during the study.

So here, for instance, in the control group, 22 percent of the subjects experienced one of these three symptoms at least once during the study. Down here, on the 20-gram-per-day group, 76 percent of the subjects experienced it at least once.

The problem with looking at it that way is it is not very sensitive. It doesn't give you a very good picture of what is really going on because it gives equal weight to this guy here, subject No. 11--I can't quite read that. I think it is subject No. 11. He had a symptom once during the entire eight-week study period.

This poor fellow here, after the first week, was

experiencing one of those three symptoms virtually every day, yet they are counted the same if you count it in terms of subjects reporting the symptom at least once during the study period.

So we believe that reporting it in terms of an average daily rate is a more accurate and more useful way of understanding this data.

[Slide.]

The next slide shows exactly the same analysis, same control, 32 grams a day, about three-and-a-quarter ounces of chips out of 1,120 days, subject days. We have 371 days of which a subject reported one of those three symptoms, an average rate of 33.1 percent, very significant.

[Slide.]

The next slide shows, basically, the same data but combined over time, over the eight weeks. I can't read the eight, but there is an eight there. Again, this is the average daily rates on the vertical scale and the red line, for instance, are people eating 32 grams a day. Green is 26 grams a day and so on.

Now, the point is, for instance, if we look at the 20-gram-per-day group, the green line, the average daily rate--that is to say, the average daily symptom rate is 30.8 percent; that is to say, 80.8 percent of the subjects are experiencing a symptom every day.

But that doesn't tell the whole story of what is going on with this. We have heard, in some of the previous studies, simply about a lag period in symptoms. If you look at just the first week of the study, we can't distinguish between these subjects. They all appear to be about the same rate.

Now, I have to point out that the number of subjects per group was only about 20, so one subject represents a 5 percent change. So our sensitivity at low end is probably very poor. Nevertheless, when it gets up to after two weeks, we see a rapid increase after about ten days or so into the third week. The 20-gram-per-day group is showing average daily rates of over 40 percent.

[Slide.]

This next slide, I am trying to make a very important point here. It is exactly the same analysis only, instead of just looking at the three symptoms of diarrhea, loose stools and fecal urgency, we threw in every GI symptom that subjects would report, so it includes bellyaches, gas, everything.

The point I want to make is that it really doesn't look that much different than the previous slide; initial lag, rates go up to above 40 percent, stay steady, decline after the feeding stops. The point I want to make is that all you need to describe the effects of olestra on these

subjects, the symptoms to look at are diarrhea, fecal urgency and loose stools. Any other symptom may be associated with it, but it is not necessary to describe the data.

So, with this somewhat lengthy introduction, I want to go back. What this provides us is sort of a dose response. This gives us the data that lets us predict for any given--well, within reason, any olestra consumption level for any period of time, up to eight weeks, anyway. We can predict what average daily rates subjects are going to be experiencing diarrhea, loose stools or fecal urgency in any future study.

With that in mind, I want to turn, now, to the three studies; the movie-theater study or the acute-response study that we heard about this morning, the consumer rechallange study which was partially published. I don't think it has been completely published, but perhaps it has. And the so-called six-week home consumption study that we have not seen published but we have had the opportunity to at least review some of the summaries that Proctor and Gamble has submitted to the FDA. So we have a little bit of data about that for analysis.

First the movie-theater and consumption rechallange studies. Both these studies are very similar in some ways in that the both involve either one olestra, in

the case of the movie-theater study, or two isolated exposures spaced one to three weeks apart of about 18 to 20 grams of olestra consumed in chips.

Now, in the movie-theater study, they used, apparently, just average subjects. There was a very broad conclusionary criteria. The consumer rechallange that we heard about, the second rechallange study that we heard about today, used individuals who complained to P&G's hot-line number, but it only had a participation rate of, somebody said 10 percent.

I calculated 9 percent and that seems pretty low to me. What it seems to me to say is that we can't really say very much about why those people are any different than the general population if they are, indeed, different at all.

And it didn't involve anything like the rigorous prescreening that the previous rechallange study, the so-called fecal-parameter study did. There wasn't a prescreening phase to make sure that those people weren't just assuming--perhaps, they had mistakenly identified some other GI complaint that is associated with olestra.

So if you look at this figure now, and we look now--okay, these people are consuming--they are somewhere in here. They are eating about 20 grams a day or a little bit less than that. What would we predict?

If we could have somehow magically gone back to this clinical trial and terminated it somehow, the IRB pulled their permit, or whatever, and they had had to stop after one day, what would we have seen. We would have seen, apparently, no effect. It would have missed the reality that if they had fed it to them over two weeks, that we would have seen an increase.

That is what the movie-theater study and second rechallange study were like. They were like terminating this clinical trial after a day or two days. If we could have, somehow--if P&G had got those movie watchers to watch that movie every day--maybe they would have had to change the screening a bit, I don't know--but if they had watched that movie every day and eaten an average of 2 ounces of chips and if they had gone for two weeks or more, we would have expected, I think, to see some effects after two weeks. After one day, no.

Next, I want to turn to the six-week home consumption study. I like that study. I think it was a good study because I think it was a good attempt to see what the effects that were identified in the clinical trials, how they would be expressed in the real world with real consumers making real choices.

The symptom list that subjects in the six-week home consumption study, unfortunately, it was a little bit

odd in that diarrhea, which was one of the key symptoms identified in the clinical trials that you want to look at, diarrhea was simply dropped from the list of symptoms that consumers could pick.

Maybe it has just been dropped from P&G's lexicon. I don't know. But it was replaced with what they call more frequent bowel movements. I assume that those are the same. For the purposes of my talk, I am going to use them interchangeably throughout the rest of my talk.

As a toxicologist, of course, I want to know the dose. What dose were those subjects over that six-week period eating of olestra every day. What was the average daily consumption so that I can compare it to this data, P&G's data, and predict what kind of rates we would expect.

It is difficult to estimate the exact amounts of olestra consumed by subjects in those studies. I didn't see it reported in what we saw. Nevertheless, it was possible to estimate consumption rates from the data that was provided to FDA. This is based on a couple of points. First of all, consumption patterns remained stable throughout the study, throughout the six-week study.

Secondly, olestra or olestra-labeled chips were reported to be about half the chips selected in both the olestra and the control group and this was consistent throughout the study. If you go through all these numbers,

we came up with an average olestra consumption for the median and top 10 percent of chip eaters, the 90th percentile, of 6 and 10 grams per day of olestra.

Of course, what you want to do is compare--look at this; what would you predict. First of all, there are some problems with doing this type of comparison. I would certainly grant, in a clinical trial, the subjects were at a fixed dose every day of olestra.

In the six-week consumption study, people were free to eat whatever they wanted. They could eat a little or none or a lot of olestra each day, so you can't make direct comparisons. Nevertheless, we can make some predictions. You would predict, I think, for the median dose of 6 grams per day that they are going to show up somewhere between the placebo and the 8 grams per day, somewhere between 1.4 percent and 3.2 percent, after six weeks anyway, average daily rates of diarrhea, loose stools or fecal urgency.

The top 10 percent of chip eaters, the 90th percentile, eating 10 grams a day, are going to be somewhere between 8 grams and 20 grams a day, somewhere between 3.2 and 30.8 percent of the subjects are going to be reporting one of those symptoms every day, presumably closer to the 8-gram-per-day group.

What I want to argue is that, although P&G didn't

present their data in a way that allowed us to do this direct comparison of our predicted rates of adverse GI effects that, nevertheless, we conclude that the six-week study found exactly the increased rates of PGI effects of diarrhea, loose stools and fecal urgency that we would predict at least in a qualitative sense, as close as we can estimate what they found.

Thus, it closely parallels and is consistent with the results that similar doses of olestra found in the earlier 8-week clinical trials. I have a minor statistical quibble with the way they reported their data. They reported, as you saw earlier, the eight symptoms that they looked at plus other for nine symptoms. They reported no statistical difference.

I find that when I look at more frequent bowel movements, which is their word for diarrhea, I believe, that it is statistically different if you just do a simple chi-square test. I think what they have done, I believe, is that they have thrown all these variables together and done a correction for multiple comparison of means and then found that nothing was significant.

The problem is we knew from the eight-week clinical trials that most of the symptoms that they looked at, belly aches and whatever, are not associated with consumption of olestra. What they should have done, I

believe, is looked at the three key symptoms--diarrhea, loose stools and fecal urgency--and then I believe that they would have found a significant increase.

In other words, it is not reasonable to mix a whole bunch of variables that you know beforehand are not endpoints of interest, throw them into the hopper and then do a correct for multiple comparison of means and then say there is no significance. Nothing would be significant if you could always do that.

Nevertheless, P&G had made a couple of observations about this data where they did find significant differences. They found, for example, that subjects reporting symptoms, the number of days of more frequent bowel movements or diarrhea were significantly increased in the olestra group compared to the control group, exactly the type of result that was found in the 8-week clinical trial in at least a qualitative sense.

Finally, in the top 10 percent of olestra consumers, there was a statistically significant increase in more frequent bowel movements and looser stools in the olestra group, again, exactly as we found in the clinical trials.

A major strength of the six-week home-consumption study is that it complements and it is consistent with the results of the earlier clinical trials. Taken together,

these studies clearly show that olestra consumption in savory snacks leads to consistent reproducible rates of adverse GI effects of common diarrhea, loose stools and fecal urgency.

P&G tries to argue that most of the subjects experiencing those adverse symptoms from olestra were only slightly inconvenienced by the experience or not at all inconvenienced. I think I counted something like 14 occasions where they said, okay, they had these symptoms, but it wasn't meaningful.

I think it is hard to imagine that any of the subjects that experienced those symptoms found it to be a pleasant experience, at any rate. As you heard, there is a significant amount of data that shows olestra can cause seriously inconvenient effects in some consumers of olestra at predicted realistic consumption levels.

CSPI takes the position it is not ethical, it is not good public-health policy, to introduce a food additive that causes any significant adverse GI effects for a widely used food such as potato chips or other types of chips that are generally thought of as being perfectly safe.

Thank you.

DR. JACOBSON: Let me just conclude our presentation by summarizing some of our views on the overall body of evidence concerning GI symptoms. When we come to

this conclusion, we are including the old studies like the eight-week studies that most of you have seen before, a new study that you hadn't seen that wasn't provided to the FDA until after the 1995 advisory committee. That is the fecal-parameter study that proved that olestra can cause severe diarrhea in those sensitive subjects.

It includes new data, the six-week study, and others as well as anecdotal evidence. Taken together, the old and the new data indicate that olestra, in a dose-dependent fashion, is causing GI symptoms. When moderate amounts are consumed on a daily basis, a large percentage of consumers will experience symptoms.

When moderate amounts are eaten only occasionally, a much smaller percent of consumers will experience symptoms. In addition, a small percentage of consumers--no test has ever looked at the percentage; maybe it is a tenth of 1 percent, 1 percent, half a percent, we don't know--is experiencing very severe symptoms possibly caused by an entirely different mechanism seemingly almost like an allergic reaction.

That small percentage of severe symptoms would be impossible to detect in most controlled studies. While the overall percentages of people who suffer reactions may be small, they represent enormous numbers of consumers. We believe that it is intolerable that a food additive should

cause any cramps, diarrhea, loose stools, vomiting or other such symptoms.

P&G officials say that the symptoms, if they exist at all, are trivial and that affected people should simply avoid olestra. That argument which, until now, has been accepted by policy makers, results in a great deal of harm. First, many people are being inconvenienced by even non-severe symptoms. Second, consumers do not always immediately link their symptoms to olestra partly because olestra doesn't cause symptoms every time somebody eats it.

People might have to suffer numerous bouts of symptoms before figuring out the cause. Third, some people are suffering extraordinarily severe symptoms. If olestra simply affected stool consistency, as Dr. Kessler once suggested, "consumer beware" might be an appropriate policy.

But that is unacceptable when symptoms are leading some people to say, "I thought I was going to die." The FDA is supposed to protect the public's health, not tell the public to "learn from your suffering."

Olestra simply does not meet the reasonable certainty of no harm standard for approval.

Thank you very much.

DR. BRANDT: Thank you, sir.

Questions of Clarification

DR. BRANDT: We are now open for questions,

comments, discussion by the members of the committee.

DR. ASKEW: By including loose stools in the symptoms, it leads you to a little bit different conclusion than you might draw if you analyzed the data, perhaps, without loose stools. I think people certainly would expect loose stools with the consumption of 20 to 30 grams of olestra per day; would you not?

