scientific evidence, and you will take that into account during your deliberations and your recommendation later today.

And so the first PMA for a female condom was submitted by the Sponsor in 1991. At the time, it was called the Reality Female Condom, but now we refer to it as FC1 to distinguish it from the newer version, FC2. This initial PMA was supported by pre-clinical studies of the physical properties of the female condom, some small feasibility studies of the female condom during actual use, and a six-month contraceptive effectiveness study. We approved the first female condom in 1993.

The table on this slide represents the results from the supporting pivotal study, U.S. sites only. You will hear more about the study a little later this morning from the Sponsor and FDA, but as you can see, the first row gives the six-month results, and the second row gives the one-year extrapolated estimate. Again, effectiveness is given as the percentage of women who became pregnant while relying on the device. And there's both a perfect use and a typical use rate.

The Panel found these data to show safety and effectiveness with reasonable assurance and

recommended that the PMA be approved. As a condition of its approval recommendation, the Panel suggested a set of labeling stipulations to reflect what was known and unknown especially with respect to STI protection.

Here is a list of the four points under the heading, "Important Information," that now goes on the retail box in the package insert of the female condom. I've paraphrased the actual wording. It starts with a hierarchical approach, where latex condoms for men are highly effective; second bullet, if not using a male condom, use a female condom; third bullet, use every time you have sex; and, last bullet, before you try it, read the instructions. We've already heard that that's a very good idea.

It's also worth noting that after FDA approved this device, the commissioner, the FDA commissioner went to NIH and asked for their help in filling some of the evidence gap with respect to STI protection. And NICHD sponsored a number of female condom studies, at least one of which you'll hear about later today.

So to review, female condoms are in Class III. A premarket approval application is the regulatory pathway to market in the U.S. And, to

date, FDA has only approved one PMA for a female condom, what we're calling FC1. The second PMA for FC2 is before you today.

So now I'd like to talk a little bit about condom failure mode studies. First, what is a failure mode? In short and in general, it is the manner by which a device failure is observed. It generally describes the way the failure occurs. So we're talking about acute mechanical failures noted by the user during or immediately after sex.

In the case of a condom, and I'd like to start with male condoms since that is where much of our experience with these kinds of studies originally came from. There are two recognized failure modes, slippage during use and breakage during use. It's important to note that these failure modes, by their very nature, intuitively represent some level of increased risk of either STI transmission or unintended pregnancy or both, but we don't really know to what degree the risk reduction expected from the condom has been compromised by the failure.

Steiner, et al., in a 1994 article was the first to focus on condom failure mode studies and systematically stressed the importance of standardizing key study features. Steiner noted that

there was a wide variation in studies that have been conducted up to that time, and this variation extended to design issues, study execution, and data analysis. The authors concluded that there were several areas where standardization would be useful.

And I, for the purposes of presentation, have broken into three different kinds of areas that could be improved.

The selection of study subjects. Steiner pointed out that choice of subjects can influence study results. For instance, subjects who use backup contraception and are at low-risk of STIs may not use condoms with the same degree of care as a typical user or someone who knows he or she is at high risk for an STI. Anal sex versus vaginal sex, condoms break more often during anal sex, so a study needs to distinguish between the two and analyze separately. Commercial sex workers, they break condoms less frequently and, again, one needs to distinguish sex workers from the general population and condom experience. Those with no condom experience tend to break condoms more frequently, so a study needs to distinguished experienced from inexperienced condom users.

The next category covered by the Steiner

paper has to do with definitions and questionnaires used in a condom failure mode study. It is critical that the definitions for each failure mode be carefully crafted and standardized so that everyone knows exactly what happened. And it's important to differentiate clinical events from non-clinical events. That is, the events we measure should quite intuitively represent some level of device compromise that has increased the user's risk. The reliability of the reported event rates will depend on how well each of the study subjects understands and answers the questions in a coital log. These questions should be clear and unambiguous so as to minimize response bias that could lead to underreporting.

And, finally, these studies are highly dependent on a subject's memory of each individual event. Steiner also cautions against relying on retrospective data even if the recall is confined to the last year or even the last month.

And, finally, there were just a collection of other comments from the Steiner paper that spoke to the use of lubricants, penis size and condom size, clustering, and condom quality. These are all areas where the study protocol and study reporting should keep track of that.

In the case of lubrication, inadequate lubricant can lead to unnecessary condom breakage. Subjects should be advised to make sure of lubrication, and the study should provide for a single lubricant for the subjects in the event they want more.

A condom with too tight a fit can break more easily. Study procedures should address penis size and condom size.

In a study of any significant size, condom failures tend to cluster in a smaller subgroup of users, so-called breakers, and study analysis should account for this kind of correlation.

And, finally, the Sponsor should fully document the quality of both the test condoms and the control condoms that are used in the study.

So where does that leave us today in the world of condom failure mode studies? Well, for male condoms, we're pretty sure there are just two types of failures, slippage and breakage during use. The study should be focused primarily if not exclusively on these outcomes, and the design we typically see today is a prospective randomized cross-over study.

With this design, each study subject is given a number of condoms of one type. When the

subject returns to turn in the coital logs for that set of condoms, he is given a second set of the other type of condom. Randomization determines whether he gets the test condom or the control condom first, and this is considered an efficient alternative to two parallel arms, where each study subject only gets one type of condom, which would be an acceptable design approach but would require more subjects and probably maybe take longer.

Obviously, since this is a study based on patient-reported outcomes and user recall, study measures starting with instructions, counseling, coital logs, timing of return visits should all be aimed at improving the quality of the data entry. Sample size for these studies is governed by the type test to run, the expected event rates, and the acceptable delta one can -- the acceptable difference one can tolerate, something we sometimes call the designated delta, as we shall see in just a moment.

