aspects of the proposed label but it seems to me that we have a population that, as I've heard, is at least 20 percent low literacy or illiterate. And it seems like that's a group that perhaps the label should be downgraded to address more advantageously.

DR. STAAB: I think it calls for a simplification also. The more we get into medical explanations of various issues, the more it's going to make it more complex rather than simplified. We go around the world, we see some very simple labels that don't get into all of the communications here. And I think it's hard to take that comment without putting in the graphics that associate it. I'm sure the graphics aren't able to be reviewed through the software problem you're referring to.

So it's a difficult area when you work with women's healthcare from the tampon experience and from the contraceptive experience, communication is not an easy area. And when you change something, which is one of the reason I really wanted to keep a label that people were somewhat -- at least the users were somewhat familiar with.

When you change something, you really have a risk of mis-communicating in some other place in the label or in that particular area.

But it is not an area that we can ignore and it isn't an area that we shouldn't consider making it as readable and simple as we can. I -- I completely support your comment. Make it readable.

DR. CANTILENA: Okay. I just -- I just have one question, if I may. When you refer to your surveillance system and your 800 number, who is actually going to be answering the 800. What are their qualifications and how does that information then get handed off, if you will, to the people who are going to be tracking the adverse events?

DR. STAAB: Okay. Good question. Currently, we've got one LPN who's worked for about 15 years in an OB/GYN office and we also have a nurse practitioner, I believe she has a Masters who's currently working at a University and at an OB/GYN clinic at a local hospital.

Neither of those people are contract with us but those of the people that we are interested in right in bring on board to start this program. They would not only take that information but they would more than likely, at this point, being a small company would also probably record the information that would be the basis of the annual report down the road for all these events.

For right now, it would be an LPN and a Masters in Nursing with a license, I guess license practical nurse would be her title. No, I'm sorry, a nurse practitioner.

DR. CANTILENA: Okay. So, if it's the weekend when the LPN is on, I guess, are you comfortable with, you know, medical triage? When if somebody calls in then they've had a hard, they've been unable to remove the sponge for five days, they've tried and failed and now they may have some symptoms. As the sponsor, as the manufacturer, are you comfortable with that level of expertise handling, you know, triage and are there, you know, systems that you plan on having to help that individual?

DR. STAAB: That's a good question. There are -- there's a guidance document that was put together by American Home Products originally for what they -- we call the help line, the consumer help line. The guidance document is pretty clear as to where you start and where you stop as far as giving advice goes. And there is a point where it says, see your physician, get to a clinic, get to an emergency room or something of that nature.

The people that we're choosing are -- are very mature and capable of following that information

and quite frankly they have a very good understanding of the women's healthcare issues. So, I would say, yes, we are confident. But I will also say with a caveat that we're going to learn over the next months and years about what else we need. And we're open to fore find that is, as we need to.

DR. LERNER: Just a piece of advice. I think they should be bilingual in Spanish as well.

DR. STAAB: The original -- what should be bilingual?

DR. LERNER: The help line people. The 800 help line.

DR. STAAB: We should have access to it. Okay. Currently, what American Home Products had done is they have access to the instructions in Spanish. If someone would need it, they would make them available to them. It was not put bilingually in each package. Okay.

As far as the help line goes, we haven't addressed that issue. But I think it makes sense. It's a reasonable request and I think that especially today and especially considering some of the inner city questions that might come up, I think it's a reasonable request.

You bet. Absolutely. Absolutely.

DR. CANTILENA: Yes, Dr. Gilliam?

DR. GILLIAM: I guess just to follow up on that. Are you going to do any different packaging for different areas of the country where you do have a more -- a higher Hispanic population? The Southwest, that kind of thing?

MR. DETROYER: The way today's -- the way the distribution system is set up in the United States today with supermarkets, drug chains and mass merchants, it is very difficult to control where product goes.

Right now our plan is English product, let's say going into Walmart, who spreads it all over the country. You don't have any control that this can be Spanish product here and this can be English product here.

But like American Home Products we will provide Spanish literature, if it's necessary, for a client and certainly for the clinic side of the business that's very easy to provide.

DR. CANTILENA: Okay. Any further questions? Very good. I guess without strong objection will move to a 15 minute break and promptly return in 15.

(GROUP TAKES RECESS)

DR. CANTILENA: It may not sound like it but I think we're ready. We're now at the portion of the agenda where we're going to hear the presentation from the Food and Drug Administration. And I believe in fairness Dr. Titus has allotted 45 minutes for the -- for the FDA.

First presenter is Dr. Chin.

DR. CHIN: Good afternoon. We have now come to the eagerly awaited FDA presentation for the afternoon which will be presented by myself, Claudia Karwoski, who will take about post-marketing adverse events and Gloria Chang, who will address the label changes that have been recommended.

Sorry.

I will provide a review of the administrative record for the Today vaginal contraceptive sponge over the last 20 years.

First, I will briefly run through some administrative milestones for the NDA, some information about the sponge itself and then focus on labeling issues that brought about much discussion between the agency and various sponsors over time.

The FDA for the Today Sponge was first submitted in September of 1991 by VLI. It was withdrawn in December because of inadequate U.S.

experience. It was resubmitted and finally approved in April of 1983 and was marketed by VLI from 1983 to 1987. The NDA was transferred to Whitehall in December of 1987 and Whitehall marketed the product until 1993 when it suspended, then ceased production due to manufacturing issues.

In January of 1995, Whitehall voluntarily withdrew the sponge from the market. And I just want to take a second here to emphasize that the NDA is currently an approved NDA and was never withdrawn. The product, itself, was voluntarily withdrawn from the marketplace by the sponsor.

And, finally, in March of 1999, the transfer of the NDA went from Whitehall to Allendale Pharmaceuticals.

The Today Sponge was first approved by the Division of Metabolic and Endocrine Drug Products in 1983. (Inaudible), FDA administrative side and the Division of Reproductive and Urologic Drug Products was newly formed in June of 1996 and assumed administrative responsibility for the sponge NDA.

With the Division of OTC Drug Products taking over administrative responsibilities for all OTC drugs, the NDA was finally transferred over to us in November of 1997.

Just one slide on sponge characteristics. The sponge is round and very soft, made of 70 percent polyurethane and 30 percent Nonoxynol-9. The sponge contains a total of a thousand milligrams of N-9. A loop was added for easier retrieval and later on a polyester skrim was inserted to reinforce the loop because of tearing at the time of removal.

In terms of how much N-9 is released. Spermicide release studies were done and concluded that an overall mean of 124 milligrams of N-9 eluted from the sponge with wear time up to 48 hours.

I'm sorry.

Okay. The rest of these slides are going to cover the key discussions about information that should be provided in the labeling between the agency and the sponsors throughout the development of the Today Sponge. Some of these reflect internal discussions. Others were written communications between the agency and the sponsor. Because of the passage of time, it was difficult to construct exactly when certain labeling changes were fully implemented.

At first approval in April of 1983, the following labeling stipulations were conveyed in the approval letter to the sponsor. Effectiveness was summarized as 12 months pregnancy rates per hundred

women. Rates were provided for different methods, the sponge, the diaphragm and the foam suppository with some differences noted between U.S. and international studies.

Effectiveness for the sponge at that time was considered to be in the same range as other vaginal birth control methods such as the diaphragm.

These two statements were also to be included in the labeling, that there was no evidence of significant health risk associated with the use of the product and that used during menstrual period was not recommended.

Whitehall followed up with a labeling supplement and FDA responded with the following recommendations in December of 1983.

Pregnancy rates were now stated as rates per hundred women for the sponge only. And a distinction was made between method and use effectiveness. Simply stated method effectiveness meant that consumers following instructions exactly and use the sponge each time that it's needed. Use effectiveness meant that consumers may fail to use correctly or to not use the sponge every time. Exiting labeling bears these pregnancy rates.

Other recommendations were that there

should be a statement that the sponge was not as effective as the pill or the IUD. There should not be a reference of similarity to the diaphragm. And it should not be used during menses.

Within the first year of approval, the agency was reviewing adverse events that were received, especially the reports of more severe illnesses and a latch cases of TSS, Toxic Shock Syndrome.

The conclusions reached at a joint meeting with the sponsor and investigators from CDC and FDA staff were that severe illnesses may possibly be associated with removal problems and fragmentation of the sponge and post-partum use of the sponge. Additional warning were considered at that time that the sponge should not be used post-partum and to consult a physician for removal if there's fragmentation.

As a result of a further meeting with the sponsor in 1984, FDA issued this letter of -- this letter with modifications to the labeling so that it should say, that -- to limit sponge use to 30 hours, to delete the phrase about no significant health risk and to state the association of TSS and sponge use in non-menstruating women.

Other labeling developments. In an annual report in 1987, VLI wanted to modify the instructions to wet and squeeze the sponge before use. And FDA found that acceptable but to quantify it a little further to wet thoroughly and squeeze gently.

Other labeling discussed were submitted and approved in August of 1990. Receipt of the final product label, the FPL, occurred in August of 1991, which was accepted. This final product label is the one that has been in use ever since.

So, the Today Sponge has not been marketed since it was voluntarily withdrawn by Whitehall in 1995. It is not currently available except for the diminishing stock pile -- except for the diminishing supply stock piled by Elaine in ASeinfeld@. Okay, I'll restrain myself to then -- for now. Let's go back.

The re-marketing of the Today Sponge was initiated in March of 1999 with a transfer of ownership of the NDA to Allendale. This re-marketing required that Allendale submit a chemistry supplement because of a new manufacturing sight. As part of this process, OTC undertook a review of the safety update as well as the existing labeling, which brings us next to a review of the post-marketing adverse events by

Claudia Karwoski.

Thank you for your attention.

DR. KARWOSKI: Good afternoon. My name is Claudia Karwoski and I'm from the Division of Drug Risk Evaluation in the office of Post Marketing Drug Risk Assessment.

The objectives of my presentation are to provide an overview of the post-marketing adverse events reported with the Today Sponge. To review the post-marketing safety issues that have previously been identified, such as Toxic Shock Syndrome and sponge removal difficulty and to describe all serious cases, to identify any unexpected safety issues that have not previously been identified.

I'll begin my presentation with a description of the FDA Reporting System and Toxic Shock Syndrome. I'll then provide an overview of the adverse events reported with the sponge. I'll describe the TSS cases associated with the sponge and then describe cases involving sponge removal difficulty. I'll then briefly describe any unexpected potentially serious cases and lastly I'll end with my conclusions.

Adverse event reports are submitted to the FDA by healthcare professionals or consumers either

directly through the MedWatch program or indirectly through the manufacturer. The data from these reports are entered into a computerized data base. The agencies first data base was created in 1969 and it was called the Spontaneous Reporting System. It was replaced in 1997 by the Adverse Event Reporting System or AERS.

The advantages of Spontaneous Reporting System such as SRS and AERS are that they are relatively simple and inexpensive. They enable us to detect rare events early in the marketing of a product. They also have inherent limitations. They are passive and voluntary and rely on the healthcare provider or consumer not only report the event but to provide adequate clinical data to determine the relationship between the adverse event and the product. Because its voluntary it is associated with substantial and to reporting. And we cannot use this Spontaneous Reporting System to determine incident rates of the particular events.