DR. JACOBSON: Certainly, on a daily basis, one would expect that. Yes. And, as the fecal-parameter study showed, 20 grams a day of olestra for just seven days increased rates, significantly increased rates, of severe diarrhea in that screened group of subjects.

DR. BROWN: I would just add to that. It is a good point but the point is that the FDA found that those were the three symptoms that individually were associated with increasing olestra dose. That is number one. Number two, the FDA made the strong recommendation to P&G in thinking about how to analyze those clinical trials, the eight-week clinical trials, that they really should combine diarrhea and loose stools because it is not going to be obvious to many respondents, to many subjects, exactly what the difference is.

So that was FDA's recommendation to combine those into a single variable. But, nevertheless, those are the three variables which looked at individually show a dose

response relationship with olestra consumption. It is statistically significant.

DR. LAMM: Dr. Jacobson, you have reported a large number of people reporting to your organization problems with a particular product on the market. When you get such reports, do you pass them on to the manufacturer?

DR. JACOBSON: No. We give them to the Food and drug Administration. The manufacturer, presumably, gets the reports through the Freedom of Information Act just as we get their reports.

DR. LAMM: Why don't you send them directly to the manufacturer or refer the people onward to the manufacturer so that the manufacturer can have the direct benefit?

DR. JACOBSON: We prefer to send the reports to the Food and Drug Administration which we see as being somewhat more objective then the manufacturer. But, as I mentioned, I presume that the manufacturer obtains those reports. These reports are obviously provided to us on a confidential basis. We provide them in that way to the FDA.

DR. LAMM: I would think you might provide them in such a way that, for instance, when the manufacturer has the rechallange study available to people that the people who make themselves known through you could also make themselves available for that type of study or that you might develop such a study within your own organization.

DR. JACOBSON: I appreciate that suggestion.

MS. RICHARDSON: I have questions for Ms. Blume. Ms. Blume, when you ate the potato chips at your friend's house, were you aware of the potential problems with olestra products?

MS. BLUME: I was not aware of the potential problems. I was aware that they were made out of olestra.

MS. RICHARDSON: And you mentioned that your primary-care provider made the diagnosis of olestra poisoning.

MS. BLUME: Yes, ma'am.

MS. RICHARDSON: The other two practitioners, were they aware that you had eaten olestra?

MS. BLUME: Yes; they were.

MS. RICHARDSON: Did they have any comments regarding--

MS. BLUME: The first doctor I spoke to, it was over the telephone and he felt that my symptoms sounded ulcer-related. The second physician that I saw at the urgent-care facility, I did mention the olestra. She never made any comment on that, gave me a physician examination and, based on that and the pain, the abdominal distress, that I was in felt that I was suffering from gall stones.

MS. RICHARDSON: Was Proctor and Gamble made aware of your symptoms?

MS. BLUME: No.

DR. BENEDICT: In a couple of statements that you have made and in the documentation you provided to us, you mention allergic reactions, hives and you also come down pretty hard on severe intestinal cramping.

I am wondering if you or your consultants have evolved a hypothesis about how either of these two events could be caused by olestra, physiologically, at the physiological or immunological level which is what I am.

DR. JACOBSON: In the absence of real research on mechanism in these areas, hives--conceivably, there is a contaminant in the olestra that gets in either from the original cottonseed, soybean, sugar constituents or during the shipping there could be contamination, in railroad cars, manufacturing facilities.

Or there are contaminants within olestra. Olestra is not pure sucrose polyester. I think there are polymers and other unusual substances at low levels. But whether these people really experience hives because of olestra is easily tested. Both P&G and we have numerous potential subjects for a study.

DR. BENEDICT: But just on a purely historical basis, lipids are generally of low immunogenicity.

DR. JACOBSON: Yes.

DR. BENEDICT: Secondly, how would you move this

compound in the direction of severe intestinal cramping.

DR. JACOBSON: That also.

DR. BENEDICT: I am asking for a hypothesis because it is sort of consistent with this kind of a statement.

DR. JACOBSON: Hives; I suggested several alternatives. Then hives is particularly amenable to testing, I think. With severe cramping, if it is happening at a low percentage, there clearly could be individual peculiarities in intestinal microflora, for instance, or in some special sensitivity in receptors somewhere in the gastrointestinal system.

I think it needs research. Oftentimes, the mechanism is suggested after the research demonstrates something. The research could have started a long time ago on this after it was demonstrated that olestra causes, in some people, severe diarrhea.

It is easy to suggest different alternatives, special receptors or special or peculiar microflora. I think it needs a lot more testing. I think the company insists that all we are seeing is a breaking up of the fecal matrix due to this insoluble lipid. But I don't think that there has been much research in looking at alternative mechanisms for causing severe or mild gastrointestinal symptoms.

DR. HUBBARD: I would just like to have a clarification on process. We have a general idea of what P&G does with people that call in to their 800 number. What is the general process that is followed by your organization when a person calls in?

DR. JACOBSON: There are two different pathways. If somebody calls in via our 800 number, we have somebody at the telephone with a questionnaire and a script leading somebody through the questionnaire. And then there are some open-ended comments kind of a line.

We have another path which is via the Internet where we have a website with a questionnaire that people fill out electronically and then submit it to us. When people indicate that they went to the emergency room, or hospital, in another way, we ask if they could submit their medical records to us. Then we transmit that to the Food and Drug Administration.

DR. BYERS: With regard to the rechallange study, your critique is that these participants in this study were, perhaps, not sick enough initially. However, half of them are reported to have had what was described as severe reactions.

Could you expand on this a little bit? It is hard to deal with all the anecdotal numerator data, but the trial is, I think, more informative. Could you expand some more

on your critique of this study with regard to the degree of the initial reaction that qualified people?

DR. BROWN: I think, in this case, I am willing to give Proctor and Gamble the benefit of the doubt that all of these instances were falsely attributed to olestra. Clearly, in many cases, people who report adverse GI problems, it is not accurate. Background rates for GI problems are very high.

The problem is, since the participation rate was only 9 percent--that is to say 91 percent of the subjects declined for their own reasons to participate, we really don't know very much--it is hard to say how those subjects are unique or if they are unique at all, in any way, from just the average consumer of olestra.

We recognize that, in many cases, people are going to falsely attribute adverse GI problems to olestra but not in all cases. We can't say how this population is any different or if they are different from just any other average group of chip eaters.

Does that answer your concern?

DR. BYERS: I think it is your answer. I guess my question pertains to the half of participants who characterize themselves as having had severe reactions. I thought I understood you to say earlier that one of your concerns in this randomized blinded trial was that these

patients had not had severe enough reactions initially, that they maybe had just mild illnesses.

DR. BROWN: No. My real critique of that study was twofold. We can't say how that group is at all different from anybody else. Maybe they are, but we can't say. The average consumer of olestra, based on the results that are clearly shown from the clinical trials, the eight-week clinical trials, after a single dose or two isolated doses of olestra, you wouldn't expect any particular adverse effect.

If that rechallange study had continued for two weeks, or three weeks, then I think we would have expected to see something. That is my primary concern was the short exposure time.

DR. JACOBSON: Coupled with the lack of screening the subjects to try to get a pool of sensitive subjects. In the eight-week studies, it is quite clear that symptoms are not always reproducible, that symptoms may depend on what else somebody ate during the day, how much they exercised, any number of things.

If you are going to react one in ten times, the initial--the 98 people or whatever it was that P&G had might have reacted to olestra or might not have. If they did react, it is not necessary to think that, with one more exposure, they will react.

DR. WANG: One question is when the 1-800 consumer calls in, do you include a question to ask them about their food history, or do you just assume they call you because they were reporting a reaction of olestra rather than maybe it could be from certain other foods they have eaten.

DR. JACOBSON: We don't take a complete food history but we do ask about possible alternative explanations including do they have the flu or something else and we do ask about food allergies, that kind of thing.

DR. WANG: I have another question for Ms. Blume. Ms. Blume, when you said your primary doctor diagnosed it was olestra poisoning, a follow-up question is did he order some type of stool culture?

MS. BLUME: No.

DR. WANG: Were you still suffering?

MS. BLUME: I was still suffering. He just felt that my colon was in spasm and prescribed the Levbid. That alleviated the symptoms along with the liquid diet. But he took no stool sample.

DR. WANG: Just curiosity. Would you be willing to--if you would have known about the rechallange study, ongoing, would you be willing to do that?

MS. BLUME: It lasted for a full week. And that was absolute agony. I would be very, very reluctant to put myself in that position again.

DR. WANG: May I ask, do you have a past history that you had suffered some type of gall-bladder attack?

MS. BLUME: No. That is how I am able to narrow it down and get my doctor's complete support for this. I am perfectly healthy.

DR. CHASSY: I just wanted to make a comment. I was going to ask that same question Mary just asked maybe suggesting why the participation rate is so low in rechallange studies. If you believe you know what the cause of your problem is, you would be rather foolish to volunteer for the study, maybe.

MS. BLUME: You don't want to go there again.

DR. CHASSY: It takes a special kind of personality.

DR. JACOBSON: Can I just add a word about the mechanism you were asking me about. Fifteen years ago, we identified sulfite as a probable cause of--

DR. BRANDT: Wait a second. Dr. Chassy is not through.

DR. JACOBSON: Oh; I'm sorry, Dr. Chassy.

DR. CHASSY: Yes; I had a number of questions, actually. This one is maybe more directed at Mark. Am I correct, Mark, that you endorse the kinetics and profile of the onset of symptoms that are seen in the clinical trials that you spent some time talking about, in particular that

there is a week or two of lag before the onset of symptoms in these high-dose clinical trials?

DR. BROWN: For the average person, what can I say. It is not my data. I just plotted it. It is the same lag that was discussed in some of the other studies that we heard today. They reported a lag in the stool softening and that incredible study where they were feeding people sorbitol.

But let must just complete the thought. Clearly, it shows this lag effect. The power of those clinical trials to say anything about what happens after one exposure, one day, one exposure of, say, 8, 20, 32 grams is poor. There are only 20 subjects per group so plus or minus one subject is plus or minus 5 percent response rate.

So the clinical trials--in fact, any clinical trial, it is very difficult for any reasonable clinical trial with a reasonable sample size, population size, to say something about 1 percent, or a tenth of 1 percent, response rates.

So, for the average consumer there is a lag. What happens in special cases, people who may be unusually sensitive, that data really is not particularly useful for addressing that.

DR. CHASSY: Let's move on. We have had several studies, in fact, today--you just cited a couple more of

them--which suggest that one needs to consume olestra for at least several days to have any anticipation of observing an effect and yet you bring in a number of cases which are very rapid-onset incidences that take place within a few hours at very low concentrations of olestra.

It seems to me that these two are hard to reconcile with one another, given if you add up all of the clinical studies, there are a fairly large number of people, that go up into the thousands of people, in fact, and not a single incidence of an acute episode of the kind you describe.

You further go on to describe those acute episodes as likely falsely attributed to olestra. You admit you cannot establish a cause-and-effect relationship between any of those incidences, that they are largely anecdotal, but you say there are so many of them that we think there must be fire here.

Well, you are advertising in television. You are advertising with banner toes. You are advertising wherever you can to get people to call up and make a complaint and then you are saying, "I have got so many complaints, I think there is a cause-and-effect relationship."

Yet the only data you have showed us is data that says we have to wait a week or two to see an effect.

DR. BROWN: I think you have made a number of

challenges here. I wish I could have written them all down. First of all--

DR. CHASSY: I wish you had thought about them before you got up there.

DR. BROWN: Thank you. First of all, that data in the clinical trials talks about the average chip consumer. The average chip consumer clearly, after a period of two weeks, is going to start showing rates--if they are eating 8 or 20 grams a day, are going to be average daily rates of 2 to 30 percent. Every day, they are going to be showing those three symptoms. That is No. 1.

No. 2, it was the FDA who made the conclusion, looking at that the data, that there was a dose-response effect between those--I would like to finish, please.

DR. CHASSY: I didn't ask my question right. Have you looked at what those symptoms are that they are reporting. As I recall, and maybe we can get P&G up here, none of those people who stayed in that study and continued to eat olestra--they could leave the study. They were fully paid.

DR. BROWN: Which study are you referring to?

DR. CHASSY: The clinical studies that you spent a lot of time on. Those people could have left those studies.

DR. BROWN: Well, several did, if you heard me--

DR. CHASSY: None of them had the kind of severe

episodes that we are talking about taking place with flight crews and so forth. They are two very different kinds of phenomena.

DR. BROWN: Three of the subjects were temporarily removed from the study. It is true they went back on, but some of the subjects, their symptoms were so severe that they had to be pulled from the study.

Let me just try and say this.

DR. CHASSY: That is untrue.