Male condoms made from natural rubber latex have an event -- have event rates that range between 1/2 and 2 percent, and most parties would agree that anything less than a 2 percent difference would be acceptable. So to show a new condom is not inferior to an acceptable control condom, these studies

typically -- these studies have generally followed a crossover design with 200 couples, using five condoms of one type in a two to three-week period, returning for a second set of condoms, same use period, resulting at study completion in a thousand usages of each condom minus any loss to follow-up. Even after factoring in within sub-decorrelation, that turns out to be more than sufficient.

And what can we say today about how well male condoms perform with respect to slippage and breakage? This slide represents the results from about a dozen studies of male condoms conducted since the '94 Steiner paper. Virtually all of these studies follow the study design I just described and compare a new synthetic condom to a selected male condom made from natural rubber latex.

Event rates for both failure modes for male condoms made from natural rubber latex are quite stable with slippage during use ranging from 1/2 to 1 1/2 percent and breakage during use ranging from 1/2 to about 2 percent. I should add that the failure mode event rates for some of the synthetic condoms had more than a 2 percent difference when compared to the control, and in those instances, FDA imposed mitigating labeling limitations.

So just to recap about male condoms in failure mode studies, selection of study subjects, very important. Things like literacy, motivation, condom experience, multiple acts per day. Instruction of subjects regarding protocol compliance also important. The coital log should be designed to be as simple and clear as possible, ideally, with only a few essential questions, one log per sex act. And these studies are based on user recall, so promptness of data entry is critical to its reliability. Subjects should be counseled to complete the log entry as soon after sex as possible, 30 minutes to an hour, by the next day, if that's not possible. But it's also pretty much impossible to truly oversee something like that.

So for the kind of crossover study I was describing with three to five condoms per set, the next level of study oversight is to ask the subject to return the logs for the first set within two to three weeks. The same thing for the second set. And, finally, as you saw from the last slide, the failure mode studies of male condoms made from natural rubber or latex fairly predictably give rates in the range of 1 1/2 to 2 percent.

And so where are things heading now? A

draft international standard is underway, not too far from completion, that requires a clinical failure mode for any new synthetic condom. It follows the non-inferiority model I just described. The draft standard originally specified an acceptable delta of 2 percent for each failure mode, an approach FDA has been using for more than ten years. Just recently, this was changed to looking at total failure; that is, the sum of slippage and breakage, and under that evaluation paradigm is now moving towards an acceptable delta of 2 1/2 percent for the difference between the two condom types as a measure of non-inferiority. And this is probably an equally acceptable approach.

So now let's look at failure mode studies for female condoms. This picture is different from that for a male condom. As far as breakage goes, that's a fairly analogous failure mode to that of the male condom. However, what was simple slippage for a male condom, which meant slipping off during use, now turns into one of three possible dislodgement modes for the female condom.

Something we generally call slippage now is similar to the male condom, but now we mean slips out of the vagina versus slipping off the penis. And two

additional failure modes unique to the female condom, you could think of them as variations on slippage: invagination, where the entire condom is pushed inside the vagina by the erect penis; and something called misdirection, where the erect penis pushes past the female condom into the vagina, that is, it doesn't actually enter the condom.

And you will hear more about these four failure modes from the Sponsor and FDA speakers later this morning, but the basic principle remains the same as with the male condom. All four failure modes intuitively represent some level of actual increased risk of STI or pregnancy, but, again, not quantifiable.

Most of the principles laid out by Steiner in 1994 apply to failure mode studies of female condoms. The slide here is a table taken from the executive summary you were sent a month ago showing the results from five published studies describing past FC1 studies that looked at failure modes. These studies were selected because they were relatively recent, published between '03 and '07, a fairly robust sample size, and the study methodology reasonably well-described.

It's worth noting, as you can see, that the

breakage rate across the various studies is fairly stable, all below 1 percent. And you see more variability in event rates for the other three modes, the slip rate, and these studies ranged from 2 to 10 percent; misdirection, between 1/2 percent and 5 percent; and invagination between 1 and 5 percent. And some of this can be attributed to using different definitions for the failure mode, some to methodological differences, probably some to issues related to the coital log and subject compliance, and, also, these latter three failure modes are sometimes not so easily recognized, and it is useful to counsel subjects to ask her partner to participate by helping to identify these problems.

So, again, just to recap, what have we learned, what do we know with female condom failure mode studies? The overall picture is more complex, with a total of four failure modes. The good news is that most of that picture comes from experience specifically with the FC1 female condom. That's the only female condom to be marketed in the U.S., and only recently have we seen other female condoms under development. And this picture may change as we get more experience with other female condoms, but probably not fundamentally.

As far as failure event rates go, as I mentioned, the breakage seems to be pretty stable across studies, at less than 1 percent. And as we saw in the previous slide, quite a bit more variability and reported event rates for the other three failure modes, with rates ranging up to 3, 4, 5 percent and higher. For one, some of these slippage-type failures are more difficult to identify, often requiring help from one's partner. And some of it goes back to the principles laid out in the Steiner paper, regarding things like precise definitions, adequate protocol instruction, well-designed coital logs, prompt data entry.

All of these are factors that can lead to more reliable user reports. I would also point out that some of those FC1 studies were large enough that the authors were able to look at improvement in use, and in a couple of those studies, you saw lower event rates as more experience with the product was gained.

So looking into the future a little bit, where are things going now with female condom failure mode studies? First, as with the male condom, there is a robust effort underway towards developing a performance standard for female condoms. And that standard as a key requirement stipulates the need for

a failure mode study. That draft international standard also follows the non-inferiority model I described earlier with a designated acceptable delta between the test and control condom, a delta -- acceptable difference, I should say, a delta of 3 percent. Its current status is that it's undergoing revisions and will be put out for a new ballot next year.