We also encountered limitation specific to this review. All of the adverse event reports for the sponge were entered into SRS, our old database, and were coded using very broad terminology. We had no specific terms for TSS for sponge removal difficulties

so it was challenging retrieving these cases. Each report only has four surgical terms as opposed to unlimited terms that are currently available in AERS. And the criteria for flagging serious cases varied over time.

We also noted in our review that the documentation, follow-up and completeness of many of these reports seem to decline over the years.

The TSS case definition requires five clinical criteria: fever, hypotension, rash, desquamation and abnormalities in three or more organs. Those organs include gastrointestinal tract, renal, hepatic, hematologic, central nervous system, the mucus membranes or there may be muscular involvement.

The Center for Disease Control considers a definite case of TSS as one that fulfills all five criteria. And a probable case fulfilling four of the five criteria. We also consider possible TSS cases as those that fulfilled three of the five criteria and those that only reported TSS regardless of the criteria reported.

As was previously described by Mary Delaney, there are two types of Toxic Shock Syndrome. It's considered menstrual if the symptoms occur during

menses or even a few days after the end of menses. Non-menstrual TSS includes all other causes including use of barrier contraceptives such as the diaphragm and sponge, surgical and cutaneous infections and has occurred in post-partum, post-abortions patients.

The overall incidents of non-menstrual TSS is low and has remained relatively stable over the past decade. Our database contains 5,930 reports with over 13,000 adverse events reported in association with the sponge. Each report may and often does contain more than one event. The time period for these reports is from approval in 1983 to 1997. The patients range from 12 to 55 years of age and the majority of the reports occurred in female patients. The report of serious outcomes include 168 patients that required hospitalization, ten that reported a life threatening event and two that reported disability. There were no deaths or congenital anomalies reported.

This graph shows the top ten adverse event terms reported with the Today Sponge. The red bars represent the total count of each event and the green bars represent those with a serious outcome reported. The term with the highest frequency is cervical disorder with a count of 1,072. This is followed by

vaginitis, unintended pregnancy, migration of implant, vaginal discharge, application sight reaction, pruritus, infection, menometorrhagia and unevaluable reaction. The infection reports show a larger proportion with a serious outcome. As will be discussed later, the cervical disorder and migration of implant appeared to be primarily reports involving sponge removal difficulty.

To identify cases of TSS, we searched our database for all cases from 1983 to '97 with the following adverse event terms: infection, bacterial infection, sepsis, acute circulatory failure and hypotension. We selected for review cases that met at least three of the CDC criteria or those that reported TSS. These numbers may vary a little bit differently than the information that was handed out about a month ago.

One hundred fifty-two cases of 305 that we review met at least three criteria or reported TSS. The ages range from 16 to 42 years of age with a median and mean age of 25 and 26 years. One hundred eighteen patients required hospitalization. Twenty-three reported the event as life threatening or the patients were admitted to the ICU. Twenty-three patients did not require hospitalization but were

treated as outpatients with antibiotics. And the outcome in 11 cases was not reported.

The time to onset of symptoms after the use of the sponge range from one to four days. The total time in the vagina range from 1.5 hours to six days. Twelve patients reported a vaginal time of greater than 30 hours. TSS risk factors or possible risk factors were identified in approximately 20 percent of the cases. Seventeen reported symptoms within three days of the beginning or end of menses and six may have been using the sponge while menstruating. Sixteen were post-partum ranging from four to sixteen weeks with six under six weeks post-partum. Twenty-three reported difficulty removing the sponge and 12 required medical assistance to remove the product.

So of all the 152 cases, 25 met five criteria and are considered definite, 27 met four criteria and are considered probable and 100 met three criteria or reported TSS and are considered possible cases.

This graph show the TSS cases by the year of occurrence. The red bars represent the total number of TSS cases and the green bars represent the probable or definite TSS cases. 1984 had the highest

number of TSS cases reported in association with the sponge. There were 27. It also had the highest proportion of cases that were considered probable or definite and this 74 percent.

From 1985 to 1994, the numbers of reported cases range from 17, I'm sorry, from 17 to 16 per year with an average of 12 cases per year. The proportion of probable or definite cases during those years was 38 percent or less. This may represent either that the reports lack the document symptoms because many of the earlier cases were submitted along with the CDC report form or they provided medical records in addition to the report form. It may also, however, represent increased knowledge recognition of toxic shock.

I'm next going to talk about sponge removal difficulty. Most coded -- most were coded in our database as cervical disorder and migration of implant. And this represented a little over 1,800 reports. We chose a random sample of 10 percent of these reports for review. Of the 188 cases that we reviewed, 187 reported inability or difficulty in removing the sponge. There was one report of cervicitis.

Of those cases that reported difficulty in

removing the sponge, 116 required assistance from a healthcare provider to remove this sponge. Most of these, however, were earlier on and occurred -- seemed to occur between 1984 and 1991. There were 12 patients that were able to remove the sponge after instructions were provided by the 1-800 number. The outcome of 59, however, were not reported. The sponge insertion time was reported in 108 cases and range from 30 minutes to six days. Thirty-five cases reported an insertion time of greater than 30 hours. Some common events that may have been related to sponge removal difficulties include infection, vaginal bleeding, vaginitis, urinary tract infection and pain.

Our review of the random sample of these cases indicate that sponge removal difficulty represents at least 13 percent of all of the adverse events reported with the sponge. In 62 percent of the cases reviewed, medical assistance was required to remove this sponge. The outcome was unknown in almost one-third of the cases reviewed which may suggest that more aggressive follow-up by the sponsor is warranted.

In 19 percent of all cases reviewed, sponge removal difficulty resulted in vaginal exposure of greater than the recommended 30 hours. We reviewed all reports that were flagged as serious to determine

if there were any adverse events that are unexpected or not previously known to be a safety issue. The FDA defined serious as cases resulting in death, hospitalization, disability, those reported as life threatening or those resulting as a congenital anomaly.

We identified a total of 169 reports with a serious outcome. One hundred eighteen of these were the TSS cases, 51 represented other serious events, 36 of the 51 were non-TSS infectious adverse events and 15 were non-infectious events.

Of the non-TSS infectious events, the only event that appeared to be unusual were two reports of peritonitis. The -- These provided various sketchy information and both cases were reported by the same physician. The miscellaneous cases include undiagnosed infections or reports of symptoms that may have been suggestive of an infection. The other events did not appear to be unusual or large in number for whom the product might be used for.

Of the non-infectious events, there were two sponge removal difficulty cases that were not picked up during our random search. In one case, the patient underwent an exploratory laparotomy to have the sponge removed. There were two reports of

systemic allergic reactions requiring ER treatment and overnight stay for one patient in the hospital. It's not clear if these were life threatening.

So, in conclusion, the safety issues previously identified remain a concern. TSS appears to be the most serious adverse event reported with the Today Sponge. Sponge removal difficulty appears to be the most frequently reported event. The other commonly occurring events such as vaginitis appear to be minor, however, a comprehensive review was not conducted.

Based on our review of all serious events, there were no apparent additional or unexpected safety issues not already identified.

Thank you. Next, Gloria Chang will be discussing labeling.

MS. CHANG: Good afternoon. Guess what? I'm the final speaker. By the way, I want to thank Daniel Keravitch for all his help in doing these slides.

My presentation will be covering our proposed labeling for the Today Sponge. Put it down. Okay. Basically, I'll start with an overview of the new OTC labeling rules, then the original carton labeling for the Today Sponge, proposed carton

labeling for the Today Sponge and the proposed changes to the package insert.

On March 17th, 1999, the agency published an OTC labeling requirements final rule, codified in 21 CFR 201.66. That rulemaking required standardized content and format for all OTC drug products in what they call drug facts format, format and content. The agency believed that these labeling requirements would make it easier for the consumer to recognize where to find the information and also would make the labels more legible and readable.

The drug facts labeling content requirements required the following: that all information would be organized under title, headings and subheadings; that all drug facts label information must appear on the outside of the container or wrapper of the retail package or on the immediate container if there was no outside container or wrapper; and that the headings and subheadings appear in a specific order which would allow the consumers to more quickly make a decision as to whether they should use the product, when to stop using the product and how to use the product.

The standardized headings are in the following order: title, which is always titled drug

facts; the active ingredients or ingredient and the amount; the purpose; the use or uses; the warnings. And under the warnings, there is a standardized order for the subheadings. For example, do not use; stop use and ask a doctor if.

Next comes the directions. After the directions, there is a heading titled other information. This section includes information not included in the other sections, but for which the agency feels is pertinent to the safe and/or effective use of the product, or information that is required under an OTC drug monograph.

The last section is the questions or comment sections which provide phone numbers for consumer inquiries.

The labeling rule requires standardized formats so that there is consistency in the format for all labeling. For example, there are type size specifications for the headings, subheadings and text. There are also bulleted format to improve readability.

The agency considers the labeling for OTC drug products, considers the carton, which consists of the principal display panel and promotional labeling and the required labeling, for example, the drug facts label, as part of the labeling. Also, the package

insert. Dan.

I'm going to make some comments on the 1991 labeling. As you can see, this part is called the principal display panel, and Dan's going to focus on the -- this section is the approved label which contains the directions and warnings. Basically, as you can see, the directions are in a paragraph format which we believe is difficult to read. Also, the important information is not emphasized. For example, the toxic shock statement is not prominently emphasized. And as you can see, they are in two separate sections, this section, and also the symptoms are in this section right here.

Further, there is no statement in the labeling that addresses or informs consumers of the serious nature or potential life threatening nature of this, of toxic shock syndrome. Just, I think that's that for that.

I just want to show you the other information as far as the inactive and active ingredients are on the other, the back panel. Can you go back? Should I just click? Great.

We have revised the Today Sponge labeling as follows. Oh, I have, is that the, did I click? Oh, I'm sorry. I'll start with this one.

Thus, there are some reasons for the labeling revisions are to remove misleading statements such as reliable protection without serious risks of dangerous side effects, and extremely effective.

Other reasons for the revisions are the, to improve the order of information so there is more emphasis on the warnings, in particular, the toxic shock syndrome warning. Also, to add additional important information such as AStop use and ask a doctor if@ statements, and to improve directions and other information for better understanding of the safety concerns and other public health issues.

We have revised the Today Sponge labeling as follows. First of all is its standardized order in accordance with the drug facts format. And this is a copy -- Helen, did you show the, you showed the copy of the original label. We're going to break this down to make it more readable for all of you.

Please note that the revisions are in red font, are the new additions to the label or statements which we have either moved or revised from the original labeling, and the statements in the black font are the statements pulled from the former labeling which may have reformatted into the new drug facts label.

I will be discussing particular sections of our proposed drug facts labeling. And this section is the warning section. Significant revisions were made to this section. First and foremost, the TSS warning is prominently displayed as the first specific warning. We have added the statement TSS is a rare but serious disease that may cause death. Additional revisions are what you can see on the slide.