DR. BROWN: They were added back to the study.

DR. CHASSY: I sat through the previous hearing. That is not true.

DR. BROWN: We can discuss it later. I can give you the actual quotes if you like, and the references. Would you like that?

DR. CHASSY: Yes. I think it would be real good to get the actual report from Proctor and Gamble.

DR. BROWN: Can I give you the actual quotes about what happened? Are you interested? P&G stated that six subjects, and this is a direct quote and I will give you the reference in a moment, "Six subjects in either the 20-gram-per-day olestra groups or the 32-gram-per-day olestra groups temporarily stopped eating olestra foods because of their GI symptoms." This is in the Journal of Nutrition, the Special Supplemental Issue, Volume 127, 1997, page 1726S.

This reference came from P&G's own study reports, the reports that they submitted to the FDA which, perhaps, you have not had the opportunity to review as thoroughly as we have. They stated, and I am quoting, "Two subjects in the 32-per-gram-per-day group were temporarily removed from the study. One of them, subject No. 60," which, if I threw the slide up there you could was one of the subject codes that was up there, "was given Imodium for diarrhea. The subject in the 20-gram-per-day group was temporarily removed from the study but not given Imodium."

So they were returned to the study, but their symptoms were severe enough to require at least some medication. This is the 8-week Vitamin-Restoration Study in Humans Consuming Olestra, June 2, 1993, page 37, Food Additive Petition for Olestra, Volume 185, January 29, 1993.

DR. ZORICH: Could you please just clarify how many people on placebo.

DR. BROWN: I think there was one subject.

DR. BRANDT: Excuse me. Everybody will get a chance, so don't jump in.

DR. BROWN: I will quickly summarize. My impression is that there are two types of responses. There is the average response that any human is likely to experience eating olestra over a period of time. That is what the clinical trials tell us. That is what the clinical

trials show us.

There is some evidence, less clear, mostly anecdotal, I admit, but it is hard to prove rare events. It is hard to show that rare events are real. There is, nevertheless, some anecdotal evidence supported by some experimental data that some subjects are unusually sensitive to olestra.

One of the best pieces of evidence is the earlier rechallange study that went through a rigorous prescreening phase that the most recent rechallange study that we have heard about failed to do. That study showed, in some instances, some of the subjects were showing doubling or more of stool volume, for instance.

You can't prove it. It is going to be difficult to ever prove that there really is a very small percentage, perhaps one-tenth of a percent, that is highly sensitive to olestra. The clinical trials are of no help in addressing that issue.

DR. CHASSY: Can I get this straight? You are telling me that you want the FDA to act on something that you just said you cannot prove.

DR. BROWN: I view it as something like what you do with a new drug introduction. If you introduce a new prescription drug, you look for adverse effects that clinical trials missed, that clinical trials don't have the

sensitivity to detect.

In that case, you use anecdotal data and you use professional judgment. Clinical trials can't address an issue like a rare event that occurs in 1 in 1000 subjects.

DR. BRANDT: Since this issue has come up and there has been some concern about the accuracy of the reporting, we are going to try to get copies of the two references that have been cited here so you can read them yourself.

DR. JACOBSON: Dr. Brandt, I have and would like to give out, perhaps, at the intermission, the report that the Food and Drug Administration medical officer wrote about the earlier rechallange study, the fecal-parameters study.

DR. BRANDT: That would be fine. We would be happy to have it. No problem, sir. Let me go back--I interrupted you a minute ago so Dr. Chassy could finish. You were going to comment something about mechanisms.

DR. JACOBSON: I just wanted to explain something that has colored my thinking over the years. In 1982, we heard of a report that people experience severe reactions to sulfite food additives. That was right at the time the FDA was proposing that sulfite be declared generally recognized as safe.

Everybody knew sulfites were safe. It turned out, though, that there is some subgroup of the population,

mostly people with asthma, in whom sulfites cause anaphylactic shock. Sulfites killed more than a dozen people that we were aware of and probably many more. The FDA eventually came around and banned certain uses of sulfites and limited the amounts of sulfites in packaged foods.

There is no way to detect that kind of a problem in clinical studies where it is a relatively rare event. People are not inbred rodents. There is a tremendous diversity of genotypes, tremendous diversity of environments, of diets, of drug taking, that I think we have to give some significant credence to the anecdotal reports, particularly in the light of previous controlled studies demonstrating that olestra can cause a range of symptoms from gas and loose stools all the way up through severe diarrhea.

DR. HUBBARD: As a follow up of some of early discussion, you are discussing two different types of, basically, adverse effects, one being the acute event and the second being the long-term event.

DR. JACOBSON: By "long term," do you mean from long-term consumption?

DR. HUBBARD: From long-term consumption; correct. Of the people that have communicated with you by either route, what is the proportion of people that are

communicating about the short-term event, and acute reaction versus after long-term duration exposure.

DR. JACOBSON: The great majority of people contacted us after one consumption. I don't have the exact percentage of figures. And I would say it is a small percentage of people but there are some number of people who have consumed olestra a number of times and say that they experience adverse effects each time.

DR. HUBBARD: Could you just indicate as to whether or not the priority of your concern is the reaction versus following a one-time exposure and an acute exposure versus the concern that you have over long-term consumption?

DR. JACOBSON: We are concerned about the effects of olestra, whether it is from long-term or just one-time consumption.

DR. CLYDESDALE: I just wanted to ask that if we get these copies of these quotes, I would also like to see copies of what went on with the placebo group as well.

DR. BRANDT: It should be in the complete stuff and I presume it is. We are going to see what can be done. In spite of my reputation, I am not a miracle worker and we will try our best to get what we can. Yes; the important message is to get the entire context including placebos.

DR. LAMM: What I am hearing from the two of you is that you have a unique surveillance system that is able

to pick up these individuals who are particularly sensitive to particular products, something that the clinical trials can't pick up. Yet you have here the opportunity to enter them into a type of study, whether you perform it, whether the company performs it, or whether you get somebody else to perform it, where I think you have a social responsibility to move forward to have those questions answered.

I do a lot of my work in occupations medicine and we regularly are there in the circumstances where an allegation by a worker comes up that they are uniquely sensitive to a chemical in the work place, where we provide a challenge study under a controlled clinical environment. And the same thing can be done--and I deal with it, whether we are dealing with respiratory, dermatological or other system. And I would recommend that you folks ought to design your system to be able to develop the same type of follow-through.

DR. BRANDT: Other comments or questions? Hearing none, we will now take a fifteen-minute break. I have 3:20. We will be back at 3:35.

[Break.]

DR. BRANDT: I want to remind everybody on the committee that during the last set of presentations, information came up about studies done prior to January of '96. Our instructions early on, all the material, we are

not going to rehash how the FDA came to its recommendation to approve olestra to go on the market.

That is not our concern. Our concern is to look at things that have taken place since January of 1996. So that is what we are here to look at. The FDA made their decision. They don't need us to discuss that. We discussed that plenty whenever it was, a couple hundred years ago. So that is where we are.

We now turn to folks from the FDA. I have a lot of differing information about who is going to do what to whom in this thing. I was told Dr. Rulis is going to make a few comments to begin with. Are you, sir, and, if so, let me get my clock set first.

FDA Presentations

DR. RULIS: Thank you. No; I really don't have that much to say other than, at the end of the FDA reviewers presentations, we would like to, I guess, make a sort of sum-up statement. I had thought about doing that at one time, but I have decided that I would like to ask Dr. Kenneth Falci to go through a couple of overheads to do that.

So he will do that at the end of the FDA reviewers presentations. That's all I have.

DR. BRANDT: Dr. Deborah Street from the Epidemiology Branch of the Office of Scientific Analysis and

Support. Dr. Street, thank you for being here.

DR. STREET: Good afternoon.

[Slide.]

I will be looking, again, at the analysis of the reports of adverse effects which Proctor and Gamble and the Center for Science in the Public Interest collected and sent to the Food and Drug Administration. We just received the adverse effects data from the national marketing of the product so I can't yet comment on them.

Therefore, I will be directing my attention to the test-market period from April, 1996 to January, 1998.

[Slide.]

You have already heard about the methods concerning collection of this data. Proctor and Gamble said that they had 800 numbers on all the olestra-containing products. CSPI publicized their toll-free number during various media activities. And then they collected the phone calls from those two numbers and P&G and CSPI forwarded their reports to us.

[Slide.]

When comparing P&G's and CSPI's methods, the interview format has severe differences. There are two differences which I would like to point out here. During the interviews of people calling the toll-free number on products, P&G elicited the consumer's self-report of adverse

effect whereas CSPI elicited adverse effects during their interviews with a questionnaire that contained specific adverse effects.

So the persons were asked if they had experienced diarrhea or not whereas in the P&G collection of reports, the persons just stated what their symptoms were.

Secondly, P&G estimated the daily and total amount of olestra consumed in chips whereas CSPI collected the information on frequency of consumption, whether it was one time, two times, multiple times, the type and amount of product eaten, and I was able to calculate the amount of olestra consumed for those persons who ate the savory snack one time.

[Slide.]

We have already seen this type of graph before and we have seen that there is a peak in the data shortly after the olestra-containing snacks entered the test markets. This is the P&G reports. You can see these peaks in this graph of the distribution as it first enters the three cities in Colorado, Iowa and Wisconsin.

Then, as Proctor and Gamble's Pringles fat-free chips came into Columbus, Ohio, in September of 1996 and again as the Frito-Lay's Wow chips and the Pringles fat-free chips entered Central Indiana in February and March of 1997, respectively.

You can see that it kind of levels off after May of 1997. One possibility for the peak in number of persons reporting adverse effects, as has already been discussed, is that that publicity surrounding the introduction of these products could have led persons to associate symptoms with eating the product, whether this was a true association or not.

There is likely to be greater incentive to phone in complaints when a new product is on the market and there is information about where to report the symptoms.

[Slide.]

CSPI reports show similar peaks. I want to explain why the data are somewhat truncated in this graph compared to the previous graph. There are two reasons. One, I didn't have the onset date of the symptoms. Rather, this was the month of report. We had the date of the report. The onset date was only collected in less than half of the CSPI reports.

Also, the last report that we received predominantly covered the people that reported in Indiana in this March, April, May period. More people reported to CSPI in Indiana than they did to P&G, but the converse was true in the Columbus, Ohio, area.

[Slide.]

Now I am going to compare the reports from CSPI

and P&G. You will see that is approximately the same number of reports to both phone interviews. You will see that there is about 65 percent of females reporting. The average age is 36 years and there was quite a wide age range, from 3 weeks to 96 years.

[Slide.]

I created this overhead so that you could, again, look at how many people in the young age versus the old age groups were likely to have reported. You can see about 14 to 16 percent in the under-18 years of age reported symptoms and 11 to 12 percent in those over 60 years of age reported symptoms.

[Slide.]

We have talked already today about the pattern of consumption. I am showing here the reports to P&G that 79 percent of persons reported eating olestra-containing snacks on a single day. In the CSPI reports, 62 percent of persons reported the frequency of consumption to be one time.

I want you to note the caveat that in the initial part of collecting data in the first reporting period, they didn't ask about frequency of consumption so we are probably missing some people in this group.

[Slide.]

This overhead is to talk to you about the single-

day intake, or the one-time intake and to show you that among single-day consumers or consumers who ate one time and who reported amount of snack intake, roughly half associated adverse intake with 8 grams or less of olestra.

I want to remind you because you are hearing about ounces and grams. 8 grams of olestra is found in one ounce of Pringles fat-free chips or Frito-Lay's Wow plain chips. The corn chips are between 1 to 2 ounces for 8 grams of olestra. It is less than 2 ounces.

[Slide.]

Greater than 3 percent of persons reported the following adverse effects to P&G. In this overhead, the COSTART terms have been shown. We mentioned earlier COSTART terminology and I just wanted to explain this one more time.

When the persons called in to P&G, they explained their own symptoms and that led to over 70 ways of describing abdominal pain. For example, someone might say, "I had a cramping pain in my stomach that was shooting to my lower back." Or they might say, "I had severe cramping." Or they might say, "I had abdominal cramping," et cetera.

So COSTART is the terminology developed and used by FDA for coding, filing and retrieving of postmarketing adverse drug and biologic experience reports. It provides for a method to deal with the variation and vocabulary used by those who submit adverse-event reports to FDA.

So P&G provided for us the COSTART terms, the verbatim terms and the persons narrative used to describe the adverse-health effect. In this list, you will observe that the highest proportion of persons complained about diarrhea and then the next two high proportions are abdominal pain and flatulence.

[Slide.]