And on another front, some researchers are exploring the use of semen biomarkers as a more definitive measure of risk exposure. Versions of PSA assays, that is, prostate-specific antigen, have been tried and look promising. Something like this might be used in a complementary fashion with a more conventionally designed failure mode study, but it is too early to tell where this effort will lead.

Finally, I'd like to just turn our attention to the PMA before you today. As I've mentioned and as you'll hear from the Sponsor, this PMA is for a new version of their female condom, that is, the FC2, to replace the initial version, FC1, that they have been marketing for the last 15 years.

Just a few thoughts to take into consideration as you move into the main part of the day. First, you should know that FDA values the

independent perspective that each of you bring to a meeting like this. We recognize that these meetings demand significant resource commitments by you, by sponsors, by other public participants, and for the FDA itself. We do not bring every single PMA before the Panel. And in deciding whether or not to do so, we ask ourselves whether the PMA poses one or more of the following challenges.

Is the matter of significant public interest? Is the matter controversial? Is there need for special expertise? And if the answer to one or more of these questions is yes, and we believe that a Panel discussion would strengthen our review process, that's when we decide to bring it to Panel.

And while, arguably, all three of these criteria might apply to this PMA, we especially believe that the unique expertise embodied by this Panel will add immeasurably to the strength of any decision we make. And by that I'm talking about experience with clinical trial design, experience with practical problems in running clinical trials, and, lastly, the appreciation you bring to the international perspective as it applies to reviewing studies from outside the U.S., as well as the potential public health impact of a condom in a

worldwide setting.

So, specifically, with the PMA before you today, we have a new female condom, the FC2. But many design aspects are quite similar to the predecessor, the FC1. Our PMA review approach, essentially unchanged from when we reviewed and approved FC1 in 1993, calls for a single-arm six-month contraceptive study. It does not require an STI study but relies on mitigating labeling I described earlier to balance that evidence gap. And our review approach has not changed from 1993 really because we have just the one precedent. We have not received any other PMAs in that time frame.

In short, today's PMA does not fit our current review paradigm. As you will hear, the primary focus of the PMA for FC2 is on a failure mode study comparing FC2 to its predecessor, FC1. Contraceptive and STI protection are inferred from what we know about FC1, and the Sponsor has asserted that it is sufficient to demonstrate a reasonable assurance of safety and effectiveness. And in that context, they have indicated they will keep the mitigating labeling that was part of the original PMA approval decision.

So what we're asking you here today is to

help us determine how much data is necessary to demonstrate the safety and effectiveness of the new FC2 female condom and if what we know today, 15 years after our original decision, whether we need to recalibrate what we expect in a PMA.

And, finally, I don't think my remarks would be complete without mentioning what I think we all understand, that there is an international perspective to what we are doing today. Female condoms may only occupy a niche in the overall condom market, whether we're talking about the U.S. or worldwide. However, I think we all agree, when we're talking about something as important as STI prevention, especially HIV/AIDS, that more options are better. And the female condom is unique in that it offers a female-initiated option to barrier protection.

Moreover, it's also worth noting that for some parts of the world where HIV prevalence is the highest, condom availability is the result of very significant contributions by third-party donors like USAID, UNFPA, and others. These organizations are keenly interested in whether FDA has approved a product for market. In the U.S., that decision alone may drive whether or not they can support the

purchase of that product for worldwide distribution.

So, thank you, Madam Chairman, and that concludes my remarks.

DR. CEDARS: Thank you. Are there any questions from the Panel? Dr. D'Agostino?

DR. D'AGOSTINO: Back in the 1980s, I served on the Fertility and Maternal Health Panel -- the OB/GYN drugs. And we were badgered by a number of indices on pregnancy, the Pearl Index, number of episodes, and so forth. Then we finally decided on how many people got pregnant in a six-month period, and so forth. I'm not completely clear on what the event rate is for slippage. When you say 2 percent; for example, in your Slide 33 --

MR. POLLARD: So there were two --

DR. D'AGOSTINO: Let me just --

MR. POLLARD: Okay.

DR. D'AGOSTINO: Let me get this slide if they could. Could you get up 33?

MR. POLLARD: Oh, you want me to --

DR. D'AGOSTINO: Is it possible to do that or not --

MR. POLLARD: To get which slide?

DR. CEDARS: Thirty-three.

DR. D'AGOSTINO: Thirty-three. I'm sorry

if you --

MR. POLLARD: Okay. Let's see --

DR. D'AGOSTINO: I have it in front -- well, he may not, though. If you can look -- well, here is the question. You have 175 --

MR. POLLARD: Okay. So --

DR. D'AGOSTINO: You have 175 individuals in that first study.

MR. POLLARD: So this is the -- this is the FC1. This is a slide showing several studies from the past few years of event rates from FC1 use.

DR. D'AGOSTINO: And you have breakage, 0.7. Now, is that 0.7 for the number of episodes or is it for the number of people?

MR. POLLARD: Uses. It's episodes --

DR. D'AGOSTINO: Number of uses?

MR. POLLARD: So that's not a per-person --

DR. D'AGOSTINO: Why aren't you interested in per-person? I mean, if you're talking about transmitting AIDS, one bad event --

MR. POLLARD: You could do it on a per-person basis, and sometimes people look at that in a secondary fashion. But, really, you're just trying to find out something about that condom, and so you're using the condom use as the denominator rather

than the person --

DR. D'AGOSTINO: I see. But if you're involved with, worried about safety, if a person -- if every single person in the study has one slippage, that's quite important to know.

MR. POLLARD: Well, you do some analyses here for within use correlation. I mean, you could do -- these are crossover studies, by and large. You know, certainly in the male condom area, they're crossover studies. You could do single-arm studies, where each user gets one condom, but --

DR. D'AGOSTINO: No, I think multiple uses is good. It's just the summary of the data. You know, the question is are we seeing very small rates because we're shifting the denominator, and what denominator should we really be looking at is the question I'm asking.