In addition, we've added the allergy alert section to inform consumers that this product contains a sulfite, and also that this product contains nonoxynol-9.

We have also asked that the various revisions in red to this section.

I want to focus in primarily on the Astop use and ask a doctor if.@ This section was provided to alert consumers so that they would know if certain conditions would develop during sponge use. Note that this information was not in the 1999 final printed label.

Under the directions, we have bulleted the information to make it easier for the consumer to read and added additional directions. I lost my pointer. We've, we've, we've moved the statement Ado not leave in vagina for longer than 30 hours@ from the warnings

into this section and bolded for emphasis. Next.

Under the other information heading, we added two new bulleted statements. The first is to inform consumers of the availability of the pregnancy rates, birth method, birth control methods table in the package insert and to provide public health information statement of the use of latex condoms to reduce the risks of the transmission of HIV and STDs.

Now, I'm going to go and discuss the changes to the package insert. Because of time restraints, I will only be discussing some of the major ones. First would be to improve the presentation of the efficacy data.

Second is to include the pregnancy rate birth control methods comparative table in the package insert.

Third, we added, just wanted to basically tell you that we added some references to reducing the risk of sexually transmitted diseases in the package insert. I lost the pointer. Okay.

Fourth, we made format and minor editorial changes to the package insert. As you, as you can see from the original efficacy data statement and efficacy table, I think it is basically, thank you, I think it's basically very confusing to a layperson. In

fact, I sort of got confused by reading it also.

What we did was we basically revised and simplified the statements on the efficacy statement to make it more consumer friendly, and I believe someone already discussed the revised statement.

I'll talk a little bit about the pregnancy rate table. Back in 1997, the Center for Devices and Radiological Health in collaboration with CDRH, which is the Center for Drug Evaluation and Research, and the Office of Women's Health adapted the pregnancy rate table from Trussell's Contraceptive Technology basically to, to provide the consumers with information to make the informed, to -- let me start over. To provide consumers with information to make informed choices as to the best birth control method for them. At present, the table is included with all prescription oral contraceptives and is a regulatory guidance for other CDRH and CDER birth control products.

In -- these are my conclusions. Current labeling can be improved. The drug facts format places emphasis on the warnings, such as the TSS warning and the Astop use and ask a doctor if@ are examples of that. And provides more readable and informative information to the consumer to improve the

safe and effective use of the Today Sponge. Thank you very much.

DR. CANTILENA: Okay. Thank you very much for actually staying ahead of schedule.

MS. CHANG: And I wanted to -- right. I was going to turn the podium over to Dr. Cantilena for questions and comments.

DR. CANTILENA: I'm sorry. I beat you to the punch. I apologize. Yes, actually, we are at the point now where we have some time to ask the FDA presenters specific questions that you may have. So let me open it up to the, to the committee. Dr. Uden?

DR. UDEN: We've had toxic shock syndrome data presented a few times here today. You have a database here at the FDA. There's also a database at the CDC. How many other places is, is the data, data kept and has anybody compiled the data in one place so that we can get a relatively good estimate of the risk?

DR. KARWOSKI: Well, I actually don't have the answers for that. Not that I'm aware of. I would imagine that CDC probably has the best numbers. Ours is a voluntary and a passive surveillance, and so we only rely on consumers or health care providers to report that information to us.

DR. UDEN: Are those the two major sources of, other than primary literature, finding the incidence of toxic shock syndrome?

DR. CHIN: Let me clarify that a little bit more. What we have in our database that was presented by Claudia is information that was voluntarily submitted or regulatorily (sic) required to be submitted to the FDA's spontaneous reporting system or the current AER as database.

What CDC has is TSS is a reportable disease, and so it has to be reported to CDC. And they compile the statistics that you would see for a lot of infectious disease. The difference in the database is that what we have in terms of the adverse events, it would be adverse events that were reported in conjunction with the use of a sponge. It doesn't mean that it causes the adverse event, but it was in conjunction with the use.

What CDC's information has is the number of TSS cases, but doesn't necessarily break it down into what was used in association with the case itself. So they're really separate types of numbers.

DR. CANTILENA: Other questions? Yes, Dr. Davidson? Your microphone?

DR. DAVIDSON: Thank you, forgot. I have

a couple, you know. You reported cases of disability, but you didn't say what type of disability they were. Could you tell us what disability meant in the cases?

DR. KARWOSKI: The outcomes are very subjective. That really depends on what the individual that reported the event may have thought. For the disability, there was, in my opinion, there was no apparent disability that was caused. One of them was the TSS cases. They reported life threatening hospitalization and disability, but there was no apparent long-term type disability associated with that.

The second case was a disability. Essentially, what the patient reported was that following the use of the sponge, her and her husband were not able to perform sexually as they had prior to the use of it. So that was the, the second disability that was reported.

DR. DAVIDSON: Thank you. You know, we already commented before from previous presenters that the highest rate was seen in 1984, okay. Do we have any data of the exposure, you know, in 1984, 1985, 1986 of sponge use to see if there's, if it is a relationship between the usage and the cases. Or it was the, you know, after 1984, people were better

educated, you know, to draw some conclusions why it really went down after 1984?

DR. KARWOSKI: After, actually it didn't really go down. It stayed somewhat stable. There were bumps throughout the years. We don't have any actual usage data. All we have is some data regarding the distribution of the product, so the sales of the product.

But we don't have numbers of how many people actually used the product or how frequently they may have used it. So we can't really put a denominator on that. But what we're somewhat sure of that the use did decrease somewhat over the years, and the rate of TSS, or at least, the reports that we had received didn't really decline that much, at least over, after 1985 to 1994, that they remained somewhat stable with little, you know, small fluctuations, varying, you know, throughout the years.

DR. DAVIDSON: From the data you presented, you know, even though there were some small fluctuations, the tendency was to go down. Maybe I, no? Okay. Then it remained about 47 cases per year?

DR. KARWOSKI: Well, we had only one case reported in 1995, but the product at that point was --

DR. DAVIDSON: But the product was

withdrawn, right.

DR. KARWOSKI: -- had stopped.

DR. DAVIDSON: Okay. And one final question, when you report infections, and you report vaginitis in different sections, the vaginitis was also included in the infections or were they reported totally separate for everything?

DR. KARWOSKI: The vaginitis in our database are considered infectious type of complications.

DR. DAVIDSON: Then it was reported twice?

DR. KARWOSKI: May have. There may have been an infection and vaginitis at the same time.

DR. DAVIDSON: Thank you.

DR. CANTILENA: Yes, Dr. Neill?

DR. NEILL: I have two and a half questions, the first to Dr. Karwoski. You discussed the, a couple of examples of monitoring systems. Can you give me an example of a system that's currently in use that actively as opposed to passively monitors adverse events for a currently marketed OTC product that's subject to an FDA, NDA or OTC monograph?

DR. KARWOSKI: We don't currently know of or are aware of any type of systems that would do that.

DR. NEILL: So for other similar products to this that would fall under similar FDA regulation, there's not an active process in place. So if we were to shortly hear a charge that were to ask us to consider whether or not there should be some active collection or an active process for monitoring adverse events, this would be a first. Is that safe to say?

DR. KARWOSKI: That, this would, as far as I'm aware.

DR. NEILL: Okay. My other questions have to do with putting statements about efficacy on the carton. And it's sort of a question and a half, so I'll ask them together, and whoever from the FDA or Allendale wants to address this, please feel free.

Is FDA aware of any product that's similarly under an NDA or OTC monograph that has efficacy labeling on the carton by virtue of it being required to be there by FDA, and if so, is there language in the recent Federal Register regulations that require that? My understanding being that the proposed label that you just reviewed includes all of the bullets and components that are required.

And I guess my perception is that if we're being asked to judge whether or not efficacy data for this should be on the carton, comments about, you

know, having additional process hearings to make sure it happens for other products aside, I'm curious to know are there other products for which that's already happened, that the FDA has asked that that happen?

DR. GANLEY: Yeah, the one that comes to mind, at last on the carton is Rogaine or topical minoxidil, where it's included in other information, where it provides efficacy information to the consumer at the point of purchase. There are other products that provide efficacy information in package inserts. H2 blockers for heartburn, for example, would be an example.

DR. NEILL: Are, were those for Rogaine and some of the H2 blockers required by the FDA to be on the carton?

DR. GANLEY: Yes, they're marketed under NDAs and so we, we require that. I don't believe there's any monographs that would fall into that category right now.

That doesn't say that in the future there won't be, but, but from a regulatory point of view, you can require someone to do that.

DR. CANTILENA: Yes, Dr. Blewitt?

DR. BLEWITT: Just two, two points I think that are relevant here. First, I think that with

regard to comparative efficacy, that has not been required. So you make, make a statement about individual efficacy. You wouldn't have, at this point in time, there is no, there are no comparative efficacy statements required on labeling.

In addition, the, with regard to adverse events monitoring, it seems to me that any, any product that's subject of a new drug application has to both monitor and submit to the agency reports of adverse events that they received, so, so that is required.

DR. GANLEY: Yeah, I just think that, I got the, my impression of your question was that there was some type of phase four commitment where we required a company to go out actively and look for cases in a population as opposed to an individual passively reporting it. I think that's what your question --

DR. NEILL: Yes, exactly. For an OTC product where, as a health care provider, I'm not involved except in some circumstances in a decision to go and pick it up off the shelf, I'm not going to fill out a MedWatch form and send it in for a patient that by all rights may never see me and may only speak to the, may only speak to the company. And so I'm

interested in active looking versus passive.

DR. CANTILENA: Other questions for FDA, Dr. Johnson?

DR. JOHNSON: Yes, my question is primarily directed to Dr. Chang, and that has to do with the comparator table of efficacy. And I'm wondering if you can comment on Dr. Greenslade's comments about how that table was derived. I mean, frankly, the sentence he read bothers me a little, and the fact that it's in other contraceptive products doesn't, doesn't necessarily make it what sounds like good data.

MS. CHANG: I believe that the agency wanted some kind of a method that, to have the consumers basically make an informed choice. It's generally not to, to improve that process of selecting their birth control method. And it was mainly for informational purposes so they can make that choice, that maybe because of their condition they should not use this product, because of, of the dangers of getting pregnant, they should use another product that may have more of a, a better pregnancy prevention claim for an efficacy statement.

DR. JOHNSON: Well I, yes, I think it's a great idea to provide information to consumers so they

can make decisions, but if the information is flawed or is not based on real data, then I'm not sure that that is useful information for a consumer.

MS. CHANG: I believe, and I can ask Dr. Chang on that, Dr. Chin on that one, but basically, Dr. Trussell, it was more of a retrospective type of a data base. Is that right, Ling? Okay.

DR. CHIN: Let me see if I, I'll try to clarify this. The Trussell table is a reference table. In terms of trying to get a sense of birth control rates for the different, or pregnancy rates for the different birth control methods, we have to come up with one reference, one table that hopefully would give consumers a sense of how effective each birth control method is. And I agree. If you look at the methodology that was applied to how that table was developed, it is definitely not consumer friendly. It's above most everyone's reading of it, and, and I tried to get through it. It's very difficult.