Now I am going to compare the findings in the P&G reports to the findings in the CSPI reports. Because I am using the CSPI questionnaire terms, I wanted to make the two reports more comparable, so I am showing you verbatim categories. Now, just to make you aware of this, verbatim terms are the consumer's description of the symptom using his or her own words but excluding extraneous words or descriptors.

So someone that was in the COSTART category diarrhea may have said, "I had diarrhea." And I have also included under this category people who said they had the runs or they had watery stools. They may have said they had loose stools. They may have said they had fecal urgency, which they may have said was that they had to run to the bathroom and that increased urge to go to the bathroom.

In order to compare loose stools in the two groups, I looked at the people who said they had loose stool but who did not say they also had diarrhea. So we could

make that comparable because in the CSPI report, 68 percent of persons said they had loose stools but when you look out the people who also said diarrhea, then you see that these two groups are fairly comparable.

You will observe that in the CSPI data, the highest proportion of persons reported abdominal cramps. You will also note that the proportion of persons reporting specific adverse effects is somewhat higher in the CSPI reports compared to the P&G reports.

This may be partially due to using a questionnaire list. For example, a higher proportions of persons reported fecal urgency to CSPI. This may not be a term that persons are usually comfortable using when self-reporting symptoms or it may be a difference in how the interviewers probed for the symptoms. I am not sure.

[Slide.]

The next most common complaint was flatulence or gas to both P&G and CSPI. Here, again, I have shown the categories of verbatim complaints under the COSTART term "flatulence." So a person may have said they had flatulence. They may have said they had gas. They may have said they had bloating. They may have said they had rumbling or gurgling of their stomach. And I have compared these with the CSPI terms.

[Slide.]

Here are some other unpleasant and less-frequently reported adverse effects. I have not shown the symptom "vomiting," which was reported by 7 percent of persons interviewed for the P&G reports because this term was not used on all CSPI questionnaires. The information was not specifically collected in the Columbus, Ohio test markets.

[Slide.]

These are the additional adverse effects reported by ten or more persons to P&G. Again, this is using the COSTART terms. Headache was reported by 42 person. Rash, by 17 persons. A few persons reported constipation. The least reported symptom in this group was back pain.

So, in sum, for all the reports, we observed that abdominal pain, diarrhea and flatulence are the predominant complaints in these data.

[Slide.]

P&G collected information on the time from consumption of the olestra-containing savory snack to the onset of individual symptoms. I am emphasizing individual symptoms here. CSPI collected a latency time for symptoms overall. But I was interested in the individual symptoms, particularly abdominal pain and diarrhea.

Here we see that, among persons with single-day intake of olestra-containing savory snack, the median time to onset of abdominal pain is five hours in persons

reporting time information. You see that the range is from five minutes to seven days.

If you look at the 90th percentile, I found that 90 percent of persons had onset of abdominal cramps within twelve hours. The median time is seven hours for diarrhea, whether you look at COSTART or the verbatim term and 90 percent of persons had onset of diarrhea within 20 hours for the COSTART term and 24 hours for the verbatim term.

So all of these symptoms occurred within a day of eating the snack for 90 percent of the people.

[Slide.]

The median duration for these symptoms in person who eat snacks on a single day is 24 hours for abdominal pain and diarrhea. You can see there is quite a wide age range for diarrhea when you use the COSTART terms or, in fact, if you look at any of the symptoms.

But 90 percent of persons, at the 90th percentile--in other words, 90 percent of persons experienced duration of cramps for less than or equal to four days even though there is a very high day range, four days, 90 percent of people experienced them within the duration of four days or less. 90 percent of persons experienced duration of diarrhea for three days or less.

[Slide.]

Now, I want to consider the issue of the severity

of symptoms. I consider this in three ways; one, the extent of interruption of the daily activities, the person's own perception of the severity of their symptoms, and the extent to which medical care was sought.

[Slide.]

The comments section on the CSPI reports contained information about disruption of usual activities. The comments that I have shown here were, for the most part, mutually exclusive except for one person who was inconvenienced both while driving and while working. Inconvenienced was either stated as such--they said they were inconvenienced by their symptoms--or they stated that they had to stop the car to go to the bathroom, or they said they had to lie down at work or go to the bathroom frequently.

So you can see that, overall, about 12 percent of persons commented on interruptions of their daily activity.

[Slide.]

P&G has shown this earlier, but they collected information on how consumers characterize individual adverse effects. It is how they thought their adverse effect appeared to them. 33 percent said that reports of diarrhea were characterized as severe. 40 percent of reports of abdominal pain were characterized as severe and 38 percent of reports of flatulence were characterized as severe.

[Slide.]

As you will see in this overhead, according to the reports that we have received by January 1, 1998, about 9 percent of consumers reporting adverse effects to P&G contacted a physician. Now, this was either by phone or in person. 86 of the person say that they actually visited a physician and, of those 86, 26 persons visited an emergency room and five were admitted to the hospital.

In the CSPI reports, 79 consumers said they sought medical advice from a health professional, 56 from a physician and the rest from other medical-care professionals. 0.6 percent of these people went to an emergency room or an urgent-care facility and one person was admitted to the hospital.

Dr. Karl Klontz will be speaking shortly about the medical reports received from persons who sought medical care for their symptoms.

[Slide.]

So we have already discussed some of the limitations of passive surveillance and let me go through it one more time. The reports received are from self-selected non-sampled persons who may or may not represent the populations' experience with the product.

Persons reporting adverse effects are more likely to report problems of an acute short-term nature than

adverse effects occurring after long latency periods. That is because it is difficult for people to associate symptoms that occur a long time after their actual exposure to see that those two things are associated.

We can't directly calculate incidence rate of these adverse effects because we, basically, are dealing with numerator data. And there is a lack of a comparison group of persons who did not eat the products that we can look at possible confounders of an association, if there was one at all.

[Slide.]

Someone has already mentioned the advantages of passive surveillance. The advantages are that analysis of reports may lead to hypothesis generation about the possible causes of adverse effects and they can detect events too rare to have been observed in clinical trials.

[Slide.]

So, in conclusion, what we found in this passive surveillance is that the majority of consumers who reported adverse effects consumed olestra-containing snacks on a single day. Among single-day consumers who reported amount of snack intake, roughly half associated adverse effects with an intake of 8 grams or less of olestra.

[Slide.]

Abdominal pain, diarrhea and flatulence were the

predominant complaints in this report. And time to onset of abdominal pain after intake of olestra-containing snacks was fiver hours or less in 50 percent of persons eating snacks on a single day.

[Slide.]

Time to onset of diarrhea after intake of olestra-containing snacks was seven hours or less in 50 percent of persons eating snacks on a single day. And, with common symptoms and the limitations of passive surveillance, we can't determine if these symptoms occurred because of the olestra-containing snack or some other cause.

[Slide.]

So, in conclusion, we have been evaluating the outcomes of other postmarketing studies undertaken by P&G which can more directly examine the association between olestra intake and adverse effects.

After Dr. Karl Klontz describes the medical reports in greater detail, we will be hearing about these other studies.

Dr. Klontz.

DR. BRANDT: Hang on one minute. I forget to tell the committee that during your absence of the break, our friend, Dr. Larsen, passed out some more material which is at your place. Dr. Larsen's aversion to trees is well-known. He keeps copying stuff. But, nevertheless, you have

got it.

My only comment about this section is that we are overwhelmed by epidemiologists. But Dr. Blackburn told me that we were lucky. Isn't that what you said?

DR. BLACKBURN: No. I said that you were underwhelmed by epidemiologists.

Dr. Klontz?

DR. KLONTZ: Good afternoon. Karl Klontz. I am a medical officer with FDA's Center for Food Safety and Applied Nutrition. I am an epidemiologist as well.

DR. BRANDT: Welcome back to this committee.

DR. KLONTZ: Thank you.

[Slide.]

What I would like to do in about six minutes is summarize our review of medical records that we received from Proctor and Gamble and CSPI from individuals who reported experiencing adverse effects and had seen a physician.

As Dr. Street mentioned, in their postmarketing surveillance system, Proctor and Gamble received a total of 117 reports of individuals who stated that they had contacted a physician either by phone or in person. 26 individuals reported going to an emergency room and five had been hospitalized.

In their postmarketing surveillance system, CSPI

reported that 79 individuals had sought medical help. Eight had gone to an ER and one had been hospitalized.

[Slide.]

FDA received medical records for 21 consumers who reported adverse effects after eating olestra. Fifteen of these reports were provided by CSPI, six by Proctor and Gamble and one report we obtained independently from a consumer.

You will note from the top line that I mentioned 21 consumers whereas the second line adds up to 22. The reason for that is the one record that we had obtained independently was subsequently provided by CSPI.

In addition, FDA medical officers contacted six consumers to determine whether there was a need to pursue medical records. Three of these individuals declined to give FDA permission to obtain those records and for three it was determined that medical records were not needed.

[Slide.]

Five of these individuals were seen by a physician in an office visit. Thirteen had been evaluated in an emergency room. And three had been hospitalized.

[Slide.]

Of these 21 individuals, 14 were female. The median age was 45 years and the range in age was from diaper age--no specific age was given there--up to 76 years of age.

[Slide.]

What were the physician-described etiologies in the medical records of those illnesses that consumers had attributed to olestra ingestion. For ten patients, no etiology was specified in the medical record. In addition, for eight patients, no specific etiology, or a specific etiology other than olestra ingestion was specified. And, for three individuals, the physician and the medical records specified olestra as the etiology.

[Slide.]

I would like to give you an example now, one example of each of these three categories to give you a picture of what these medical records were saying. Let's begin with an example of a medical record which specified no etiology for the symptoms.

This was an eleven-year-old male who ate 1 ounce of olestra-containing chips in the evening. The next morning, at school, he reportedly experienced hyperventilation and nausea and abdominal pain. His mother took him to the emergency room and she reports that, at that time, he was "out of it with eyes rolled back and he had vomited one time."

This child did have a history of seizures but was not on any medications at the time. He did not have fever. He had no concurrent illnesses and reportedly had no trauma

at school. The physical exam was unremarkable and the clinical impression simply was abdominal pain and the patient was discharged.

[Slide.]

Let's turn to an example now of a medical record which specified a specific etiology other than olestra. This was 67-year-old female who ate 12.5 ounces of olestra chips over six days. She reportedly developed flatulence on day 1 and then, on day 6, reported experiencing stomach pain and nausea and cramping.

In the emergency room, she was found to have periumbilical pain that localized to the right lower quadrant and, because of the concern for appendicitis, she underwent an appendectomy.

The pathology diagnosis at the hospital was acute appendicitis, minimal, and, because of the degree of inflammatory changes that were reported on the pathology report, we, at FDA, contacted that consumer and requested, and got permission, to obtain pathology slides of that appendix.

An independent review of the slides by actually four FDA pathologists confirmed the presence of inflammatory cells throughout the wall of the appendix meriting a diagnosis of acute appendicitis.

[Slide.]

While we are on the topic of diagnoses other than olestra ingestion, what were some of the conditions that were specified in the medical records that we reviewed. As you can see, gastritis and irritable-bowel syndrome were mentioned in some individuals by physicians in some of the medical records, acute gastroenteritis in two instances.

A urinary-tract infection was diagnosed in one patient and an ovarian cyst in another. And Clostridium dificil colitis in yet another patient.

Finally, let me give you an example of one of the three medical records which specified olestra as the etiology.

[Slide.]

This was a 49-year-old female who ate some olestra chips and, an hour later, she developed "chest heaviness, a feeling that she couldn't get a full breath," and she was having belching and felt tired and admitted, in her words, to being "under a lot of stress at that time."

In the emergency room, her physical exam was unremarkable. Her EKG specifically was normal. She was given a GI cocktail with some relief and then discharged home. Now, I have put down for you the words of the physician in the emergency room. He said, "I think her symptoms may very well be due to olestra which she has not used before.

"The symptoms started about an hour after consuming these chips. She has no cardiac risk factors. Her symptoms sound much more gastrointestinal in nature and her EKG is normal."

[Slide.]

In conclusion, 18 of the 21 records that we reviewed, the physician attributed the symptoms to an etiology other than olestra or, in fact, provided no etiology at all. In three of the 21 records, the physician attributed the symptoms to olestra.

It is important to underscore that a review of these individual records really does not allow for one to make any definitive conclusions regarding the role, if any, of olestra ingestion in the etiology of illness but such reviews can be helpful in generating hypotheses that may merit further investigations. FDA will continue to look at medical records as they come in and occasionally seek to get a medical record from a consumer if we believe that is necessary.

The next study is going to be an assessment of the stool-parameter study and that will be summarized by Dr. Kenneth Falci.