MR. POLLARD: Yeah, yeah.

DR. D'AGOSTINO: I mean, with pregnancy, we used to talk about -- you know better than I do --

MR. POLLARD: Yeah, but I would argue that's the difference between looking at a failure mode study and looking at --

DR. D'AGOSTINO: Right, exactly --

MR. POLLARD: -- with the clinical outcomes

like that.

DR. CEDARS: If we can just have one more short question, Dr. Padian?

DR. PADIAN: I'm not sure if you're the right person to ask this, but I wondered about the rationale of giving someone five condoms -- you know, in the study we looked at, I think it's ten at each set, as opposed to trying to give them enough to cover all acts. And the related issue is whether the number of acts, you know, that are -- yeah, you get it.

MR. POLLARD: Yeah, and I would say there's a trade-off there, in terms of how quickly are you going to ask them to come back, you know, and whether or not they are at high risk of STI. So it's going to depend on your population. It's going to depend on what time frame you ask that set of subjects to return. So if you're going to give them a really long time period, then you probably -- you know, and they're at very high risk and you know they've got no other alternative.

DR. PADIAN: You know, I just was --

DR. CEDARS: I think that --

DR. PADIAN: Sorry.

DR. CEDARS: That may be a better question

for the Sponsor.

DR. PADIAN: Okay. Because I have a follow-up --

DR. CEDARS: Because that goes to the study of the design.

DR. PADIAN: All righty. I'll hang on until then.

DR. CEDARS: We are running a bit behind today. So we are going to take a break, but I want this to be strictly a ten-minute, strictly a ten-minute break. So I actually have that it's about 10:34. So if we could have everyone back in ten minutes, we will get started in ten minutes. So please try to return on time.

(Off the record at 10:34 a.m.)

(On the record.)

DR. CEDARS: Please, if everyone can take their seats, we need to get started. Can we please quiet down the conversation in the back of the room? And if the Panel can take their seats as well? I'd like to congratulate everyone. That was very nearly close to ten minutes, so thank you for your cooperation.

We will now proceed to the Sponsor presentation for FC2 Female Condom. I'd like to

remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel. We'll begin the Sponsor presentation, and the first presenter is Dr. Mary Ann Leeper. Dr. Leeper?

DR. LEEPER: Madam Chairman, members of the Panel, good morning. We are really pleased to be here today. The Female Health Company and FDA have been in discussions about the FC2 Female Condom for approximately three years, particularly in the aspect of whether or not we would need to include a contraceptive study for the FC2 approval.

I'm hoping and Female Health Company is hoping that by the time we finish our presentation this morning and we answer all of your questions this afternoon, that you will agree with us that no additional work will be needed in order for you to recommend approval of the FC2 Female Condom.

I thought that perhaps a little bit of history would be of interest to you to set the stage about the evolution of the female condom. And our story all started about 20 years ago when we decided that it was really important for women to have a method that they could use to protect themselves

against HIV, STIs, and unintended pregnancy. We wanted a simple device, something that women could insert themselves, that it would stay in place during use, that it wouldn't tear, and that, of course, it would block bacteria and viruses.

We developed the FC1 Female Condom according to a procedure following the -- as if it were a Class II medical device and filed a 510(k). And immediately following that filing, it was several Panel hearings were held. And it was determined that, in fact, what we needed to do because it was an unusual design, no real experience with female condoms, that what we really needed to file was a full PMA and that that full PMA needed to include a six-month contraceptive study.

We completed that work, and in 1993, FDA approved, as Colin told you this morning, FC1, with two contingencies. The first contingency was that we needed to have -- carry very restricted labeling, which Colin outlined for you earlier. And, secondly, that that restricted labeling would have to be maintained until a definitive study, male condom versus FC1, evaluating the ability to prevent STI infections was to be completed.

That study was to be designed and

implemented by FDA and NICHD, and that all we were -- our part in that process was to supply the female condoms. And we did that. FDA and NICHD designed the protocol, implemented the study. It took about five to six years to complete the study. And about five or six publications have come out since that study has been completed.

It is that study which FDA addresses in its executive summary to you that, in retrospect, they feel that the protocol that they implemented was not adequate. So as of today, we still carry the restricted labeling.

Up until now, approximately, oh, I'd say 165 million female condoms have been distributed to about 145 countries. And the major use for FC1 is in the -- what we call the global public sector. It's for women who mainly -- for women who are at high-risk to HIV/AIDS and, of course, STIs, particularly in the developing world. Approximately 90 percent of our -- of the distribution of FC1 is in the developing world.

About five years ago, USAID, particularly Jeff Spieler, said to me, "Mary Ann, this is an important drug -- device. The female condom plays a role. There is a demand there, but we cannot meet

that access. We cannot meet that demand unless you lower the cost. You have to lower the cost." So we went to work to lower the cost of FC1 in order to increase the access to address the need that was so very, very clear.

What we felt was that the design and characteristics of trying to reduce the cost of FC1, we didn't want to change the design or the use, how you use it, any part of the characteristics. The only thing that we really felt that we could do to lower the cost was to find a material where we could change the manufacturing process. Now, this is FC1 on the left-hand side. Let's see, this is -- there it is. Okay. This is FC1, FC2. FC1 is made of polyurethane, and the process of making this product is a welding process. We have to weld the two sides of plastic together, and there is a seam. And this seam is a potential part of failure. So we have to weld this process. And then the outer ring is also made of polyurethane and is also welded onto the sheath.

So what we wanted to do was to go from a welding process to a dipping process. It allows you to get through much labor -- less, significantly less labor intensive, faster production of a product per

unit period of time, and you get rid of the seam. So we had to find a material that would allow us to do that. And we did. We found the nitrile product, and Mike is going to be talking to you about this in a little while. And what we did was we got rid of the seam, and we got rid of the welding of the outer ring. We used a rolled outer ring just like male condoms are used.