But the agency undertook a point of reference by which information that is from a reliable source and Contraceptive Technology is an accepted reliable source for contraceptive information. And as far as contraceptive rates, I mean as far as pregnancy rates are concerned, that's an accepted point of

reference.

Aside from that, the agency tried to make that table more consumer friendly. We did adapt it somewhat and the table was subject to focus group discussions, so that the presentation of the table is slightly different than the table in Trussell's table. It's more consumer friendly than that. It is really just a means of providing information across the board of all the various methods, knowing that we do not have one single clinical trial that will do head to head comparisons of every method, and by which we can come up with the usual standards of comparing effectiveness by each method. And that's the point of the table. Does that clarify it?

DR. JOHNSON: I mean, it, it clarifies, but I guess it doesn't sort of get at the base of how, how valid is the data in that table.

DR. GANLEY: Well, I think one of the things you have to remember that this was a table that's included in prescription products. There's a learned intermediary there who can read it and hopefully understand it.

And I think there's two things to, to understand here -- is conceptually, should we have that information in OTC products, number one. And

number two, is how should that information be prevented (sic)? I would agree with the presentation that I find it very unconsumer, it's not consumer friendly and, but the question, I, the first question is should we have comparator information so the consumer can make that choice. And then we can decide on what the adequate reference is and how to present that information. I think that's what we're trying to get at.

You're looking at a table that a, a physician can read, understand certain caveats in it and convey those to a consumer, and I would totally agree that a consumer, and even I have a problem looking at that table and understanding the rates in the comparator columns that he had pointed out earlier, so.

DR. CANTILENA: Yes, Dr. Blewitt?

DR. BLEWITT: Yes, I, I agree with Dr. Johnson though, and I agree with the point that's being made, but if the data are quote flawed, which is a term that I've actually used myself, if there are better data that exist, or if there are better ways to find out what, what the real data are, then, you know, that would be the ideal situation, but I think to take data that, or, I ask that the sponsor speak to this,

too. If these are not hard data, then you're taking soft data or inferential data it sounded like to me and now you're making it more consumer friendly. So I don't think that that accomplishes what you want to accomplish either.

I, I agree that in a situation like this, you know, where pregnancy is the risk, if you will, that the women should understand what the comparative benefits are, of products are. The question is how good are the data, the comparative data that they're trying to interpret.

DR. CANTILENA: Yes, you know, actually, I have a, a question if I can ask the, the folks on the committee who actually practice in this area just to get sort of your read. Are the numbers that are in that table, Drs. Greene and Lerner, are they within, you know, the ballpark, or --

DR. LERNER: No.

DR. CANTILENA: Okay. Could you, could you comment a little more on exactly what you mean by, you know, they're not in the ballpark and especially if there's a way in which you can present, you know, relative information.

DR. LERNER: In, in our out-patient clinic which is just a very typical, you know, low socio-

economic Medicaid type patient population, we have a beautiful poster -- I don't know the source of the poster; I'm sure I can find out -- that actually has all the benefits and, you know, sort of the advantages, the disadvantages, a little, pretty graphic on all the different methods. And the, you know, estimates on efficacy rates. And you know, that's sort of what we, you know, use in all our, you know, OBGYN techs.

I'm sure the American College of OBGYN or the, you know, family planning organizations must have reasonable data. I'm sure there's data out there, other than Contraceptive Technology, not that I'm belittling that, but I kind of am. That I think that as a much more global scope, that we might, or you might sort of do an, a detailed in-depth review of some of the references and just try and find out with some, you know, find out some reasonable numbers and then just, you know, put them in all of the, all of the inserts as needed because I, I don't think they are.

You know, we quote, you know, roughly what we've seen which is barrier methods, roughly in the ten percent range, so to think that the Today Sponge has 40 percent, which was listed on that, just is

really way out of, of the realm of what we, we sort of quote to patients and our estimates.

DR. GANLEY: I think in the one column that was pointed out were typical use rates, and you know, I would agree with the comments earlier. But I think something like the lowest expected rate of pregnancy, is that way out of the ballpark? Where it actually lists the vaginal sponge as nine percent?

DR. LERNER: No, that's reasonable.

DR. GANLEY: Yes, that's what I'm, so there is some information there that shows you in terms of order magnitude compared to other methods.

DR. LERNER: But then the table needs to be modified.

DR. GANLEY: Right, I'm --

DR. LERNER: No, then the table needs to be modified.

DR. GANLEY: Right, I --

DR. LERNER: And just, you know, we usually quote, you know, abstinence, a hundred percent, you know, tubal ligation, you know, 99.5 percent, OCPs 98 to 99 percent, you know, condoms, diaphragm, you know, everything, withdrawal, you know.

DR. CANTILENA: Okay. Further comments, Dr. Greene? Would you like to add to that?

DR. GREENE: Yes, I'd, I'd like to address that. I certainly agree. I think that the numbers quoted here are way out of line and much higher than we would normally quote our patients. And most reference material that we would use, certainly, the American College of OBGYN does have a, a patient information literature that has numbers that don't resemble this even closely.

I would like to revisit, since we're at this point, the issue that was brought up a little earlier, which is your denominator. And I would certainly favor or recommend that the, sort of the industry standard is how many pregnancies occur among a hundred women using the method for one year, a hundred women years.

Now, that can be made, that can be made readily understandable for patients. And the problem of having less than one woman per hundred women years is understandable. Patients understand that. And whether it's one in a thousand or one in two thousand, most women don't worry about those differences too much. If you just say less than one woman in a hundred using the method for a year, people understand that.

And with that as the standardization, I

think you could get numbers here that are very easy for lay people to understand, and much more in line with what we generally quote our patients.

DR. CANTILENA: Okay, thank you very much.

DR. LERNER: And just one further thing. I, I do assume that we use all the American College of OBGYN. They have tons of patient and physician information stuff, so I, I do encourage you all to sort of look into that.

DR. CANTILENA: Okay.

DR. GANLEY: Yes, I just want to point out one thing that, you know, Dr. Greenslade hadn't really touched on. And one of the reasons, I think, in our proposed labeling where it said one out of ten is we really didn't know where that rate came from and what it was pertaining to, because if you actually look at the current labeling, it's written as in clinical trials of today, vaginal contraceptive sponge since 1979, over 18,000 women worldwide have completed over 12,000 cycles of use. The results of these clinical trials are as follows, pregnancy rates per 100 women. And they just list them.

And I think it goes back to what Dr. Chin had reported, that when this was initially approved, if you remember, the, the pregnancy rates, it was 12

month pregnancy rates. And then a year later, we're just talking about pregnancy rates without any time frame. And that's why, you know, we went through the regulatory history, because we're a little confused as to what rate we're talking about there, too. But I think we understand your point.

DR. CANTILENA: Okay, Dr. Uden?

DR. UDEN: If I can -- are we done with that? Because I wanted to ask a question about the allergy alert, so if we're not --

DR. CANTILENA: Is this a question that's you know, specifically to FDA?

DR. UDEN: Yes, it's specifically to FDA.

DR. CANTILENA: Yes, okay.

DR. UDEN: Dr. Karwoski, in the allergy alert, it, in the suggested label changes, it was TSS and then allergy alert was right after that, if you're allergic to metabisulfites.

I noticed in the data that you reported that there were only two allergic reactions. Has there been any allergic reactions associated with the sponge that have been systemic allergic reactions or are these local allergic reactions, and are they presented in your, one of your graphs as pruritus?

DR. KARWOSKI: We didn't, I didn't go back

and pull all cases of any, you know, allergic type of reactions. These two were systemic type of reactions. There are other cases, but we didn't review that.

DR. CANTILENA: Okay. Dr. Krenzelok?

DR. KRENZELOK: Back to the more mundane, being the director of a poison center, I'm always sensitive to what children put in their mouths. Now, I notice on the label it says keep out of the reach of children. That seems right.

Unless I've missed it, I didn't see anything about proper disposal methods of the sponge after it's been used. And it might get tossed into the toilet inappropriately or into a garbage can or wrapped up or whatever. But children see those as attractive nuisances, as disgusting as that might seem.

I guess my question is in your passive surveillance system review, did you find -- I'm not worried about the toxicity of, of at least, the parent product. But did you find any instances of, of choking among small children at all, who might have gotten these, chewed them, swallowed them and had a problem?

DR. KARWOSKI: We didn't go and look at those specifically, but the lowest age that we found

for an adverse event report was 12 years old, so I would assume that no, we haven't had any reports.

DR. KRENZELOK: Okay. Thank you.

DR. CANTILENA: Okay, what I think I'd like to do now is move actually to the charge to the committee by Dr. Ganley and then we'll still have ample time for discussion prior to going into the questions.

DR. GANLEY: Yes, I'm just going to keep my remarks brief since I had made some earlier remarks to try to focus the discussion. I think the one thing I, I just want to emphasize again that, you know, one of our purposes for reviewing the entire data base is as a division, we weren't familiar with this product. And so we weren't familiar with the safety of the product. And we thought it warranted a safety review to see if the other information needed to be included in there.

In doing that, I think we developed a comfort level that there was still a benefit, the risk benefit still favored this product to be marketed. That's number one.

And I think the other thing that I want to make a point of that in the years since the sponge discontinued the marketing, the, the agency has gone

to great lengths to try to improve the OTC labels. And we've developed standards now that are actually in the codified regulations.

And so, I think our position is that we should try to improve this label before it goes back on to the market, once they get their chemistry issues resolved. And we can just go to the questions now.

And these are just the questions that we had brought up. And one was given the material provided in your briefing packages and presented today, does the revised labeling adequately convey the risk associated with the use of the product? The current carton label does not contain information on the efficacy of the product.

Should the carton label include efficacy information so that the consumer will have this information available at the point of purchase? And I think in writing this question, we were focusing more on the information that had come from the clinical trials, rather than the comparative. But if you want to comment on the comparative part -- and we were looking at more in the vein, I think, of what is currently on the topical minoxidil for hair growth as providing that type of information.

And if, yes, it's this type of

information, should it be on other OTC products? That's the important thing there.

Are there other aspects to the labeling that we, that should be revised? We're interested in any comments. And the other thing is to please provide comments on the type of post-marketing surveillance for adverse events the sponsor should conduct. And I think the reason for that is, as Claudia had pointed out, as years progress, the reports that have come in have been lesser quality. It's very hard to look at these things as a safety reviewer and make some determination of causality. And we, we think it's very important that these reports, if they're, if they're given to a sponsor, be well written, someone follows up on them, collects information and then provides them to us.

I think the other issue is the type of information we should ask in terms of the company getting calls from consumers about difficulty removing the sponge. And how should that be cataloged? What kind of follow-up should be provided? Should the company contact the consumer a day or two later just to see that everything's okay? And those are the types of things that I think we're interested in. Thank you.

DR. CANTILENA: Okay. Thank you, Dr. Ganley.