DR. FALCI: Mr. Chairman, my name is Ken Falci. I am the Office Director of the Office of Scientific Analysis and Support in CFSAN in FDA. Today, Dr. Hugh Gallo-Torres

was supposed to give this talk and he has had a death in his family and would not be able to do that today.

So we have asked him to produce a summary of his results. I intend to read those into the record today.

"To the Food Advisory Committee on olestra from Dr. Hugh Gallo-Torres, M.D., Ph.D., Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Review. Subject: olestra, stool-composition study, Food Additive Petition 148.

"I have reviewed the stool-composition study concerning olestra. In this statement, I will give a brief synopsis of my review and analysis of the study. I will be available by telephone to answer questions that the committee might have.

"This was a well-designed and apparently well-executed study. The double-blind character of the trial was preserved by the consumption of corresponding placebo snacks. The levels of olestra tested are adequate. 20 grams per day represents the worst-case chronic consumption value predicted by the FDA while 40 grams per day exceeds the chronic daily intake by the highest subgroup by severalfold based on the MRCA data.

"The dose of the positive control, sorbitol, 40 grams per day, represents 80 percent of the ED50 for a 50-kilogram individual for sorbitol-induced diarrhea. The ED50

for laxation is 1 gram per kilogram per day body weight.

"The procedures to carry out measurements were all adequate and equally appropriate was the statistical methodology used to evaluate results. I reviewed the results of each evaluation parameter as did Dr. Curtis Barton, and FDA statistician. In some cases, our statistical analysis differed from the study sponsor. Parametric analyses were used whenever the assumptions of the analysis were satisfied and baseline measurements were used as a covariate in many of the parametric analyses.

"Sorbitol served as a positive control and demonstrated that, under these experimental conditions, a response to a positive comparator would be elicited. The consumption of sorbitol resulted in rapid-onset liquid rice water stools, significant decrease in mean stool consistency, basically, with an increase in mean stool-water output of approximately 10 ounces per day.

"The was a statistically significant increase in increased bowel movement frequency. Only consumption of sorbitol but neither dose of olestra resulted in a statistically significant increase over placebo in the severity of three of the six GI symptoms evaluated; cramping, nausea and urgency.

"The consumption of 40 grams per day of olestra was accompanied by some, although not in all, modest effects

on stool characteristics and symptoms. In spite of differences in analyses, results of our evaluations were substantially the same as those reported by the sponsor. The analyses performed by both the reviewers and the sponsor agree that there are statistically significant changes compared to the baseline or the placebo group with increasing dose of olestra in various stool characteristics.

"These are increases in mean stool output, increases in mean stool water output, decreases in mean stool consistency, increases in bowel movement frequency and decreases in mean stool-water content and increases in stool sodium. Stool chloride and potassium levels of output were only statistically significantly higher for the 40-gram-per-day olestra group compared to placebo.

"I note that there are some individuals in the population with underlying medical conditions that already are losing electrolytes by routes other than fecal--that is, kidney or skin--due to their clinical condition. Also, it should be noted that among the 18 subjects who consumed the lower dose of olestra, 20 grams per day, one experienced severe urgency that was higher than the urgency reported by any subject in the 40-gram-per-day group of olestra or sorbitol.

"My overall conclusion is that these changes are not clinically significant. Dehydration due to water loss

by the fecal route is not expected with olestra consumed under the experimental conditions. The reviewer agrees with the sponsor that changes in these parameters are of little medical consequence in healthy individuals with normal gastrointestinal function."

That concludes his statement.

DR. BRANDT: Thank you very much.

DR. FALCI: I will then ask Dr. Klontz to come and review the rechallange study.

DR. KLONTZ: Thank you.

[Slide.]

This is the consumer rechallange test of Olean salted snacks to be called the rechallange study.

[Slide.]

The study objective here was to use blinded conditions and standardized eating occasions to rechallange consumers who believe they had experienced GI symptoms because they ate chips made with olestra.

[Slide.]

Who was eligible to participate in the study? As you have heard, there were 1,100 consumers who had called the postmarketing surveillance system from April 22 of 1996 through June 5 of 1997 to report having experienced adverse GI symptoms associated with eating olestra-containing snacks.

Phone calls inviting consumers to participate in the study were made to about two-thirds of eligible households.

[Slide.]

As you have heard, the design of the study was a double-blind, placebo-controlled, four-period, two-treatment, within-subject, crossover design conducted at several different study sites.

[Slide.]

What was the feed schedule? As you have heard, the subjects visited the study site four times at weekly intervals. The test products were given in random order. At each visit, subjects were given 2 ounces of either potato chips made with olestra that would contain 16.2 grams of olestra, or full-fat chips made with triglyceride.

[Slide.]

How were the products presented? Well, they were packaged in plain, food-grade, bags made of white foil laminate. Each bag was labeled with a declaration of contents and ingredient lists for both Olean and full-fat triglyceride potato chips and each bag bore the olestra product information statement.

[Slide.]

Subjects were then contacted by phone three to five days after eating the products. They were asked if

they had experienced any "digestive changes" since they ate the potato chips earlier in the week. Now, those who answered yes were asked further questions about food intolerances or medication use and illnesses among household members.

On the other hand, subjects who responded no were asked product-attribute questions to diminish the potential for skip bias--in other words, an attempt to keep the phone calls about the same length.

[Slide.]

Logistic regression was employed to compare the incidence of GI symptoms between the two treatment groups and, in retrospect, with the study size of about 100, there was 80 percent power to detect a 13 percent increase in the incidence of GI symptoms assuming, number one, the true placebo incidence rate was in the range of up to 26 percent and, number two, observations within individuals had little or no correlation.

[Slide.]

What were the results? As you have heard, 98 consumers were enrolled into this study. That represented 8.9 percent of the 1,100 who were eligible. 92 completed all four visits. There were six subjects who dropped from the study before completing all four visits, but none of these subjects who dropped out did so because of symptoms

that were associated with olestra consumption.

[Slide.]

Now, GI symptoms were reported by 65 of 92; that is 71 percent of subjects who completed the study. These 65 subjects reported symptoms after a total of 100 exposures to either full-fat chips or olestra chips. 54 percent of the exposures associated with GI symptoms involved Olean chips while 46 percent involved full-fat chips.

As you can see, that was not a statistically significant difference.

[Slide.]

This slide summarized the incidence of GI symptoms by treatment in the rechallange study with the symptoms being listed on the left and the statistical testing on the right. As you can see, whether you look at any GI symptom or specific symptoms by themselves, there was not a statistically significant difference in the incidence between individuals when they ate Olean versus when they ate triglyceride chips.

[Slide.]

This slide looks at the data a little bit differently. It summarizes the categories of GI symptom responses among the subjects. As you can see, 27 individuals reported no symptoms after any exposure to test products. Five reported symptoms after both Olean

exposures, 21 after a single Olean exposure, four after both full-fat exposures, 17 after one full-fat exposure.

And then there were 18 individuals who reported symptoms following both Olean and triglyceride-chip consumption.

[Slide.]

What are the conclusions from the study? First of all, the study subjects were adequately demographically similar to consumers who called the postmarket surveillance system. In fact, there was no difference in the incidence of reported GI symptoms following Olean chip versus full-fat chip consumption.

That is the principle conclusion. Now, Dr. Brandt, with your permission and, with discussion with Dr. Rulis and Mr. Levitt, spend two minutes on the previous studies, the eight-week clinical trials, because I think it can shed for the committee, possibly, a little bit of new light on the rechallange study.

Although it is less likely, and I really want to underscore that--it is less likely--the lack of a difference seen in the rechallange study may have occurred because some olestra-sensitive subjects could manifest GI symptoms following only some exposures to olestra.

What is the evidence for that? There is evidence supporting this possibility in the two previously conducted

eight-week clinical trials and, as you know, they were given various doses of olestra over a 56-day period eating either 0, 8, 20 or 32 grams per day divided over three meals.

[Slide.]

This is the placebo group. As you will note, there are cells going across the table. Each cell represents a day of experience for an individual subject and the subjects are actually listed on the left-hand side. Where you see red, that is diarrhea. Where you see yellow, loose stools. Green is abdominal cramps. There were 17 subjects in the placebo group.

[Slide.]

This is half of the individuals in the 20-gram-per-day group. As you will note, a number of individuals experienced no symptoms at all during the entire 56 days of study.

[Slide.]

But let's look at some of the other subjects in the 20-gram-per-day group. I would like to focus your attention on subject No. 250--I can't quite see the number. Let's look at this subject right here--who experienced loose stools on day 3, 4, 5, nothing for two days, and then two days of loose stools, nothing for a while, loose stools, reported diarrhea, nothing for about six, seven, eight days, diarrhea, nothing, loose stools.

It is important to state here that this doesn't mean that the day where you see a day of color that their whole day was preoccupied with that particular symptom. It may not have been. It may have been a single symptom, and that is important to underscore.

There were other individuals including this individual down here who reported diarrhea beginning on the first day of the trial and then a period of no symptoms at all, loose stool, no symptoms and a number of days of symptoms.

[Slide.]

My point here is that, from this study, we can see, for the lack of a better term, an on-off pattern. Thus, I suggest is possible--it is possible--that, for some consumers, the original symptoms in the rechallange study could have been due to olestra ingestion but, upon rechallange with olestra, they failed to manifest those symptoms again.

Could this phenomenon alone have accounted for the lack of a different scene in the rechallange study? No; I don't think so. I don't think this phenomenon was common enough to explain the negative finding in the rechallange study due to this phenomenon. But it is at least a concept that has not been discussed before this committee and, for that reason, I wanted to raise it here.

Thank you very much.

The next speaker will be Dr. Patrick McCarthy who will discuss the acute-consumption study.

DR. McCARTHY: Good afternoon.

[Slide.]

I am going to discuss the theater test. The theater test was an acute-consumption study.

[Slide.]

The objective of this study was to document if subjects experienced different GI symptoms after eating olestra chips compared with regular triglyceride chips.

[Slide.]

The theater test was designed to have 1400 subjects and an 80 percent power to detect a 5 percent difference in all reported GI symptoms between treatment groups.

[Slide.]

The theater test used these methods. Subjects self-selected by responding to an advertising flyer. Subjects were instructed to complete their evening meal, one to two hours before the movie-start time. At the theater, they were given a drink, a 13-ounce bag of chips, and then allowed to snack for two hours.

Chip consumption was determined by the pre-movie weight of the chips minus the post-movie weight of the

chips. At follow up, subjects were questioned about GI or digestive symptoms. If a digestive symptom was reported, then an adverse-experience form was completed.

[Slide.]

In this study, there were 1,092 subjects. There were more adults than teenagers and adult females accounted for approximately 50 percent of the subjects.

[Slide.]

The most commonly reported symptoms were abdominal pain, diarrhea and flatulence. You can see here the actual number of symptoms that were reported. Approximately 15.8 percent of the olestra consumers were symptomatic versus 17.6 percent of the triglyceride chip consumers.

[Slide.]

The study was planned to have an 80 percent power to detect a 5 percent difference between all symptoms reported between groups. Actually, when the sample size decreased from 1,400 subjects to 1,092 subjects and the rate in the triglyceride group increased from 10 percent to 17.6 percent, the power dropped from 80 percent to around 51 percent.

[Slide.]

This overhead shows the median and 10th and 90th percentile of consumption. Again, subjects were given a 13-ounce bag of chips. The overall median consumption was

about 2.3 ounces. Males in both groups tended to consume more chips than females. And the 90th percentile consumption for olestra, males, was about 6 ounces of chips versus about 7.5 ounces of chips for the triglyceride consumers.

[Slide.]

Approximately 4.3 percent of the olestra consumers reported abdominal pain versus 5.5 percent of the triglyceride consumers. The difference in symptoms reported was not significantly different nor was the difference in diarrhea significantly different between groups. The reports of flatulence between groups was marginally, borderline significant. There were more reports of flatulence in the triglyceride group.

When all symptoms were combined, there was no difference between symptoms reported for the olestra consumers and the triglyceride consumers.

[Slide.]

This slide shows the adverse effects reported. Most of the subjects reported mild symptoms. The subjects that reported moderate symptoms, most of them were in the triglyceride group. Only about 0.8 percent of the subjects reported severe symptoms.

The duration of symptoms for subjects reporting abdominal pain and those reporting flatulence, the duration

was just slightly longer than the duration of symptoms for subjects that reported diarrhea.

The median duration of diarrheal symptoms for those reporting mild symptoms was four hours, those reporting moderate symptoms, 11 hours and those reporting severe symptoms, about four hours.

[Slide.]