Our whole strategy was if we have the same design, if we have the same instructions for use, which we had spent years educating NGOs and outreach counselors on how to use the female condom, so we didn't want to change any of that. But if we had the same design, we had the same use, if the failure modes were the same, which we'll be talking about in great length over the next several hours. And if it compared in terms of the rate of failure as FC1, and we had already established that FC1 was safe and efficacious, completed failure mode studies and a contraceptive study, and we showed that FC2 failed at the same way and at the same rate as FC1, then we felt that the least burdensome way to establish FC2 as an effective barrier would be met. We would have shown that it looks the same, it acts the same, it has the same failure mode, the same rate of failure,

it must be the same -- have the same rate of efficacy as an effective barrier as FC1. We felt it was the least burdensome approach to get this product developed and get it to the women who needed it.

We put together a PMA supplement to FC1 PMA, and we went about to do a viral permeability study to show that viruses did not permeate the sheath. We wanted to show that it was safe and biocompatible, and we wanted to do this comparative study.

We went to the experts for all of those studies, the viral study, the safety and toxicity study, and we went to the Reproductive Health and HIV research group, who we call RHRU, they are located in Durban, South Africa, to do the study. Now, why did we go to RHRU? Because they had done more clinical studies on the female condom than any other organization, period, in the world. They had done more studies, and they had been contracted to do these studies by the World Health Organization, by USAID, by Family Health International, by PATH. All of these have identified that RHRU was an expert in doing these studies. So we went and we put together -- RHRU agreed to design the study and implement the study.

We completed all of the work, formed a dossier, got the -- using that dossier, we got the CE mark of approval, and then we presented that dossier to the World Health Organization, who had called a group of World experts to look at this dossier. They spent three days studying everything that was in the product. They came up with a list of questions. We answered those questions over a period of time. And the World Health Organization then said the data supports that FC2 performs in the same manner as FC1 and that it was acceptable for UN agencies to distribute FC2, period, that they could distribute FC2.

Since that time, oh, I'd say about 22 million FC2 female condoms have been distributed in the last two years in about 77 countries. UNFPA is the largest distributor of FC2, and the feedback that we have received from UNFPA, to date, is that they are really pleased about how FC2 is being accepted and used, that the demand is high, and that they are going to continue to increase their volume in terms of distributing FC2.

And, to date, I would say, ex-U.S., all of the countries have switched from FC1 to FC2, the two largest ones, Brazil and South Africa are just

about -- they are now preparing tenders to switch from FC1 to FC2. And so, to date, we're really pleased with the increased acceptability and use of FC2 and the performance of FC2. By switching to FC2, we've been able to lower the cost already by about 30 percent. And as that volume increases, the cost will continue to decrease.

Now, we took that same dossier and submitted it to FDA. The dossier that we submitted to WHO we submitted to FDA. FDA, upon reviewing the dossier, suggested that a PMA supplement to FC1 was not what they wanted. What they wanted was a full PMA. We went back, did a little more data, and submitted that to FDA. And now we're here today to talk about what's in that dossier and whether or not it's acceptable.

If you look at the data that -- what FDA has suggested, there are three basic concerns or points that FDA would like you to consider. First of all, no contraceptive study. Secondly, is FC2 robust enough to do the job? Is it doing what we are saying that it's doing? And, number three, the adequacy of the RHRU protocol. And, specifically, about the adequacy of the RHRU protocol, they have raised several points they would like you to discuss today

and which we will be discussing in great length as we go through our presentation this morning.

The points raised by FDA are reliance on the one-on-one interviews rather than relying on the coital logs for the database; number two, recall, will they remember that an event happened during the interviews; that slippage, per se, is not on the coital log; concern about there aren't enough slots on the coital lots if somebody has, a woman has, say, two or three sex acts in a given day, and what if she had two invaginations on that given day, would she record the second invagination since there was only one slot for that day for invagination; no coital logs, some women did not complete coital logs; whether or not commercial sex workers should be included in the database for the analysis; and was the study blinded.

As I said, we'll be going to talk about each one of these points, but let me just say right up front as we go into the discussion that there were no meaningful differences in the findings between the database that included the commercial sex workers and the database that did not include commercial sex workers. By the database that, if you look, the results, the findings of women who completed coital

logs and women who did not complete coital logs, the findings were similar. And, most important, of course, is that the performance of FC1 and FC2 were comparable for each of the clinical failure modes.

So, in summary, we wanted to make sure we had an effective barrier, that it was safe, biocompatible, that we could make it consistently, and we wanted to show that FC2 performed in a comparable manner as FC1. And the studies showed that FC2 is safe and effective -- as safe a barrier and biocompatible barrier. Its failure rates were the same, are comparable, to FC1. And a very other important point is that the performance of FC1 in the RHRU failure modes study, the findings from that were the same or similar as the FC1 findings in the failure modes study in the PMA that support its approval 16 years ago. And this is important because the question is, is the RHRU capturing all the events? And the answer is yes because FC1 performed in the RHRU study with the same results that it did 16 years ago.

MR. POPE: Good morning, Panel members. I hope you can hear me. My name is Mike Pope. I'm the Vice President of Global Operations at the Female Health Company. I've been associated with female

condom development and manufacture now for 19 years, initially in the development of the manufacturing process for FC1, which is housed in our London facility, of which I'm responsible, and more lately, the development of the manufacturing process for FC2, which is housed in our Malaysian facility. This presentation is about five minutes. In the middle of it is a very brief video, which I'd like to show you. And here we go.