I think, actually, just before we go to the, to the specific questions, what I'd like to do is invite the committee, actually, individually. We'll sort of go around the table, just to offer sort of general comments regarding some of the issues in terms of what they've seen.

Some of, you know, the conflicts that, you know, they've identified, and then after we go around and everyone's had a chance to sort of air their concerns or express their opinions regarding sort of the global issues, then we'll come back and go through the questions, one by one. So we'll, actually, if you don't mind, perhaps we can start over on this side. Dr. Krenzelok, if you'd like to share with us your thoughts at this point without actually specifically answering questions.

DR. KRENZELOK: All right. Thank you very much.

Just a couple of things that have, have sort of dawned on me as we've discussed this. From the standpoint of, of this as a, a package that might contain three or six or nine or twelve sponges, as I stated earlier, it seems to me like there needs to be

information on each and every sponge that talks about how to use the product properly and so on, rather than there being a single package insert for the container. Again, given the portability of them and the ease of taking them and throwing them into a purse or a briefcase or something of that nature.

Another thing that, that I'm sensitive to, again, working in a, in a 24-7 type of situation is the fact that I think here's an opportunity to be very proactive with surveillance. So that in sort of a passive way, to have 24-7 availability, not just through pagers, but have a real live body there, a competent person. And one of my thoughts on that is perhaps that it might be wise to out-source something like this to a nursing triage service, like Ask-A-Nurse, who's there's 24 hours a day, seven days a week as a, as a possibility.

And then the other thing along those lines, and, and it's been addressed before is the importance of some of those people having bilingual capabilities, at least Spanish and English for this country. So those are just the thoughts that I had.

DR. CANTILENA: Great. Thank you for those comments.

I guess, you know, one possibility would

be to out-source through a poison control center.

(Laughter)

DR. KRENZELOK: That would be a conflict of interest.

DR. CANTILENA: Dr. Blewitt, would you like to share with us some comments?

DR. BLEWITT: I guess my, my own observation at this point is that the issues are very, very narrowly focused now. I don't see a great deal of difference between the sponsor and, and the agency on, on, on the principles involved in the labeling. It's just a matter of how those things are worked out.

The only thing that we haven't discussed, and I don't know whether it's up for discussion. But in the review package, there's a consumer information leaflet. And there's, there are about three pages Of --

DR. CANTILENA: Can you help find us that --

DR. BLEWITT: Well, two, two pages. This is in the section on 2000 label submission, and it comes after the drug facts labeling. And, again, I don't know if this is up for discussion. But it seems to me that as I read through this, I had a few concerns, that it's been significantly edited. It's

been, as far as I can see, substantially expanded in size. And I'm, without getting down to the details of it, a question again arises as to whether the consumer's receiving too much information here.

So I, for instance, on -- well, I will give you a for instance. There's a comment in here you can avoid the risk of getting sponge-associated TSS by not using the sponge. Well, that seems to be a rather reasonable and unnecessary statement. I mean, you won't get it if you don't use it, for sure.

But the, the major point is that there are a lot of red additions. There are black, there are deletions, but it's a much larger consumer information leaflet than it was originally. And without being judgmental about it, I would just ask people to consider whether that's just overloading the consumer with information to the point where they won't read it.

DR. CANTILENA: All right. If you use, if you use headers in the format, though, isn't, you know, isn't it sort of easier to, to help sort of the scanner to be able to?

DR. BLEWITT: I have no question about the, the format. It's, it's only in terms of the amount of content, the volume of content.

DR. CANTILENA: Great. Thank you very much, Dr. Blewitt. Dr. Johnson, would you like to share some comments?

DR. JOHNSON: Most of my comments probably relate specifically to the questions. I mean, I think that it's pretty clear that this is a safe product, and that there's not much question that another contraceptive method for women is a good thing. And so, I think that it, it really does seem to be just a matter of working out the, the little details in the labeling.

DR. CANTILENA: Okay. Dr. Uden?

DR. UDEN: The only thing I'll add is, is I'm concerned about the consumer comprehension of the present label. The old one, the new one that's been submitted, suggested by the FDA and that, that maybe a consumer comprehension study needs to be done to determine whether they can, somebody can understand it. And, you know, maybe it needs to have cartoons on, cartoons in the, in the package insert so that people can really understand how to use it.

DR. CANTILENA: How do, how do you feel the 2000, you know, proposed label compares, you know, to the '91?

DR. UDEN: Much better.

DR. CANTILENA: Dr. Williams?

DR. WILLIAMS: I agree with what has been said previously. I have no new, I guess, information, more than I've used in the past. I've used this product when I was in my practice and it was available. So we were very conscious of the pitfalls about the use of it as well as the literacy of the patients that we had to deal with who had to come in contact with it. And so we had to use more counsel in our private office to, to ensure that they knew well about this product. So I think the cautions have been expressed are ones that I, I concur with.

DR. CANTILENA: All right. Thank you very much.

Dr. Davidson?

DR. DAVIDSON: Well, I'm pleased to hear everybody actually making some redundant conclusions. You know, I'm going back to, to the clarity of the message, you know. I don't mind if we have more material. It's up to the patient to read what we give them, you know. But there are some messages that need to be clear, and I think we clearly stated what are the messages that, that need to be out there.

I want to remind that the translation to Spanish needs to be friendly, you know. It needs to

be basic and to the point. And, you know, not to forget that we really want to have an 800 number that covers minorities as well.

DR. CANTILENA: Okay. Thank you very much.

Dr. Lerner?

DR. LERNER: I made plenty of comments so far. You know, again, I think it's great. I think one of the most important aspects will be that 800 number. And I don't mean to sort of trivialize your intention or purpose, but I think that that's going to be, I think our main concerns are the toxic, toxic shock and the questions of removal. And that clearly is going to be where the patients head first.

So I think they're going to, the training of people is going to be very important. Additionally, I think just, I can't overestimate where the placement on the label or on the carton needs to be. There's a, a section that just sort of said questions and comments, but that sort of didn't give it enough impact. I know within the, you know, narrative it said, you know, if you have trouble removing it, call the, the talk line. But I think maybe if the phone number is written in, you know, larger font or bolder numbers or something. Just sort

of if the patients are ill or having problems, they can just key right into it.

DR. CANTILENA: Dr. Gilliam?

DR. GILLIAM: A couple comments. The first goes back to one of the earlier speakers today, talking about incidents of vaginal irritation if it's used for several days in a row. And, on a quick glance, I don't see that that's really mentioned in the package insert, and possibly that should be added.

I do think that a efficacy statement should be added. And I like the one that Dr. Greenslade had used earlier.

I think there should possibly be stronger warnings not to use it while a woman in menstruating, and possibly move that statement up to underneath the toxic shock. Or, in addition, as a lot of the women that do, did get toxic shock, it happened, they were menstruating and using the sponge. And they were not, they were, shouldn't have been doing so.

And then lastly, I, I think that there really needs to be a package insert in the carton in both Spanish and English, since you can't really control the distribution of the product in, because of our growing Hispanic population in this country. That's all.

DR. CANTILENA: Thank you. Dr Greene?

DR. GREENE: I'll reserve my specific comments for the answers to the questions. I just generally feel strongly that this should be made available, and I don't think there's a big difference between the sponsor and the agencies, just a matter of getting the details of the wording of the insert and the carton.

DR. CANTILENA: Thank you. Dr. Neill?

DR. NEILL: A couple of questions that will help me in later answering charge three about specific items of the label to be revised, and I'll direct these to Dr. Krenzelok. I'm less worried about children eating these than sex partners, and I'm wondering -- I have no idea about the toxicity of nonoxynol-9 or the sponge itself, which I presume would simply be passed right out the other end when it ends up in the mouth and alimentary tract of a sex partner. Do I need to be worried about nonoxynol-9 when it's ingested?

DR. KRENZELOK: No, it's, it's very innocuous, from my experience. As a toxicologist, that is.

(Laughter)

DR. CANTILENA: Thank you for adding that

clarification.

(Laughter)

DR. CANTILENA: We were starting, starting to worry about Pittsburgh.

(Laughter)

DR. NEILL: Well, since you brought it up, Ed, you know, the other question that came to mind aside from this, you know, oral ingestion that I had was in occupying my mind with all of the different permutations that might occur in the course of sex as it happens, I was -- and this does not pertain to any of our charge. It was just I thought interesting and maybe a little entertaining. I was wondering what happened to the efficacy of this product with food, alcohol, any or all of the above in many different kinds of combinations. Please, don't anybody feel compelled to answer that. And then, I've got a couple other specific questions that we'll get to when we get to the charge.

DR. CANTILENA: Okay. Thank you very much. I think in the, in the interest of time, I'll, I'll just reserve my comments to, as, as they sort of pertain to the questions. So if there are no other issues that people want to discuss, why don't we proceed with the questions then?

First question, given the material provided in your briefing packages and presented today, does the revised labeling -- and here, we're specifically talking about the 2000 proposed labeling that's in your document -- adequately convey the risks associated with the use of the product?

And what I'd like to do is, this is a yes, no answer. And as opposed to going around the table, why don't we just ask for a show of hands. So all those who feel that the answer is yes, that is, the revised labeling does adequately convey the risks, please raise your hand.

(Hand vote taken)

DR. CANTILENA: It looks like nine. Okay. All those who feel it does not adequately convey the risks.

(Hand vote taken)

DR. CANTILENA: One, and can I ask you to actually comment in terms of what is, you know, missing?

DR. KRENZELOK: I think that, that the information about toxic shock should be emphasized in bold so it really stands out. That's the only reserve I have.

DR. CANTILENA: Okay. Thank you very

much. Second question is the current carton label does not include information on the efficacy of this product. Should the carton label include efficacy information so that the consumer will have this information available at the point of purpose? So, specifically, we're talking about including efficacy on the outside, on the carton, as opposed to on the inside, in the package insert.

And here, again, I'd like to ask for all those who answer in the affirmative that the label, the carton label should include efficacy on the outside, please indicate by raising your hand now.

(Hand vote taken)

DR. CANTILENA: Okay. Nine in the affirmative, and can I ask Dr. Neill, I assume you're voting no and not abstaining. Could you tell us, you know, what your concern was?

DR. NEILL: If we include only efficacy on this product, and we say this is effective -- in 100 women years of use, there will be X many pregnancies and do not include information about other products, I don't know that I or consumers would naturally come by the information to make that isolated nugget useful.

If we include the other comparative

information, that's something, given what I understand now about how Rogaine and some other medicines have been marketed, that I don't feel comfortable getting into.

I mean, that gets to the second part of this, which we'll get to in a minute, which is, if yeah, should it be required of all OTC contraceptive products. If the answer to the first part is yes, there's an implied question in my mind which is okay, what kind of efficacy. And that's going to require a whole another day of hearings.

And I think we also need to take into consideration the comments that were made very early today about the extent to which our discussion of inclusion of that information on all OTC contraceptive products would require that kind of process. I think that it's probably that important.

DR. CANTILENA: So, so you're saying then if, if the information on the outside was comparative in nature and valid, I assume, then, you would favor that. And, you know, as it is, in isolation with, you know, one and ten, it's not adequate, or it's not advisable.