As you can see from this slide, as reports of diarrhea increased in both groups, there was no significant difference between groups.

[Slide.]

In conclusion, the theater test had a low power for detecting a 5 percent difference between groups in the number of all symptoms reported. The results did not show a significant difference in reported symptoms between groups. Reports of diarrhea increased as chip consumption increased.

The home consumption study will be reviewed next by Stuart Chirtel.

MR. CHIRTEL: Next I am going to talk about home-consumption study which P&G described this morning just to review briefly.

[Slide.]

There were two groups, an Olean group and a control group. The Olean group contained 1,620 individuals from 568 households including 696 males and 924 females.

The control group contained 1,561 individuals from 570 different households made up of 704 males, 857 females.

Both groups consumed both Olean-labeled products and triglyceride-labeled products over a 42-day period. GI symptoms and product consumption were recorded daily for the entire study period.

[Slide.]

The focus of this talk is going to be on the total symptom days for loose stools, more frequent bowel movements and abdominal cramping.

There are two questions that I would like to address here. One, is there a treatment difference or an effect between the Olean and the control groups in the mean number of symptom days experienced over this 42-day period. The second point, a very important point, is there any relationship between the amount of both Olean-labeled product and triglyceride-labeled product and symptom days.

[Slide.]

For mathematical methods, I used household means to calculate p-values. This insures that all of the observations are independent since we know that individuals within the same household may have correlated results. They may all come down with a GI disease at the same time or they may discuss their results. So this insures independence of the observation.

I am going to assume that the symptom-day data are from a poisson distribution with extra poisson variability or a longer tail than a normal poisson. Two-tailed p-values were calculated using SAS PROC GENMOD with the wild chi-square statistic. In many of the cases, I validated this procedure with a totally nonparametric randomization test that doesn't make any assumptions about the distribution of the test statistic, only that the observations are independent.

[Slide.]

My first chart, I am looking at males and females separately. I want to know is there a difference in loose stool symptom days over the course of the study. For the Olean group, we had a mean of 0.89 symptom days, for the control group, 0.87. You can see no statistically significant difference here. And I only validated this if there was a significant difference.

For more frequent bowel movements, we had 0.66 symptom days in the Olean group, 0.42 in the control group for a difference of 0.24 symptom days over the 42-day period, p-value by the PROC GENMOD was 0.477 and the randomization test was slightly higher, at 0.819.

Very important; not a hint of difference for abdominal cramping in the males.

[Slide.]

Now, looking at females, the same things. For loose stools, we see the Olean group, 1.08 loose stool symptom days versus 0.80 for the control, a difference of 0.28 and not statistically significant by the .05 level. More frequent bowel movements; we have 0.83 in Olean group, 0.53 in the control group for an effect size or difference of 0.3 symptom days over the period. The p-value was .0123 and the randomization test value was .0011 which confirms this.

Again, very important; not a hint of any effect on abdominal cramping.

[Slide.]

I did analysis by age group. I looked at people 18 and younger, 18 to 64 and greater than 64, males and females. There were no statistically significant effects for anybody 18 and under for males or females. These were the only statistically significant differences that I saw; for loose stools, females 18 to 64, 0.43 symptom days in the Olean group, 0.99 in the control group. The effect size is 0.44 symptom days or the difference significant at the .0258 level. I didn't check this one with the randomization test because it was a very time-consuming procedure. I only did it on certain ones.

For more frequent bowel movements, we have 1.11 symptom days for the Olean group versus 0.63, a difference

of 0.47; again, significant using the GENMOD procedure at .0036. Again, nothing here on abdominal cramping.

[Slide.]

This is what the data actually look like. On the top, these are males in the Olean group. The top, this is loose stool symptom days for the Olean group. On the right side, we have, I called it the triglyceride group or the control group, again, males, loose stool symptom days. So you can see the scatter of the data.

For example, this individual had about 23 symptom days of loose stools during the study and he was eating--the scale on the X axis goes from 0 to 250 ounces. You can see there is a lot of concentration here at the 0. These points are plotted over each other.

These are unremarkable graphs. There wasn't a statistically significant difference here. More frequent bowel movements are on the bottom for males. Again, it is hard to make much from these scatter plots. There are an awful lot of points plotted over each other here, again the X axis going from 0 to 250 ounces and symptom days going from 0 to 40.

There was a difference here, if you remember, at the 0.04 level by my PROC GENMOD test.

[Slide.]

This is the same graph for females. Here we have

loose stool symptom days in the control group. This is the Olean group. We can see there is some tendency--it looks like there are a few more high flyers up here than in the control group. It is not incredibly clear, but there was a statistically significant difference in overall symptom days between these two.

This graph is kind of interesting. On the left side, we have the Olean group for females and we are looking at more frequent bowel movements. On the right side, we have the control group. I want to draw an imaginary line at 10 symptom days here. It is just quite interesting here that there does appear to be a real cluster or scattering of much higher symptom days in the Olean group.

But these graphs are difficult to interpret. So I took this data and I plotted it in a different fashion.

[Slide.]

This will take some explanation. What I did is I took the data in the prior graph and I grouped according to consumption. Anyone consuming between 10 and 0 ounces over the study was in group 1. Between 10 and 20 was in group 2. Between 20 and 30 was in group 3. So I created nine populations of consumption here.

The final consumption level, though, because there were very few people, anyone consuming more than 80 ounces went into the final consumption group. So I have,

basically, nine populations here and nine populations here.

On the bottom, this is the median. And this is the Olean group again. So we can see that, regardless of consumption, 50 percent of the people in the Olean group had 0 symptoms. This symptom day goes from 0 to about 8. So, for the median, we have 0 symptoms.

The next line is the 75th percentile for each population. 75 of the people had this many symptom days or fewer. There you start to see some tendency of a trend, but it is hard to see much.

Now we move up to the 90th percentile or the most symptomatic 10 percent of individuals. What you see here is a trend, an upward trend with increasing consumption for the 90th percentile or the most symptomatic 10 percent of individuals. Contrast that with the control group where the profiles are essentially quite flat, really.

[Slide.]

This is males. In this case, it is more frequent bowel movements. But, again, the median value, half the people had 0 symptom days regardless of how much they ate in the Olean group. You can see, in the 75th percentile, it kind of starts to go up. Again, the 90th percentile, beginning about 25 ounces, you see the beginnings of this trend here.

Again, look at the control group. You see a

certain bounciness here because the populations in these--half the people ate about 27 ounces or less, so these are much smaller samples sizes. You see a little bounce, but you clearly don't see any upward trends in the control group.

[Slide.]

This is females. Again, the medians are flat. Half the people had no symptoms. 75th percentile in the females. Again, I would call that, basically, a flat. And we go up to the 90th percentile and we it is kind of a tendency for a trend.

The control group versus how much Olean-labeled product they ate, we really don't see any kind of a--we just see a flat pattern.

[Slide.]

Females for more frequent bowel movements. Again, the control group; the profiles are essentially flat. Again, here at the 90th percentile, we see a certain bounciness but you see this tendency here.

[Slide.]

Those were just pictures. Now, I am a statistician so I am supposed to generate some p-values. On the top, I am addressing the question, "Is there a difference in the slopes between the control and the Olean group relating how much Olean-labeled product they at and

symptoms?"

For males, looking at loose stools, we see the p-value is 0038 saying that the Olean group and the control group, both eating Olean-labeled product, don't have the same slope versus symptom days. For more frequent bowel movements, we have it looks like 0.003. It is hard to read from this angle.

On females, loose stools is 0.62 so we have a significant slope there, and nothing for more frequent bowel movements in terms of slope. Again, importantly, nothing on cramping. So this table is very important. It says that if I say is there a different slope with regard to eating Olean-labeled product for the control group and the Olean group and how many symptom days they had, the answer appears to be yes.

Now, on the bottom, and this has been confusing in the past so I will try to make it slightly less confusing, I also regressed, using my poisson regression, the relationship between how much triglyceride-labeled product they ate because, as you remember, they both got ordinary, conventionally labeled chips which were ordinary conventional chips.

Is there a relationship there? There were no significant relationships for either males or females for any of these variables. So there was no indication of a

difference between the Olean group and the control group.

[Slide.]

Now what I am doing, I am making a slightly different test here going within each of the groups. I am saying, "Is there a non-0 slope within that group?" On the top, we are looking at Olean group and I am saying, what is the probability that there--I don't want to say it that way, but I am testing the hypothesis of no slope between consumption and symptom days in the Olean group. The p-value for males is 0001. For more frequent bowel movements, 0001.

And when I did the randomization test to confirm this, it was a higher value but quite significant at 009 and 007. So this says, within the Olean group, there is a non-0 slope relating consumption of Olean-labeled product and symptoms.

In the control group, there was no such significant relationship relating consumption of Olean-labeled product and these symptoms and nothing on cramping.

On the bottom half of this, I do the same test only relating consumption of triglyceride-labeled product in the two groups, and there is no significant relationship here at all.

[Slide.]

The dotted line is what my model predicts for

males, for loose stool symptom days. These values are the means of the consumption groups that I had just described before and I wanted to see how well my model fits the actual data. You can see that it is pretty good, in my opinion.

[Slide.]

This is more frequent bowel movements. My model prediction, the dotted line, and the raw individual means by these consumption groups for more frequent bowel movements, this is for males.

[Slide.]

Switching to females now, I am testing within the Olean group, is there a relationship between consumption of Olean-labeled product and loose stools. The p-value was 0184 confirmed by the randomization test, 022. For more frequent bowel movement, we have 042 and 043, again saying, yes; there is an association between consumption of Olean-labeled product and symptom days for these symptoms.

For the control group, there is no statistically significant association. On the bottom I do the same thing versus consumption of triglyceride-labeled product and we have nothing.

[Slide.]

These are the charts for females relating my model prediction versus the means. You can see there is a certain amount of jumpiness, and, again, it is a slightly flatter

curve than we had for the males. This was loose stool symptom days versus Olean-labeled chips consumed.

[Slide.]

This is more frequent bowel movements versus Olean-labeled chips consumed. For females, again, this was statistically significant. You can see a fair amount of jumpiness there.

[Slide.]

What I have done is made some estimates from my model in the amount of extra symptom days one would achieve where there were significant regressions by eating 27 ounces, which was about the median consumption for the study, 64 ounces which was about the 90th percentile, and 83, which was around the 95th percentile for consumption of the study.

So, for males, we see somebody eating the median level for the study which is probably not too far from what Dr. Zorich said, the 90th percentile was for the population of around 0.28 symptom days. Loose stools, somebody eating 64 ounces over the 42-day period, 90th percentile for the study would have the mean as 0.93 more symptom days and the 95th percentile for consumption would experience, on the average for that population, 1.45 more symptom days.

So, for more frequent bowel movements, the values are 0.23, 0.84 and 1.39. For females, we have, for loose

stools, somebody eating the median consumption, at this study, the average for the group is 0.21 more frequent loose stool symptom days, 0.6 at the 90th percentile and 0.85 more loose stool symptom days at the 95th percentile for consumption at this quite high level.

And, for more frequent bowel movements, we have 0.17, 0.47 and 0.66. One point to remember when we look at these estimates, these estimates are for the mean of the population but, in the graphs that I showed you before, with the consumption of the Olean product, the 90th percentile is going to be substantially more affected than the mean.

I have talked about the sum total of symptoms for these GI symptoms over the study, but Dr. Curtis Barton is now going to talk about the temporal relationship between consumption of the products and the onset of symptoms.

Thank you.

DR. BARTON: Stuart's analysis dealt with the data in its entirety, the data for the entire 42 days combining days when people ate olestra and days when people didn't eat olestra.

[Slide.]

I think this analysis is valuable and valid, but I think there are certain shortcomings to the analyzing of data this way. Three major shortcomings I have noted here are that it provides no information about the temporal

relationship between consumption of olestra and experiencing GI symptoms.

If there are, in fact, GI symptoms due to olestra, it would be interesting to know whether they occur the same day or the next day or two days later. And these different latencies could imply different mechanisms or have different medical implications. Also, I think that dose response interpretations are, perhaps, easier if you can say if someone eats 5 ounces of chips on one day, they are 5 percent more likely to have a certain GI symptom on the next day whereas saying that if someone eats 64 ounces over 42 days, it is hard to say what that means because, obviously, whatever biological processes are going on aren't taking 42 days to occur.

The second shortcoming is that there is a possible lack of sensitivity to this kind of analysis because it combines periods during which olestra is consumed with periods during which olestra is not consumed. Some people in the olestra group may have only eaten, say, five or six days and so you really wouldn't expect those people to be having very many symptoms.