Okay. My brief really was to develop FC2 to find a more cost-effective and simple manufacturing process whilst changing the device as little as possible. I had to simplify the manufacturing process in a way that would be capable of running in a low-cost area of the world. Currently, FC1 is manufactured in London, which is one of the most expensive manufacturing areas of the world. But the process is not capable of being moved.

My brief was to increase capacity. And, again, the process that we've chosen is capable of very high-volume manufacture, as demonstrated by male condom manufacturers and glove manufacturers.

The intent of both these things was to make the product available at a lower price, and already,

the manufacturing volumes that are coming out of Malaysia have allowed us to sell FC2 at a lower -- manufactured at a lower cost and, therefore, sell it as a lower price than FC1. We're already starting to be able to do that.

But I had to match the key performance characteristics of the two devices. There was no point in me changing the device such that the two were totally different. So we kept the same sheath dimensions, the same inner ring, same insertion method, same amount and type of lubrication. We were very aware that the outer ring that stays outside the body is a slightly different dimension to FC1. And in order to compensate for that, we increased the thickness of the ring very slightly but kept the diameter the same size. And we pack it in the same packaging materials in order to ensure its protection.

We looked at a number of manufacturing processes, and we arrived at the dipping process. As I said a little earlier, it's widely used for male gloves [sic] and medical gloves. It's capable of high volumes, capable of low cost, and it's a well-established, well-proven manufacturing process.

I'm going to show you a very brief video in

a second, but before I do, I'm just going to tell you what you're going to see. The first little video is about 15 seconds of the FC1 manufacturing process. Polyurethane is a thermoplastic. You heat it, it melts, you cool it down, it resolidifies. FC1 is fabricated from bits. We make a ring. We take sheets of material. We weld them together. We join the ring to the sheath. We then test it using helium gas and mass spectrometers. It's an incredibly complicated manufacturing process.

Yes, so that's the first video that you're going to see. It's very short. This is welding two sheets of film together, and you see there's a horseshoe shaped sheath. This is the injection molding of the top ring. These are automated manufacturing systems, injection molding machines, robotic systems. This is the process where we join the ring to the sheath. There are 26 of these machines in this room all rattling away. And then this is the helium leak tester where we test 12 devices at a time that pump full of helium, the gas is taken away from -- and analyzed in a mass spectrometer. It's a hugely complicated process.

When we developed FC1 manufacturing, we did not have the ability to find a material, such as

nitrile rubber, which would give us the same properties, similar properties to polyurethane but was capable of being dipped. That technology was not there, which is why we did this.

In contrast, I'm now going to show you the FC2 manufacturing process. Basically, we take a former of the correct size and shape. It's dipped into a nitrile material. That nitrile material is then part cured. The top ring of the device is rolled, as Mary Ann said, very similar to that of a male condom. And it's then stripped off. And it can be leak tested in the same way that male condoms are leak tested, a well-established manufacturing procedure.

So here is the FC2 manufacturing. There are the formers going into the nitrile. We colored it blue so you could see what was going on. They're not normally blue. There we're rolling the excess material into a bead at the top of the device. Now we're stripping the device off the formers. That simple process replaces everything you saw in the previous video, and that's a male condom testing machine modified to test female condoms. This is a view -- this is actually our Malaysian facility. As Mary Ann said, we've already made 22 million there,

which have been shipped into 70-odd countries around the world.

I hope you can see from that that the FC2 process is much more simple and is capable of a significant cost reduction in the manufacturing process.

Why nitrile latex? We assessed a number of raw materials for this. And we rejected all of them fairly earlier. Well, I did give serious consideration to natural rubber latex, which is of course is the, you know, sort of industry standard for most male condoms, but we reject that also, for two reasons. One, the potential allergy problems. In fact, three reasons. One, potential allergy problems associated with natural rubber.

Secondly, lubricant compatibility. We've made a big thing over the years of promoting FC1 around the world as being suitable for use with a wide range of sexual lubricants. You don't have to use it with water-based lubricants as you do with natural rubber male condoms. If we'd have made FC2 out of that, we'd have had to change that message all around the world, and that would be a very difficult message.

And, thirdly, natural rubber latex is --

you know, for a female condom, you don't need a material which will stretch to ten times its length, which is what a male condom will do, natural rubber latex will do. A female condom is a loose-fitting liner for the vagina. The material just needs to sit there. It doesn't need to have huge elastic properties. Nitrile seemed to fit that bill.

So similar elongation. It's widely used, and it has a good pedigree in glove manufacture. It has excellent chemical and solvent resistance. Hence, it pointed at the fact that it would probably be good with a range of lubricants. And it had excellent biocompatibility, already being used for other medical uses.

Incidentally, there was a question on stability earlier. We have provided data to FDA of stability of this FC2 one-year at 50 degrees centigrade, and it's stable. We have three months at 70 degrees centigrade, which is -- and we have an ongoing study at the moment of 30 degrees centigrade, 65 percent RH. It's been running for almost two years now. And the product looks very stable during those intervals.

Okay. That's the background on the material itself. We had to look at -- try to

characterize the raw material that we would be using. The tensile properties of nitrile, its strength under elongation, tensile properties, are less than that of polyurethane, 40 percent less than polyurethane. We were concerned about that. Consequently, to compensate for that, the thickness of FC2, we've increased its thickness by about 50 percent and brought it in line with the thickness of male condoms.

We're also aware that FC2 does not have a seam, a welded seam, and the welded seam is always the weakest part of FC1. Consequently, then, if you test FC1 and FC2 and you include the seam in FC1, and you test it under physiologic conditions of 37 degrees and -- motion in saline, the two products have an equivalent strength.

We evaluated, as I said earlier, nitrile has good solvent and oil resistance. So we evaluated it with a range of lubricants. It's compatible with water-based personal lubricants. It's compatible with various vegetable oils that are available that are routinely used around the world as sexual lubricants. It's compatible with petroleum jelly and baby oil, something that male condoms aren't. And, again, the FC2 compatibility results are comparable

to FC1.