DR. NEILL: Well, I, I would not oppose -- well, it's nine to one, so it doesn't matter what I

think, but --

DR. CANTILENA: It always matters.

DR. NEILL: Oh, of course. All right. I think that if it's just in isolation, that might be preferable. As somebody who has to counsel patients all the time, I actually find it less useful for me to say, or incompletely useful for me to say this is, you know, will result in X numbers of pregnancies per 100 women years. But rather, I find it more useful for me to put my patients' risks in the context of the risks that they face daily in their life.

I, for -- I don't like telling my patients and having them think this is a very risky thing, if they don't understand that walking across Market Street outside my office is even riskier. Do you understand what I'm saying? And that --

DR. LERNER: Just, just as a comment with that, I think that the decisions here are made at the corner drug store at 3:30 in the morning. And so I think that as much information as we can provide, comparative or otherwise, is going to be much more than they're going to get, you know, beeping any of us at that time of the morning.

DR. NEILL: I guess, then, my plea would be to include meaningful, comprehendible efficacy

data. For something where the outcome is as measurable as a pregnancy, that's useful. The difficulty for the agency, I think, is going to be for OTC products for which this may become an issue, for which there's an outcome which is much more subjective, like Rogaine.

DR. CANTILENA: Okay, I guess, can we ask another question then, Dr. Ganley, of, of the committee and, you know, regarding the format of the information, whether it's now comparative or just, you know, isolated for the product? If, if you're not opposed, then I would like to propose a question to the committee then. If efficacy label, if, if the efficacy information on the outside of the carton contained, you know, comparative information to other methods of information, would you favor it included on the outside of the carton with this product?

DR. GANLEY: Can, can I just make a comment for anyone?

DR. CANTILENA: Okay.

DR. GANLEY: I'm, I think the one thing that we have to be sensitive to is that the size of these boxes are a certain size. And there's so much information you can get on it. And I think you have to take into account that if you're going to put

comparator information, it is going to take up a lot of room.

And so, I think you need to keep that in mind when, you know, if, if -- and that's, that's become a problem for us in, and certainly, I think that Allendale would agree with that. And if there's another way to show or to direct a consumer to the package insert, I think that, you know, that we, we cannot forget those things, that there's a limited size on these boxes.

DR. CANTILENA: I guess the --

DR. GANLEY: Unless we just sell 12 packs, or 18 packs or something.

DR. CANTILENA: Yeah, I guess, I guess, you know, the reason I was suggesting, you know, this question is really at, at the time the consumer is making the choice about, you know, purchase, should they know how this compares to other methods, which are over the counter or, or otherwise? And that, but, I guess it's sort of a, a hypothetical because, all right, you know, obviously if, if the box has to be, you know, five by six feet in order to get all the information that, it would not be a practical thing. So I guess that's where that where was coming from. Any other, any other comments? Dr. Johnson?

DR. JOHNSON: Well, I think, already in the package insert, there's a statement this is much less effective than the pill and IUD. So it might be possible to put on there in 100 women over one year, you would, there would be approximately ten pregnancies. This is much less effective than hormonal methods such as the pill or Norplant and the IUD. And I think, you know, that doesn't go into a lot of real specific comparator data, but does give, give them a point of reference. Because I think most women understand that the pill was a very effective birth control method and can sort of use that as a comparison.

DR. CANTILENA: Yes. Dr. Lerner?

DR. LERNER: But sort of to answer the second part, the part A, and then sort of reflect it back, I think that if we say then that we do agree that this kind of information should be required of all over the counter contraceptive products, then we can sort of, or you guys can sort of make some sort of standardized mechanism so that you can put it in a certain sort of well-circumscribed way that's consistent so that when the consumer is going down the aisle, you know, there's sort of a particular place that they can look and see, you know, the comparative

efficacies, and therefore, sort of save room, sort of in the same way that you'd go down and look at the saturated fat in your Snackwell cookies or something, you know. Just sort of the number of grams or whatever per any given serving.

DR. CANTILENA: Okay. Well, then, how about if we -- I'm sorry. Dr. Neill?

DR. NEILL: I, I similarly would favor a condensation into a single sentence which made sure to include the other OTC. If the point is to allow people to make a decision about condom, semicid, foam, jelly or sponge versus, you know, pill, et cetera. While pill's important, if they're there at three in the morning, they ain't going to get it.

The, the other issue related to this second part of the question -- I'm trying to imagine how, in the bathrooms of all of the gas stations that I stopped at on my way to Tennessee, the condom dispensing machine is going to include that comparative information for shelfkeeping units are like, that are a single condom. And I don't know, does, you know, this doesn't need to be addressed right now, but I could imagine that for some of the other forms that aren't as bulky and don't have the advantage of having a six-pack box that it might raise

some more practical issues for them, more so than the sponge. And it's just something to sort of keep in the back of the mind.

DR. CANTILENA: Okay. Well, how about if we actually call that question that I posed, which is basically to have the comparative efficacy available on the outside of the carton with all the caveats in terms of how it should be simplified, et cetera, et cetera, which I think is an excellent comment. All, all in favor of having the comparator information on the outside of the carton, please raise your hand.

(Hand vote taken)

DR. CANTILENA: Dr. Davidson, did you vote? Yes?

DR. DAVIDSON: No.

DR. CANTILENA: Okay. So we have nine in favor, and perhaps I can just ask you to comment why you did not.

DR. DAVIDSON: You know, I, I think it's important but I think that, you know, we can have that information inside. If you give the information of that product on the outside, because if you look at the package, you know, there's other more important information that should be outside, including you're going to state that this is not a 100 percent

effective, you know.

For, for the information, see the package insert. You know, I think we need to make it a little simpler for the people, you know, that buy these products. Otherwise, if you put a lot of information outside the package, you know, people are going just to read a couple of things and then no more. That's my recommendation.

DR. CANTILENA: Okay. Thank you. I believe we haven't formally answered 2A although we started to a couple of times. 2A, if yes -- yes, meaning it should be on the carton, should this kind of information be required of all OTC contraceptive products? And again, we'll first ask all those in favor of having it available on all OTC contraceptive products, please raise your hand?

(Hand vote taken)

DR. CANTILENA: I think this time we are unanimous. Okay, the next question, question three, are there other aspects of the labeling that should be revised? And here, I guess, we'll just open it up to comments, perhaps going around the room, starting around this side with Dr. Neill. Any other aspects of labeling that should be revised when we're now, our frame of reference is the 2000 label?

DR. NEILL: Yeah, I have I think three questions that I would propose be considered for inclusion in the section, other questions you may have. The first is what if it comes out? I realize that difficulty with removal is, you know, the single biggest complaint or reason for phone calls, but if it comes out, can you put the same one back in? Do you have to use a different one? If it comes out and you don't have another one, is that the end of sex?

The other question would be, there's just two, not three. It's related to one that Dr. Gilliam asked a few minutes ago. Can this be used several days in a row? And I think that would also allow an appropriately prioritized discussion of the extent to which increased sensitivity may occur if it's used several days in a row. My perception being, yeah, certainly, it can be. However, you may experience more irritation with this. And I think that's a valid concern that needs to be in there somewhere.

DR. CANTILENA: And here, you're talking about in the package insert and not the label? I mean the front part?

DR. NEILL: In the package insert, right.

DR. CANTILENA: Right. Thank you. Dr. Greene, any, any comments about other issues of

labeling?

DR. GREENE: Not really; just minor. I was glad to see under six, there are other questions you may have, that the first thing it addresses is the use of a latex condom. And I do think that's important. And the only minor sort of editorial suggestion is that in that section where it says will help reduce the risk of transmission of human immunodeficiency virus, HIV, and acquired immune deficiency syndrome. I, I would just suggest that that just be changed to read the virus that causes acquired immune deficiency syndrome. That's just technically a little more correct, but I don't have any major problems.

DR. CANTILENA: Thank you very much. Dr. Gilliam?

DR. GILLIAM: Just the comments I, I made earlier, especially regarding the irritation and stronger warnings not to use during menses.

DR. CANTILENA: Dr. Lerner? No further comments. Dr. Davidson? Dr. Williams? Dr. Uden?

DR. UDEN: Only that I think it could be written in a lot less technical terms than what it is, so.

DR. CANTILENA: The insert, the?

DR. UDEN: Yes, the package insert, yes.

DR. CANTILENA: Thank you. Dr. Johnson?

DR. JOHNSON: My comment is primarily a practical one regarding what goes on the outside of the box. And it has to do with the directions. I mean it's not very clear to my, me, why we need to tell them on the outside of the box that they need to wash their hands, wet the sponge, put the, the dimple side facing up. I mean, it seems to me if you're trying to save space, those are things that someone will look for once they buy the package, once they open it and they're ready to use it. So it seems like you could get rid of a lot of the things in that direction section. And then you would have more room for things like how effective is this product, which I think is much more important.

DR. CANTILENA: Yes, follow up to that, Dr. Neill?

DR. NEILL: Yeah, I -- while there's probably room for some editing there, I think at least part of the purpose is to allow people to make a decision about whether they want to use it. And if there's an advantage to having that kind of explicit direction, it's that some consumers may see that and decide as a result yes, they really want to use this,

as opposed to another method or they really don't want to use that. And simply directing somebody to the package insert inside removes that portion of the information that helped them use it.

And, you know, it's just, who knows whether that would be the major contributor about a decision to purchase? Personally, I think for information on the outside of the package, if the FDA or somebody doesn't say something about where the price sticker goes, everything we're talking about means nothing. And I'm not suggesting that we talk about where the price sticker goes.

DR. CANTILENA: Further comments, Dr. Johnson? Thank you. Dr. Blewitt? Dr. Krenzelok? Yeah, I guess, really, I would concur with a lot that has been said. I, I would also just, under number seven, points to remember, it's not, it doesn't jump right out at you that the product needs to be left in place for six hours after the last act of intercourse. And I, I would understand, or I understand that if you remove it shortly after, it's high likelihood to, you know, not be effective.

So if there's some way to emphasize that clearly on the insert. It, you know, doesn't have to be on the outside, but just to make sure that people

don't use it like some other methods where, you know, you remove it right away after you -- yeah, it's, right. But it's sort of, you know buried down there. And that's sort of the final point, so if there's some way to emphasize that, that I think would be helpful.

DR. UDEN: Can I make a comment on that? Because what that does is effectively you cannot have sexual intercourse from 24 hours to 30 hours. So if somebody has it from 24 to 30 hours, they can't leave it in for six more hours. So this is only good for sexual intercourse for 24 hours, and then it has to be left in. And then there's that window there where they're not supposed to have sexual intercourse if they're going to follow the directions explicitly.

DR. CANTILENA: Yes, Dr. Johnson?

DR. JOHNSON: I, I did find one other thing I wanted to comment on. And that was the pregnancy rate tables. I mean, I think I sort of made it clear I really dislike that table, one because I think they can't understand it. And secondly, because it sounds like the data has at least some problems.