Even people who eat, say, 20 out of the 42 days, they still have 22 days that they didn't eat olestra. They may have had five or six days in a row that they didn't eat any olestra and you wouldn't expect to see symptoms in that

case, either. So, just combining eating and non-eating periods would tend to dilute whatever effect you saw.

A third shortcoming of this kind of analysis is possible bias due to subjects altering their consumption patterns due to experiencing GI symptoms. To take an extreme hypothetical example, let's say one group of people begin the study. They start eating the chips with olestra. They like it. They don't have any symptoms so they just keep eating more and more and, at the end of the study, they have eaten a lot of olestra and have had very few symptoms.

Let's say another subgroup of people start the study. They like the taste of olestra. After a few days, they start having symptoms. And, after, say, a week or ten days, they have had GI symptoms for six or seven days and they say, "Well, that is enough. I am not going to eat any more."

So at the end of the study, these people have had quite a few symptoms but they have eaten very little because they quit eating after having the symptoms. So if you combine those two groups of people, you would end up concluding that the less olestra people ate, the more symptoms they had and that would not really represent what occurred in the study.

[Slide.]

On the next overhead, I decided to look at how

people do or whether they do change their behavior as a function of having GI symptoms. So I arbitrarily designated a day on which they had more frequent bowel movements as being day 0. If you go backward in time from that to, say, three or four or five days before having a symptom, you have kind of an ambient consumption level here of 0.8 or 0.9 ounces of chips per day.

If you then go and look at the day after experiencing the symptoms, you find that, regardless of which group they are in, if they have the symptoms, they reduce their consumption considerably, about 35 to 40 percent from what they were eating several days before having the symptom.

Then you can see that, as time passes, they begin to gradually eat a little more and by the time a week has gone by, they are nearly back up their previous level of eating.

There is one more feature of this graph which you may have noticed and that is on day 0, the day of the symptom, we see a very high level of consumption for males in the Olean group and a fairly high level for the females in the Olean group as well. This strongly suggests that there are symptoms occurring in the Olean group on the day of consumption of the Olean-containing chips.

[Slide.]

So, on the next overhead, I performed an analysis of the percentage of occasions that GI symptoms were reported on the same day that the Olean-labeled chips were eaten. You see the list of symptoms. This is the percentage for the Olean group, the percentage for the triglyceride group. The effect here is just the difference between those two percentages.

I computed the differences before rounding so they don't quite add up in all occasions. You have the 2.9 percent of males having more frequent bowel movements on the day of consumption as opposed to 1.2 percent for the control group and then a difference of 1.6 percent.

Let me forewarn you that, in a minute, I am going to put up a complicated graph and that the vertical axis on that graph is this effect. So it is the difference in the percent of occasions for the two groups.

So what I have found in doing the statistical tests here is that you have statistically more cases of gas and more frequent bowel movements on the same day of consumption for males. You have statistically less nausea for the Olean group on the day of consumption.

For females, you have statistically more gas, looser stools and more frequent bowel movements for the Olean group on the day of consumption.

[Slide.]

I did the same analysis for days on which the Olean-labeled chips were not consumed. You can see all of the symptom occurrence are much lower. There are a couple of isolated significant results, less cramping for the Olean group and more bloating for the Olean group in females.

But the main point of this graph is that none of the effects on gas, more frequent bowel movements or looser stools which were seen on the eating day are seen on non-eating days.

[Slide.]

Now, those tables considered only an isolated day. That is probably not a reasonable thing to do because there is probably some cumulative effect of eating olestra on multiple days. So this graph shows the effect size for a percent of occasions of more frequent bowel movements. On day 3 of a three-day eating sequences, I have depicted all eight combinations of eating and not eating for three days here.

If they didn't eat for the entire three-day period, that would be a no, no, no. If they ate all three days, that would be yes, yes, yes. If they ate only the second day, that would be no, yes, no. On the X axis here, I have the four combinations of eating and not eating for the two previous days with the third day being a question mark, either yes or no.

So here you have y, y, ?; this means that they ate each of the previous two days. N, y; they didn't eat two days ago, they ate yesterday. Y, n; they ate two days ago but not yesterday. N, n; ate neither day. So, as you go from left to right, there is a greater frequency of having eaten the two previous days.

The middle two both ate one of the two previous days so I put the more recent one toward the right. So I call this a frequency/recency scale. The dotted line, then, are occasions of not eating on day 3. And the solid line are the occasions of eating on day 3. The vertical axis, which I prewarned is the effect size, the difference between the Olean and triglyceride.

So the two main things that you can see from this graph are first that there does seem to be a frequency/recency type of effect of having eaten more on the previous two days, both within the group that hasn't eaten on the third day and within the group that did eat on the third day which is the day for which symptoms are evaluated.

The other thing you can see is the eating versus non-eating on the third day. For each of the four combinations of what they did on the previous two days, there is a noticeable effect of having eaten on that day.

[Slide.]

The next overhead shows the same thing for females

for more frequent bowel movements. A similar pattern, not quite as much of a frequency/recency effect for the people who did not eat on the third day.

[Slide.]

So I then, on the overhead, I went back to looking at individual days. So this is the percent of occasions that more frequent bowel movements are experienced on the same day as eating by the amount of Olean-labeled chips eaten on that day.

The amount of chips eaten were recorded originally in terms of proportions of a bag. Proctor and Gamble recorded these as approximate ounces of chips and submitted them as these numbers. But the three-and-a-quarter ounces represents half a bag. 1.63 is a quarter of a bag. The 0.81 represents a category of less than a quarter of a bag.

[Slide.]

So you can see that for the triglyceride group, there is maybe a little bit of a dose response, at least up until you get to the highest dose. For the people eating olestra, you can see that there is quite a clear dose response here and it is very consistent for both males and females.

If they didn't eat any olestra on that day, they had about a 1 percent chance of having more frequent bowel movements. Less than a quarter bag, a 2 percent chance. A

quarter of a bag gives them a 3 percent chance. Half a bag gives them a 4 percent chance. And all of the higher categories grouped together, you get a 6 or 7 percent chance of having more frequent bowel movements on that day.

[Slide.]

So I looked at this on the next overhead in terms of what level of consumption would be statistically significant. And so I started with the lowest dose and then gradually just combined the higher doses with those data because looking at the higher doses alone doesn't work very well because some of the sample sizes get very small.

But as I added the higher groups here for more frequent bowel movements for males, I get the quarter-of-a-bag category is statistically significant.

[Slide.]

On the next overhead for females, for loose stools, again the quarter-of-a-bag category is significant. For more frequent bowel movements, the lowest level, the less-than-a-quarter of a bag is statistically significant.

These numbers are probably biased toward being too low because again, on this table and the previous table, I am only considering a single day's consumption. From the complicated graph I put up, you could see that the amount of consumption over the two previous days is also important.

So what I decided to do then was to look at the

total amount of Olean-labeled chips consumed over a period of three days and see what dose it took to become statistically significant there.

So, for males, for more frequent bowel movements, this level is three-and-a-quarter ounces, or the equivalent of half a bag of the chips over a three-day period.

[Slide.]

On the next overhead, you can for loose stools, it is 4.88 ounces and for more frequent bowel movements, three-and-a-quarter ounces, which is the same as it was for males.

[Slide.]

So the results that I see here are that the GI symptoms, more frequent bowel movements, loose stools and gas were seen on the same day as olestra was eaten. The symptoms increased with increased consumption over the previous two days and there was a clear dose-response relationship for the GI symptoms.

Stuart and I have given you the details of the statistical analyses of the frequency of GI symptoms. There are more data in this study and Dr. Thomas Wilcox now will give you a broader view of the study from an epidemiological perspective.

DR. WILCOX: I would like to speak to you about some of the quite interesting aspects of the study results of there rather unique study. First of all, clearly it was

a big dose. People ate a lot. The 90th percentile ate 2.3 ounces a day for 35 days out of a 42-day study. This is a lot of chips.

It was a big study, a big study powered to detect very small effects. If there is an effect, you should be able to detect it with this study.

The FDA analysis did detect a significant trend for dose response for more frequent bowel movements and loose stools versus olestra ingestion. Now, when we got this result--I had the same question that Mark Brown had before; what is more frequent bowel movement.

[Slide.]

This is the daily record. This is the forum that the participants in the study hopefully filled out each night before they lay down to sleep. It talked about what did they eat, how much did they eat of olestra, triglyceride, labeled chips.

They also asked, "Have you any digestive symptoms today that you want to report?" And then question 5 gave you some choices. It goes from heartburn, nausea, vomiting, gas, bloating, abdominal cramping or pain, more frequent bowel movements, looser stool and an option for other digestive symptoms.

The more frequent bowel movements, I sort of wondered exactly what that meant and I wondered if it was

associated with looser stool. We did some calculations and we discovered that 75 to 80 percent of the people who had checked "yes" on a daily record for more frequent bowel movements would also check "yes" for looser stool. So I suspect that these stool symptoms are similar to those that were found in the clinical olestra trials that were mentioned earlier today.

What is not similar in this study with regard to the clinical trials is abdominal cramping or pain. We found no indication that the abdominal cramping or pain had occurred in the participants in this study associated with olestra.

[Slide.]

This is an example for abdominal cramping or pain. Yes was checked about 580 times for people in the olestra group, so they had 580 symptom days. The triglyceride group was checked 590 times, so they had about the same number of symptom base for abdominal cramping in both groups.

This is an example for more frequent bowel movements. There were 1230 symptom days in the olestra group where there were about 760 in the triglyceride group for more frequent bowel movements.

Question 6 is quite interesting also. It asks, how do the symptoms affect you. Noticed but did not affect. Noticed and slightly affected. 98 percent of the people

with symptoms in the olestra group checked one of those two categories. 97 percent in the triglyceride group checked one of those two categories, so these symptoms did not seem to prevent them from doing what they normally did.

In terms of question 7, "Did you take any medication?" there was essentially no difference between the two groups. The same for doctor visits in these two groups.

[Slide.]

You have just heard a lot of statistical results that were quite surprising to me. The risk increases with increasing dose on a single day and it also increases with consecutive days of consumption. A total of 3 to 4 ounces eaten over three days can measurably increase your risk if experiencing the stool symptoms.

The symptoms tend to occur on the day of ingestion. This is what we find reported in the adverse-reaction monitoring system but we had trouble trying to understand how that might occur since the transit time in the gut is at least two days.

But we find a similar thing in this study. We don't really know how to explain this.

The symptoms are mild with respect to activities but when symptoms occur, consumption decreases. If you can remember that curve that Curtis displayed where the amount eaten goes up and then symptoms occur, and there is a

precipitous drop, and then the amount eaten gradually returns to baseline.

I would suspect that that precipitous drop might suggest that the symptoms are less than pleasant to at least some of the consumers.

Overall there is a low chance for experiencing symptoms on average. Stuart mentioned that I guess 27 ounces ingested over the 42-day period of the study would increase your chances of loose stool by 0.28 symptom days. This is, on average, a very small amount. But I think he also pointed out that symptoms are not distributed evenly. The most symptomatic 10 percent can experience quite frequent symptoms.

[Slide.]

Perhaps these graphs are familiar to you by now. These are quite ingenious, I think. Stuart, I am quite impressed by how you figured this out. This 90th percentile line is dose along the x axis. This states that if someone has this amount of consumption, the most symptomatic 10 percent will have four or more days of loose stool symptoms.

In larger doses, it could go up--the most symptomatic 10 percent could have eight or more days of loose-stool symptom days during the 42-day course of the study.

[Slide.]

If we can try this next slide, I have used some high-tech graphical methods to remove part of Stuart's graph and insert my approximation of the mean dose response in his model. You recall his models that tried to fit the data. This is loose stool symptoms in males and females combined, and you can see, as dosage increases up to over 100 ounces for the period of the study, symptoms go up from a little under one symptom day to, perhaps, two symptom days.

So one or two symptom days over a 42-day period may be of little consequence to many consumers, but if you are in this very symptomatic group of the 90th percentile of symptoms, you might be talking four, five, even eight days of symptoms. And that might be of more consequence to the people eating olestra.

That concludes my remarks. Now Ken Falci will provide FDA's tentative overview summary of what the new studies show.

DR. FALCI: It should only take me about ten minutes to summarize everything that was presented here in about the last hundred minutes or so. Again, my name is Ken Falci. I am the Office Director of the Office of Scientific Analysis and Support in the Center for Food Safety and Applied Nutrition at FDA.

I occupied a unique position in the fact that all

of the studies that came in to the FDA came in to my office and all of the presentations that you heard today were from people in my office from the Epidemiology Branch as well as from the Division of Mathematics.