We assessed its viral barrier properties. It's an accepted protocol that's used for many medical devices in the field of HIV prevention. We tested FC2 against FC1 against male condoms, and all three were shown to be excellent barriers to a particle, which is a factor of five times smaller than the HIV infectious particle.

We can talk about the strength of condoms. It seems these days that the international standards and ASTM standards have reduced the requirements for condom strength down to burst characteristics. Not can you cut a -- out of it and see how strong it is, but if you pump it full of air, how big will it go and what pressure will it burst at? Those are the burst characteristics. And so that's something that we've characterized for FC1 and FC2, obviously.

The FC1 burst specification was set back in 1991, when we were making prototypes. And we looked at the data of burst characteristics of FC1 and kind of did some fairly unscientific work back then, and said, okay, these were our release specifications for FC1. For FC2, the International Standards Organization has been considering how to set these sorts of things for new female condoms, and we

followed their guidance at the time, which was to test 2,000 devices, blow them up, measure the volume, measure the pressure. Those 2,000 devices should come from the same manufacturing lots used in the clinical study so that you're characterizing exactly the performance of the products that we used in vivo.

Consequently, the minimum specifications for FC1 and FC2 do differ slightly. However, when you actually measure what's going on, and we've looked at the last manufactured lots of FC2 and FC1, we find that the actual burst pressures are very similar, FC1 to FC2, and the burst volume is very similar, FC1 to FC2. So the FC2 air burst strength is comparable to FC1. There is no major difference there.

That really comes to my last slide, which is just trying to summarize. We were trying to make the two devices as equivalent as we can, bearing in mind we were changing the manufacturing process and changing the material. The burst properties, the most telling physical property of the device. The burst properties of FC2 are comparable to FC1. The softer outer ring does not impact the failure modes, including invagination. Results are comparable to FC1, and you'll see that from the clinical study.

The break strength of the FC2 device is comparable to a welded FC1 device. Its compatibility with a wide range of sexual lubricants is as good as FC1, and its barrier properties are similarly as good as FC1 and as a male condom.

I think, you know, I hope we achieved the objective of developing a product which was as similar to FC1 as we possibly could, but using a process which has the capacity for reducing the manufacturing cost. That's the end of my presentation.

MS. BEKSINSKA: Good morning, Dr. Cedars, Panel, and audience. Thank you for allowing me to present the study today. My name is Mags Beksinska, and I'm the clinical investigator on the RHRU trial I'm going to present. And I work for the Reproductive Health and HIV Research Unit in South Africa.

So the aim of our study was to -- sorry -- evaluate the functional performance and short-term acceptability of the FC1 and the FC2 and also to compare the rates of clinical/non-clinical breakage, total clinical failure, invagination, misdirection, and slippage in our study.

The study was carried out in the Durban

area where the HIV rate of antenatal women is 40 percent and higher in some areas. We conducted the study from one clinic in an urban area, Commercial City Clinic, where we saw three groups, three study groups, the Urban Family Planning clients, STI, and student clients who were from the local tertiary institutions. We went to Umbumbulu Clinic about 45 minutes out of Durban, where there were rural women. And our commercial sex workers lived and worked in the hotel very near Commercial City.

And the trial was a randomized, double-blind crossover trial, where participants were assigned to one of the two sequences, either using FC1 first followed by FC2 or in the opposite order.

So in our methodology, we required, as many contraceptive studies do, performance studies do, the women to be using an effective method of contraception, and they were using mainly hormonal contraception, and all were sterilized. They were screened for STIs.

We asked them to use ten condoms of each type and to record the use of those condoms on a log and to return as soon as they had used all ten condoms. So we made an appointment, but we asked them to come back as soon as they'd finished. At

each visit, we conducted a pelvic examination to exclude infections, and we had a one-to-one interview at each follow-up visit with the log as a reference to complete a questionnaire.

Our statistical design we used. For the sample size, we used the WHO guidelines, which recommends use of at least 1,000 condoms of each type and at least 200 participating couples using five condoms each. We exceeded both of those because we felt it was important to increase the sample size to cover for any loss to follow-up.

Our data collection, we collected data from a coital log, which was confirmed at the interview, or information provided during the interview was entered as part of the questionnaire database. So as we've already said, some women, especially the sex workers, didn't bring back a log. But the same questions were asked in the questionnaire. And the questionnaire formed the dataset, and the data was double-entered in EPI-INFO.

And just to discuss our staff, we had four nurse researchers interviewing the women. They're all master trainers, which means they're qualified to train trainers in the female condom and in barrier methods training. Two of the four were experienced

also at an international level and continued to train around Africa and beyond. They have extensive experience in training providers and clients in FC use. And, also, all of them have been involved in the previous female condom research study in our unit and some of them in more than one. And they've also been involved in developing training materials in IEC for the Department of Health.

So in our instructions, the nurses instructed women on how to use the coital log in their home language, English or Zulu. We used a pelvic model to demonstrate the fitting, and this is just one of the several leaflets that we had -- offer in English and in Zulu. And they were given a range of leaflets to take away with them. And also when we demonstrated, we demonstrated the various failure modes and how to avoid them.

And now I'm actually going to do a demonstration of the failure modes. We felt this was important because though most of you will know the female condom, I think the debate around the issue is around the failure modes and how different they are for male condoms. And Colin Pollard already has said that these differences are quite complex.

We all know that male condoms have breakage

and slippage, and, traditionally, when we talk of female condom failure modes, very much they were using the same failure modes as a male condom. So this is a female condom I inserted earlier. And here we are, just so you can see, but the female condom is inserted correctly here, and the outer ring is the full circle, and it's lying flat over the genital area.