And I think certainly we need some comparator data, but I think written in the form that Dr. Greenslade suggested is, is much more useful for the patient.

DR. CANTILENA: Okay. Thank you. What I'd like to now do is just turn to the final question. And I know the hour is late, but I would really ask your, you know, patience to, to really give this some thought because I think it's possibly a very important issue.

Question four, please provide comments on the type of post-marketing surveillance for adverse events the sponsor should contact, excuse me, should conduct. And here, we have issues of active collection, follow-up reporting analysis of cases of difficult sponge removal, provisions in place and, to facilitate adequate adverse event reporting.

So again, we started here last time. Perhaps we can start with you, Dr. Krenzelok, and have you address some of these issues on post-marketing surveillance.

DR. KRENZELOK: Well, I don't think we should hold them to a higher standard and ask them to have active surveillance on, on this particular product. But I would strongly encourage, as I mentioned earlier, that a 24-7 server should be really encouraged, competent people, and they should in some way encourage the people that use the product to use that service if it's there. And then I think that

would really help identify adverse events should they occur.

DR. CANTILENA: Thank you. Dr. Blewitt, any comments on this area?

DR. BLEWITT: No. I would simply agree with what Dr. Krenzelok has said.

DR. CANTILENA: Thank you. Dr. Johnson?

DR. JOHNSON: Same thing. I, I agree that active marketing or active surveillance is not something probably necessary and maybe the sponsor just needs to present a very detailed plan about their consumer hotline and, and how they'll collect their data.

DR. CANTILENA: Thank you. Dr. Uden?

DR. UDEN: Yeah, I don't think we should hold them to a higher standard. I mean, unless this question, I mean if, if we did, then we would be setting a precedent for every, every product that would come in front of this advisory committee or in front of the FDA from here until the end, I would, I would assume. I mean, what would be special about this product that we would ask this versus other products that might, that might become OTC? Other than that comment, I just hope that the sponsors would have complete and consistent information in, in their

system, so that it's as complete as possible.

DR. CANTILENA: Thank you. Dr. Williams?

DR. WILLIAMS: The only concern I have is to look at the CDC data as that comes available regarding the reintroduction of the product. We have a reportable disease and that could be easily monitored.

DR. CANTILENA: Thank you. Dr. Davidson?

DR. DAVIDSON: I agree with everybody but, you know, one thing I forgot maybe for the low literacy people, you know, a video on how to use the, you know, the device will help us. And I don't know if the sponsor is willing to, you know, make a video for those very low literacy people.

DR. CANTILENA: Thank you. Dr. Lerner?

DR. LERNER: Well, we've discussed a lot about the consumer hotline. But I think also a physician hotline or some way to get the practicing clinicians, you know, sort of plugged into the system so that when they do encounter any adverse outcome, there's a, either a phone number or something accessible -- medical letter or in the journals or however you do that with other stuff.

DR. CANTILENA: Thank you. Dr. Gilliam? No further comments. Dr. Neill?

DR. NEILL: I would never make it on Jeopardy pushing this button. The, it's a generic comment that has to do with the repetitive nature of this question which I think goes to the question of the MedWatch system. If I were to ask my residents, okay, what's MedWatch, you know, I'd get a 1 out of 36 response rate.

And, so generically, I guess I would put in a plea to the agency or some higher up muckety-mucks that have, you know, budget dollars to do whatever might be done to help improve that system as a monitoring system given that it's, you know, relying on lazy physicians like me to both understand that I'm seeing an adverse event and pick it up and report it.

And I realize that there have been a lot of things done to make that easier. I used to literally go and photocopy the little form out of the back of the PDR. But I threw all the PDRs out of my office because I hate them as a drug reference and have taught my residents not to use them. And so now, we've got to go to the web and do all this other stuff, and then the network's down so, again, just a long plea, you know. Whatever you can do to improve that, make it easier, market it.

Here's a, here's an idea. We can take

these FDA NDA fees and take a portion of those or, you know, we can always hit the sponsors up for something, right? Rather than making them pay for an adverse, an active adverse event reporting system, we, we take some portion of the money that we, I mean ask from them for their NDA and put that specifically towards some of this MedWatch -- I don't know, a MedWatch czar or something, however that works.

DR. CANTILENA: Okay. Thank you very much. I, I guess I would only add just a couple of small comments on this issue. One, one is, you know when I hear a couple things about being a small start-up company and all the employees being here at the meeting, I get concerned that the follow-up and, you know, safety is not going to be adequate. I'm sure that the plans would be, and I would hope that, you know, you would have agreement on this with, with the FDA that as it goes on the market or hopefully just before the cash flow starts that you would clearly invest in having adequate, you know, facilities, adequate, you know, personnel. And just make sure there's a very tight, you know, linkage between the 800 number and follow-up and the adverse events.

And, and I would say that even because this has not been on the market for basically five or

six years, it's an opportunity to see how well the system actually works. So even if you could agree on perhaps, you know, quarterly reports instead of annual reports to see sort of the linkage between the 800 number and the adverse events and, and the follow-up on the adverse events.

And I would just, as some free advice to the sponsors, invest in quality individuals who have experience in this area because it'll, you know, make, you know, your job a lot easier, and all the people who are watching a lot easier as well if there's good, you know, documentation and follow-up.

So that's my two cents. Now, I guess, I'll, I just have to ask the FDA if there are any other issues that we have not addressed, any questions that were not adequately answered that you'd like us to address at this time?

DR. GANLEY: No, I think we got an idea of what your position is, and we appreciate all the comments. I, I think Dr. Neill made a interesting point there, you know, about the reporting to FDA. And, and one of the things that was not included in the, the labeling rule was a requirement to include a MedWatch number on there. And I get a sense that you would actually, or to have some information that you

could, if people could complain to FDA, if not to the sponsor. And I'll just point out that the questions and comment

MS. CHANG: Good afternoon. Guess what? I'm the final speaker. By the way, I want to thank Daniel Keravitch for all his help in doing these slides.

My presentation will be covering our proposed labeling for the Today Sponge. Put it down. Okay. Basically, I'll start with an overview of the new OTC labeling rules, then the original carton labeling for the Today Sponge, proposed carton labeling for the Today Sponge and the proposed changes to the package insert.

On March 17th, 1999, the agency published an OTC labeling requirements final rule, codified in 21 CFR 201.66. That rulemaking required standardized content and format for all OTC drug products in what they call drug facts format, format and content. The agency believed that these labeling requirements would make it easier for the consumer to recognize where to find the information and also would make the labels more legible and readable.

The drug facts labeling content requirements required the following: that all

information would be organized under title, headings and subheadings; that all drug facts label information must appear on the outside of the container or wrapper of the retail package or on the immediate container if there was no outside container or wrapper; and that the headings and subheadings appear in a specific order which would allow the consumers to more quickly make a decision as to whether they should use the product, when to stop using the product and how to use the product.

The standardized headings are in the following order: title, which is always titled drug facts; the active ingredients or ingredient and the amount; the purpose; the use or uses; the warnings. And under the warnings, there is a standardized order for the subheadings. For example, do not use; stop use and ask a doctor if.

Next comes the directions. After the directions, there is a heading titled other information. This section includes information not included in the other sections, but for which the agency feels is pertinent to the safe and/or effective use of the product, or information that is required under an OTC drug monograph.

The last section is the questions or

comment sections which provide phone numbers for consumer inquiries.

The labeling rule requires standardized formats so that there is consistency in the format for all labeling. For example, there are type size specifications for the headings, subheadings and text. There are also bulleted format to improve readability.

The agency considers the labeling for OTC drug products, considers the carton, which consists of the principal display panel and promotional labeling and the required labeling, for example, the drug facts label, as part of the labeling. Also, the package insert. Dan.

I'm going to make some comments on the 1991 labeling. As you can see, this part is called the principal display panel, and Dan's going to focus on the -- this section is the approved label which contains the directions and warnings. Basically, as you can see, the directions are in a paragraph format which we believe is difficult to read. Also, the important information is not emphasized.

For example, the toxic shock statement is not prominently emphasized. And as you can see, they are in two separate sections, this section, and also the symptoms are in this section right here.

Further, there is no statement in the labeling that addresses or informs consumers of the serious nature or potential life threatening nature of this, of toxic shock syndrome. Just, I think that's that for that.

I just want to show you the other information as far as the inactive and active ingredients are on the other, the back panel. Can you go back? Should I just click? Great.

We have revised the Today Sponge labeling as follows. Oh, I have, is that the, did I click? Oh, I'm sorry. I'll start with this one.

Thus, there are some reasons for the labeling revisions are to remove misleading statements such as reliable protection without serious risks of dangerous side effects, and extremely effective.

Other reasons for the revisions are the, to improve the order of information so there is more emphasis on the warnings, in particular, the toxic shock syndrome warning. Also, to add additional important information such as AStop use and ask a doctor if@ statements, and to improve directions and other information for better understanding of the safety concerns and other public health issues.

We have revised the Today Sponge labeling

as follows. First of all is its standardized order in accordance with the drug facts format. And this is a copy -- Helen, did you show the, you showed the copy of the original label. We're going to break this down to make it more readable for all of you.

Please note that the revisions are in red font, are the new additions to the label or statements which we have either moved or revised from the original labeling, and the statements in the black font are the statements pulled from the former labeling which may have reformatted into the new drug facts label.

I will be discussing particular sections of our proposed drug facts labeling. And this section is the warning section. Significant revisions were made to this section. First and foremost, the TSS warning is prominently displayed as the first specific warning. We have added the statement TSS is a rare but serious disease that may cause death. Additional revisions are what you can see on the slide.

In addition, we've added the allergy alert section to inform consumers that this product contains a sulfite, and also that this product contains nonoxynol-9.

We have also asked that the various

revisions in red to this section.

I want to focus in primarily on the Astop use and ask a doctor if.@ This section was provided to alert consumers so that they would know if certain conditions would develop during sponge use. Note that this information was not in the 1999 final printed label.

Under the directions, we have bulleted the information to make it easier for the consumer to read and added additional directions. I lost my pointer. We've, we've, we've moved the statement Ado not leave in vagina for longer than 30 hours@ from the warnings into this section and bolded for emphasis. Next.

Under the other information heading, we added two new bulleted statements. The first is to inform consumers of the availability of the pregnancy rates, birth method, birth control methods table in the package insert and to provide public health information statement of the use of latex condoms to reduce the risks of the transmission of HIV and STDs.

Now, I'm going to go and discuss the changes to the package insert. Because of time restraints, I will only be discussing some of the major ones. First would be to improve the presentation of the efficacy data.

Second is to include the pregnancy rate birth control methods comparative table in the package insert.

Third, we added, just wanted to basically tell you that we added some references to reducing the risk of sexually transmitted diseases in the package insert. I lost the pointer. Okay.

Fourth, we made format and minor editorial changes to the package insert. As you, as you can see from the original efficacy data statement and efficacy table, I think it is basically, thank you, I think it's basically very confusing to a layperson. In fact, I sort of got confused by reading it also.

What we did was we basically revised and simplified the statements on the efficacy statement to make it more consumer friendly, and I believe someone already discussed the revised statement.