Overall, when you look at all of the studies, and I have to summarize it that day, you really find that the data before us is somewhat unremarkable. We really didn't observe any significant, unexpected effects that we weren't already aware of. In essence, there were basically no red flags. At least tentatively, we can conclude that. Generally, we believe that nothing was observed that the people in the nation have not already been informed about, at least on the label.

[Slide.]

Just to review quickly, then. The overall tentative FDA conclusions basically were that in the passive postmarket surveillance, we saw three adverse reports or adverse effects; abdominal pain, diarrhea and flatulence. Over 50 percent of the people that were in the study ate about 8 grams or less.

The median time to onset of abdominal pain was recorded at about five hours and the median time to onset of diarrhea was about seven hours in the physician review of the medical records that was discussed, when you look at all the eaters of olestra. The company has indicated that there

were some number of millions of serving sizes that were eaten in the population.

We have received about 1,300 adverse reports recorded from Proctor and Gamble and about 1,300 reports from CSPI. Some of them are duplicates, so there are about 2,500 recorded events out of all those serving sizes eaten.

Additionally, we have about 120 adverse reports reported from P&G of people that have actually gone to a healthcare professional. About 80 additional ones have come from CSPI. Some of them may be duplicates but we don't believe it is more than 5 percent so we have about approximately 200 people that have actually received advice from a healthcare professional.

This is data that runs from about April of I think it is 1996 to January of this year. Of all of this data, we have only 21 physician reports that we had received and only three of them attributed the etiology to olestra by an examining physician. That is not a large number.

In the stool-parameter study, basically, in the report that I read into the record, to summarize that, there was really no clinical significance in the stool-parameter study regarding total output of stool, total water output and stool consistency or frequency.

But more important than that, and what we probably can focus on and I hope you do, is despite the study

participants calling themselves, or labeling themselves, as having diarrhea, there was really no clinically or medically recognized diarrhea by our physician.

In the rechallange study, we had a great number of people go on, about 98. We did not see 98 people being rechallanged with olestra and having adverse reports. In fact, what you see is that if you rechallange these individuals twice with olestra, you will get about five of them that will be reactive and say that olestra was their problem.

But, at the same time, we have full-fat chips and four of those people had the same kinds of adverse reports. So, in the end, we are left with no statistical significance as far as the rechallange study is concerned.

[Slide.]

On the next slide, the acute-consumption study with dealt with the theater study, we had people go into the movie theater. The company did check them out and ask them for adverse reports for the last three days. Again, we found no statistical difference in adverse reports reported in the acute study, the theater study, regarding diarrhea, flatulence and abdominal pain.

Finally, the last study that you just heard was the six-week consumption study, the home-consumption study. Here, again, we did find an increased incidence of more

frequent bowel movement and loose stools. We did find that. Symptoms do occur on the day of ingestion and there is really no noticeable effects in activities.

You are going to have to judge that for yourself as far as more frequent bowel movements are concerned. But as far as we are tentatively concluding, there is no noticeable effect on activities.

Finally, although you have heard a lot about more frequent bowel movements and loose stools, the study population, when you look at the entire population in this home-consumption study, and this is real-life living, eating chips every day, and you look at all of the symptoms ranging from flatulence to loose stools, you have a loss of about a third of a symptom day in the study.

This, to some extent, disappears in the vast background levels of adverse reports on digestive symptoms in the nation today.

And that pretty much summarizes our conclusions and thank you very much, Mr. Chairman.

DR. BRANDT: Thank you very much.

Questions of Clarification

We are going to start with committee discussion but I am going to take the prerogative of the chair for a moment and do a couple of things. One is to announce to everybody in the audience that if you wish to sign up to be

a presenter in the public session in the morning, please go out and do it before you leave today. You need to register, whatever the FDA calls it these days.

Second, I have two questions and a comment. The first is that I rarely go to the grocery store and order two or three ounces of potato chips. How much do those little bags that used to cost a nickel hold?

DR. ZORICH: One ounce. The small ones are an ounce.

DR. BRANDT: The old nickel bags are an ounce? Good. I am glad to know that. That really clarifies it. It depends.

The second thing is CBS Evening News last Thursday had a thing on olestra and they said that the FDA had receive 5,400 people that had called with adverse complaints. So far, what I have heard is 2,500. Can CBS not count, or what?

DR. FALCI: I think, since there are going to be a number of questions, I will have my whole staff come up and we will get close to the microphone so we can instantaneously respond to your questions. So if Dr. Klontz and Dr. Street and Dr. Wilcox can come to this area--

DR. BRANDT: It is not going to take three people to answer that question, is it?

DR. FALCI: I am assuming there will be quite a

few more. Now, I am quite well defended, actually.

DR. BRANDT: Do we know how many? I am just curious about why they would report 5,400.

DR. STREET: We just received the data, the national data. We received it actually nine working days ago. There are 4,000 people in that data. So if you count the test-market period and that 4,000, that is going to be 6,000.

DR. BRANDT: So they were wrong on both counts. Okay.

The third comment; you all keep referring to stool-softening as a symptom. And yet, when I watch t.v., I see millions of dollars in ads for products whose sole purpose is to soften stool. Why are we considering that a symptom? Why are we using that term instead of calling it what it is?

DR. WILCOX: I think the study participants refer to it as loose stool. That may well be soft or it may be loose. It is a little hard to tell sometimes.

DR. BRANDT: All right. I have had my shot.

Dr. Harlander?

DR. HARLANDER: I am struck by how similar the symptoms are with olestra chips and full-fat chips and I am wondering if FDA is considering a label on full-fat chips. I'm kidding. It is late in the day.

DR. BENEDICT: I am not sure. Perhaps this is for Dr. Barton, but it can be for whomever. In the one curve where there was some pre-olestra dining and then there was some olestra dining and there was a spike and then there was a drop, does that correlate with overall food consumption or was that only olestra? My question is when people undergo these symptoms, do they stop eating and does that, then, concentrate the amount of olestra in their intestinal tract or do they just continue to dine on everything else and stop eating olestra for those two or three days after the original event?

DR. BARTON: I don't know. I don't think we had any data on total food consumption. I think we just had the chip consumption.

DR. BENEDICT: Thank you.

DR. CLANCY: I want to ask a couple of questions of Mr. Chirtel. But I think maybe Dr. Barton started to answer one of these questions. You gave, in your kind of summary tables, your calculation of the mean days of extra symptomatology out in both the control and the olestra group. Did you calculate ranges on those?

MR. CHIRTEL: Can you be more specific? Do you mean confidence intervals? Do I have a confidence interval on that?

DR. CLANCY: Right.

MR. CHIRTEL: Yes; I do. We took it off just for simplicity in the slides but I have 95 percent confidence intervals for all of my estimates.

DR. CLANCY: For all of the estimates?

MR. CHIRTEL: Yes.

DR. CLANCY: But, also, across the entire population, particularly at the high end because that is where the concern is.

MR. CHIRTEL: When you use the model approach as opposed to slicing and dicing by consumption group, that reduces your power and the beauty of a model, if it is a correct one, is that you have a lot more power to detect a trend, so the model speaks through the entire range.

DR. CLANCY: So going, then--

MR. CHIRTEL: If you want it for a high consumption, would you want a 95 percent confidence limit for one of the symptoms? Is that what you are talking about?

DR. CLANCY: Yes; like males for loose stools.

MR. CHIRTEL: I can do that.

DR. CLANCY: Dr. Barton put it a different way. You looked, at the 90 percent, you said that the number of days of symptomatology might go up to eight. That was a part of this range--

MR. CHIRTEL: Do you want males and females

combined, males, or females?

DR. CLANCY: It doesn't matter.

MR. CHIRTEL: For males, loose stools, we will take it at the highest, at 83 ounces which was the 95 percent for consumption. The estimate for the mean symptom days was an additional 1.45, but the likelihood ratio confidence interval for that was from 0.44 to 3.19. That is for the mean. So there is a wide range on this at that end of the curve.

DR. CLANCY: The other question is related to this 95th percent. The combination of the difficulty of interpolating the very high consumption against a difference in numbers of days of symptomatology. Although there is a curve, obviously we know there is a variation around that.

But I am concerned about your conclusion, Dr. Falci, basically suggesting that there are not any significant adverse effects. But in 2 percent, in any of the analysis that any of you did or that Proctor and Gamble did or that CSPI did, in approximately 2 percent of the population that is in your studies, those are definitely reported as adverse effects.

I don't take from you that you have not accepted them as adverse effects. My concern is that 2 percent in terms of their not being taken into account, represented well enough in the analysis, et cetera.

DR. FALCI: I guess I would say that I said generally not significant. I was summarizing all of our studies, but I did also mention that we did have more frequent bowel movements as well as loose stools as an adverse reaction.

Stuart, anything additional?

MR. CHIRTEL: No.

DR. FALCI: We recognize that that is there; yes.

DR. FEINLEIB: With regard to the rechallange studies--I guess this is for Dr. Klontz. This was described as a four-period within-subject crossover design. Yet all the analyses seem to be treating them as independent groups. Does an analysis which takes into account the within-subject crossover confirm the analyses you have shown us?

DR. KLONTZ: I am not sure that we specifically looked at it the second way you mentioned it. However, from talking to our statisticians, the mode that was presented was the preferable route and, as you know, there really was no difference at all there.

Do either of our statisticians want to comment?

DR. BARTON: The data analysis that Proctor and Gamble submitted to us did account for the fact that these were repeated measures in the same subjects. We approved of those methods. But when you looked at the data in that study, there was just no difference between--there were just

not differences between the two groups and you could pretty much see that just by eyeballing the data.

DR. BYERS: I have a question about this analysis that probably it would be helpful if you put that EKG effect up there. I understand, I think, your conclusions. They sound reasonable. But I don't understand the scale. You were showing percentages of 2 and 3 percent. And if you could just explain to me what specifically that means, I think that would help me to understand your analysis better.

Here, for instance, up to 1.8. I'm sorry; that was ounces of Olean. I'm sorry. Maybe one of those figures that shows the percents that are like 2 or 3 percent in these columns. I guess I am trying to resolve that with what I understood this morning to be the case that people ate this product on about half of the days.

Some of your earlier figures in which you had columns, two columns, many of those numbers were 2, 3 percent. If you could just explain to me what that means. If you could just orient me, take one of those percents there, the 3.4 percent gas, for instance, and just explain to me, this is what?

[Slide.]

DR. BARTON: This would be on days when males ate Olean-labeled chips, in the Olean group, on 3.4 percent of those days, they experienced gas.

DR. BYERS: And overall they ate chips on about half of the days; is that not correct?

DR. BARTON: Yes.

DR. BYERS: So then, the triglyceride column, the 2.2 means what?

DR. BARTON: That is also the percentage of days when they ate the Olean-labeled chips were triglyceride, of course. So, on 2.2 percent of those days, they experienced gas.

DR. BYERS: So this is the prevalence of these symptoms on the days in which these chips were consumed.

DR. BARTON: Yes.

DR. BYERS: Thank you.

DR. LAMM: Do you have the same information on the days that they didn't consume the chips?

DR. BARTON: Yes.

[Slide.]

Here you can see that almost all the numbers are smaller even for the triglyceride group who, of course, were not eating olestra on the other days, anyway. So there could be either some effect of eating the triglyceride chips or another distinct possibility is that there is a placebo-type effect, people thinking that they are eating the olestra chips.

DR. LAMM: In the summarizing sort of sense, do I

understand from the passive surveillance, you are finding an association with respect to abdominal cramps or pain with frequent bowels and with loose stools and in the active surveillance, you are finding an association with frequent bowels and loose stools but no association with abdominal cramping, and that, furthermore, you are finding there is a great deal of question as to whether there is an independence of the two measures, frequent bowel movements and loose stools?

DR. WILCOX: I think that in the home-consumption study, the more frequent bowel movements and the loose stools seem to go together. There is an association there. In terms of the passive surveillance, the most common symptoms reported are diarrhea, abdominal cramps and gas. But we don't have any associations in the that passive surveillance. We have no denominators.

DR. LAMM: Any particular thoughts why abdominal cramps shows up in passive surveillance and not in active?

DR. WILCOX: The abdominal cramps showed up quite clearly in the clinical studies where people were constrained to eat a great deal and eat it every day. In terms of the passive surveillance, as was pointed out here, people are eating just one ingestion of 1 or 2 ounces, and they report they experience the similar symptoms.

We don't really understand why that would be.

at

DR. BRANDT: We are recessed for the day. We will reassemble at 8 a.m.

[Whereupon, at 5:30 p.m., the proceedings were recessed, to be resumed at 8:00 a.m., Tuesday, June 16, 1998.]

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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