I'll talk a little bit about the pregnancy rate table. Back in 1997, the Center for Devices and Radiological Health in collaboration with CDRH, which is the Center for Drug Evaluation and Research, and the Office of Women's Health adapted the pregnancy rate table from Trussell's Contraceptive Technology basically to, to provide the consumers with information to make the informed, to -- let me start

over. To provide consumers with information to make informed choices as to the best birth control method for them. At present, the table is included with all prescription oral contraceptives and is a regulatory guidance for other CDRH and CDER birth control products.

In -- these are my conclusions. Current labeling can be improved. The drug facts format places emphasis on the warnings, such as the TSS warning and the Astop use and ask a doctor if@ are examples of that. And provides more readable and informative information to the consumer to improve the safe and effective use of the Today Sponge. Thank you very much.

DR. CANTILENA: Okay. Thank you very much for actually staying ahead of schedule.

MS. CHANG: And I wanted to -- right. I was going to turn the podium over to Dr. Cantilena for questions and comments.

DR. CANTILENA: I'm sorry. I beat you to the punch. I apologize. Yes, actually, we are at the point now where we have some time to ask the FDA presenters specific questions that you may have. So let me open it up to the, to the committee. Dr. Uden?

DR. UDEN: We've had toxic shock syndrome

data presented a few times here today. You have a database here at the FDA. There's also a database at the CDC. How many other places is, is the data, data kept and has anybody compiled the data in one place so that we can get a relatively good estimate of the risk?

DR. KARWOSKI: Well, I actually don't have the answers for that. Not that I'm aware of. I would imagine that CDC probably has the best numbers. Ours is a voluntary and a passive surveillance, and so we only rely on consumers or health care providers to report that information to us.

DR. UDEN: Are those the two major sources of, other than primary literature, finding the incidence of toxic shock syndrome?

DR. CHIN: Let me clarify that a little bit more. What we have in our database that was presented by Claudia is information that was voluntarily submitted or regulatorily (sic) required to be submitted to the FDA's spontaneous reporting system or the current AER as database.

What CDC has is TSS is a reportable disease, and so it has to be reported to CDC. And they compile the statistics that you would see for a lot of infectious disease. The difference in the

database is that what we have in terms of the adverse events, it would be adverse events that were reported in conjunction with the use of a sponge. It doesn't mean that it causes the adverse event, but it was in conjunction with the use.

What CDC's information has is the number of TSS cases, but doesn't necessarily break it down into what was used in association with the case itself. So they're really separate types of numbers.

DR. CANTILENA: Other questions? Yes, Dr. Davidson? Your microphone?

DR. DAVIDSON: Thank you, forgot. I have a couple, you know. You reported cases of disability, but you didn't say what type of disability they were. Could you tell us what disability meant in the cases?

DR. KARWOSKI: The outcomes are very subjective. That really depends on what the individual that reported the event may have thought. For the disability, there was, in my opinion, there was no apparent disability that was caused. One of them was the TSS cases. They reported life threatening hospitalization and disability, but there was no apparent long-term type disability associated with that.

The second case was a disability.

Essentially, what the patient reported was that following the use of the sponge, her and her husband were not able to perform sexually as they had prior to the use of it. So that was the, the second disability that was reported.

DR. DAVIDSON: Thank you. You know, we already commented before from previous presenters that the highest rate was seen in 1984, okay. Do we have any data of the exposure, you know, in 1984, 1985, 1986 of sponge use to see if there's, if it is a relationship between the usage and the cases. Or it was the, you know, after 1984, people were better educated, you know, to draw some conclusions why it really went down after 1984?

DR. KARWOSKI: After, actually it didn't really go down. It stayed somewhat stable. There were bumps throughout the years. We don't have any actual usage data. All we have is some data regarding the distribution of the product, so the sales of the product. But we don't have numbers of how many people actually used the product or how frequently they may have used it.

So we can't really put a denominator on that. But what we're somewhat sure of that the use did decrease somewhat over the years, and the rate of

TSS, or at least, the reports that we had received didn't really decline that much, at least over, after 1985 to 1994, that they remained somewhat stable with little, you know, small fluctuations, varying, you know, throughout the years.

DR. DAVIDSON: From the data you presented, you know, even though there were some small fluctuations, the tendency was to go down. Maybe I, no? Okay. Then it remained about 47 cases per year?

DR. KARWOSKI: Well, we had only one case reported in 1995, but the product at that point was --

DR. DAVIDSON: But the product was withdrawn, right.

DR. KARWOSKI: -- had stopped.

DR. DAVIDSON: Okay. And one final question, when you report infections, and you report vaginitis in different sections, the vaginitis was also included in the infections or were they reported totally separate for everything?

DR. KARWOSKI: The vaginitis in our database are considered infectious type of complications.

DR. DAVIDSON: Then it was reported twice?

DR. KARWOSKI: May have. There may have been an infection and vaginitis at the same time.

DR. DAVIDSON: Thank you.

DR. CANTILENA: Yes, Dr. Neill?

DR. NEILL: I have two and a half questions, the first to Dr. Karwoski. You discussed the, a couple of examples of monitoring systems. Can you give me an example of a system that's currently in use that actively as opposed to passively monitors adverse events for a currently marketed OTC product that's subject to an FDA, NDA or OTC monograph?

DR. KARWOSKI: We don't currently know of or are aware of any type of systems that would do that.

DR. NEILL: So for other similar products to this that would fall under similar FDA regulation, there's not an active process in place. So if we were to shortly hear a charge that were to ask us to consider whether or not there should be some active collection or an active process for monitoring adverse events, this would be a first. Is that safe to say?

DR. KARWOSKI: That, this would, as far as I'm aware.

DR. NEILL: Okay. My other questions have to do with putting statements about efficacy on the carton. And it's sort of a question and a half, so I'll ask them together, and whoever from the FDA or

Allendale wants to address this, please feel free.

Is FDA aware of any product that's similarly under an NDA or OTC monograph that has efficacy labeling on the carton by virtue of it being required to be there by FDA, and if so, is there language in the recent Federal Register regulations that require that? My understanding being that the proposed label that you just reviewed includes all of the bullets and components that are required.

And I guess my perception is that if we're being asked to judge whether or not efficacy data for this should be on the carton, comments about, you know, having additional process hearings to make sure it happens for other products aside, I'm curious to know are there other products for which that's already happened, that the FDA has asked that that happen?

DR. GANLEY: Yeah, the one that comes to mind, at last on the carton is Rogaine or topical minoxidil, where it's included in other information, where it provides efficacy information to the consumer at the point of purchase. There are other products that provide efficacy information in package inserts. H2 blockers for heartburn, for example, would be an example.

DR. NEILL: Are, were those for Rogaine

and some of the H2 blockers required by the FDA to be on the carton?

DR. GANLEY: Yes, they're marketed under NDAs and so we, we require that. I don't believe there's any monographs that would fall into that category right now.

That doesn't say that in the future there won't be, but, but from a regulatory point of view, you can require someone to do that.

DR. CANTILENA: Yes, Dr. Blewitt?

DR. BLEWITT: Just two, two points I think that are relevant here. First, I think that with regard to comparative efficacy, that has not been required. So you make, make a statement about individual efficacy. You wouldn't have, at this point in time, there is no, there are no comparative efficacy statements required on labeling.

In addition, the, with regard to adverse events monitoring, it seems to me that any, any product that's subject of a new drug application has to both monitor and submit to the agency reports of adverse events that they received, so, so that is required.

DR. GANLEY: Yeah, I just think that, I got the, my impression of your question was that there

was some type of phase four commitment where we required a company to go out actively and look for cases in a population as opposed to an individual passively reporting it. I think that's what your question --

DR. NEILL: Yes, exactly. For an OTC product where, as a health care provider, I'm not involved except in some circumstances in a decision to go and pick it up off the shelf, I'm not going to fill out a MedWatch form and send it in for a patient that by all rights may never see me and may only speak to the, may only speak to the company. And so I'm interested in active looking versus passive.

DR. CANTILENA: Other questions for FDA, Dr. Johnson?

DR. JOHNSON: Yes, my question is primarily directed to Dr. Chang, and that has to do with the comparator table of efficacy. And I'm wondering if you can comment on Dr. Greenslade's comments about how that table was derived. I mean, frankly, the sentence he read bothers me a little, and the fact that it's in other contraceptive products doesn't, doesn't necessarily make it what sounds like good data.

MS. CHANG: I believe that the agency

wanted some kind of a method that, to have the consumers basically make an informed choice. It's generally not to, to improve that process of selecting their birth control method. And it was mainly for informational purposes so they can make that choice, that maybe because of their condition they should not use this product, because of, of the dangers of getting pregnant, they should use another product that may have more of a, a better pregnancy prevention claim for an efficacy statement.

DR. JOHNSON: Well I, yes, I think it's a great idea to provide information to consumers so they can make decisions, but if the information is flawed or is not based on real data, then I'm not sure that that is useful information for a consumer.

MS. CHANG: I believe, and I can ask Dr. Chang on that, Dr. Chin on that one, but basically, Dr. Trussell, it was more of a retrospective type of a data base. Is that right, Ling? Okay.

DR. CHIN: Let me see if I, I'll try to clarify this. The Trussell table is a reference table. In terms of trying to get a sense of birth control rates for the different, or pregnancy rates for the different birth control methods, we have to come up with one reference, one table that hopefully

would give consumers a sense of how effective each birth control method is. And I agree. If you look at the methodology that was applied to how that table was developed, it is definitely not consumer friendly. It's above most everyone's reading of it, and, and I tried to get through it. It's very difficult.

But the agency undertook a point of reference by which information that is from a reliable source and Contraceptive Technology is an accepted reliable source for contraceptive information. And as far as contraceptive rates, I mean as far as pregnancy rates are concerned, that's an accepted point of reference.

Aside from that, the agency tried to make that table more consumer friendly. We did adapt it somewhat and the table was subject to focus group discussions, so that the presentation of the table is slightly different than the table in Trussell's table. It's more consumer friendly than that.

It is really just a means of providing information across the board of all the various methods, knowing that we do not have one single clinical trial that will do head to head comparisons of every method, and by which we can come up with the usual standards of comparing effectiveness by each

method. And that's the point of the table. Does that clarify it?

DR. JOHNSON: I mean, it, it clarifies, but I guess it doesn't sort of get at the base of how, how valid is the data in that table.

DR. GANLEY: Well, I think one of the things you have to remember that this was a table that's included in prescription products. There's a learned intermediary there who can read it and hopefully understand it.

And I think there's two things to, to understand here -- is conceptually, should we have that information in OTC products, number one. And number two, is how should that information be prevented (sic)? I would agree with the presentation that I find it very unconsumer, it's not consumer friendly and, but the question, I, the first question is should we have comparator information so the consumer can make that choice. And then we can decide on what the adequate reference is and how to present that information. I think that's what we're trying to get at.

You're looking at a table that a, a physician can read, understand certain caveats in it and convey those to a consumer, and I would totally