So when we look at the various failure modes, if we look at the forces in play when you have a female condom -- a male condom slips off a penis. The force on a female condom is to push it inside the vagina because this is where the pressure is.

So when we have invagination, and invagination previously called slip-in, so I think there's also been a confusion with slippage because people often thought of slippage either way. It could have slipped out and it could have slipped in. But, really, these are two very different events.

Slip-in is the most comment event, invagination, of the failure modes. And if we see that if the -- if the outer ring catches, it can't be pushed inside. So here we have a partial invagination, where part of the outer ring is actually pushed inside the vagina. And this is a

full invagination, where in fact the whole outer ring and the -- is the whole outer ring, meaning the whole condom has been pushed into the vagina. That is invagination. And it's quite difficult to get it out again.

So, here, we put it back into position again, and then I move onto the next failure mode, which is misdirection, which has previously been called rerouting and incorrect penetration. So, often, when you read papers, they -- the whole failure modes have been using different terminology. And in most papers, you will not find a definition. They'll just say pushed in here or pulled out here. But there's not a really precise definition. Misdirection is when the penis, and perhaps it is the many -- we can speculate how these things happen, but perhaps the penis catches the side of the ring and moves in at the side. And you can see that if this happens, that maybe eventually, the whole outer ring will be pushed inside. So you may start with misdirection and you may end up with some form of invagination. But all invagination, whether it's a part of the ring or the whole of the ring, is considered to be a failure mode, okay?

Now, finally, we move onto the slippage

out. So if you think the force is going into -- pushing in, how does it slip out? We can see what complete slippage is because that means the whole condom comes out. But what is partial slippage? This has always confused the people working in the area, right. Is slippage, partial slippage, just one centimeter, two centimeters? Is it half the condom? Is it almost hanging out? No one has really specified what partial slippage is.

And what we know with the male condom, once it's on the penis, it stays in place unless it slips off. With the female condom, it's different. The device is fluid. During sex, it does move a little bit, a little bit in, a little bit out. That is not a failure mode. It's just moving. But as long as it stays in place.

Now, complete slippage, once the inner ring is in place is quite something because then you have to pull the whole condom out and you have to put it back in or reinsert a new one. I'll just have to clean my fingers now. Otherwise it'll slip off the thing.

So these are all the failure modes now I've demonstrated. And moving on how we use those failure modes to instruct people to how to use the log. We

instructed them to record whether there was no problem or a defined problem. The nurses discussed which day of the week they were going to start the log by crossing through, and I'll show you the log in a minute. And we also tell women they could write their comments or notes at the back of the log, which they did. And we also gave an appointment to come back as soon as they'd finished ten uses.

So we discussed with them when they might finish their ten female condoms, said come back straight away. Or we made an appointment, but we said if you finish earlier, come back as soon as you finish. And you can imagine, some of the sex workers, they came back within, you know, maybe 72 hours. Some of the students came back within a couple of weeks because they also had a lot of sex.

So going to our coital log design, we collected information on number of condoms used, the number of sex acts, breaks, invagination, and misdirection. And we did not have slippage on our coital log. But we did use a coital log design similar to a WHO design, which was a contraceptive efficacy study which we were involved in, in 2002.

So let me show you the -- it's not really very clear for you. I don't know if you can see, but

this is the log that we used for the contraceptive efficacy study. And you can see here the male condom failures, and you can see there's no problem. Slipped off and broke. But then also you see for this study, they just took slipped off, because at the time of the, you know, the definition was not well developed, and slipped off came onto the female condom failure modes whereas we believed at the time a condom can slip in, it can slip out, but it cannot slip off a vagina.

So there were four international centers that used this log, and the main problem was around the slippage definition, so much so that one of the centers reported no failure modes because of the issues involved in this.

So here is our adapted log. You can see that we've just removed the male condom failure modes, and we've kept everything the same, but we did not have slippage.

So why did we use this log even though it had had this problem with slippage? Well, we used it because it was very simple to use, and the women in the study who were students understood how to use it. It was a hard card. It was a one-page format. It was easy to use. Many of our women in the rural area

only had primary education, and it had been used before for condom studies. And our staff had experience in using the exact same log. And, also, the intervals required for women to return were the same.

So just to summarize those differences again, we removed the term "slipped off" from the log, as it was misunderstood. And, also, it related to when sometimes men put on a female condom and use it like a male condom. So that is what it was being reported as in this WHO study.

So, finally, just to move on to a bit of clarification about this definition. The definition has changed considerably over time. There used to be two primary definitions, partial and full, but within those, there was many sort of sub-definitions. And here is just a few of them I've put there, which includes the moving in and out, riding the penis like a male condom, the female condom comes out and the penis comes out of the female condom, and the female condom comes out still covering the male penis, so a bit like the male condom.

So what did we use in our study? We used two very broad definitions, full and partial. So for complete slippage, we decided to have any event where

the female condom completely left the vagina in any way was a complete slippage. Partial, we said any time the condom, the woman actually felt the condom was going to come out of the vagina. But what we didn't include is if there was a bit of that movement -- well, I won't go into -- a tiny bit of movement in and out, we did not count that as slippage.

And then moving on to the WHO technical review in 2006, they reviewed all the definitions together. The most debatable issue was the slippage. And it was decided that moving a slight in and out was not going to be counted as a clinical failure. Partial slippage, as it's said here, established as long as the female condom continues to cover the penis, it is not technically defined as a clinical slippage failure. So in all the studies we see in the future on whatever female condom, we assume slippage rates will go down considerably because these will not be included.

Now, this definition was finalized in 2006, and there was a paper published on definitions from the group at WHO. Now, this paper came out in 2007, and it advises all researchers to use the exact definitions from that meeting and several other

things to take note of. Now, obviously, this was not available for researchers who were publishing studies in 2006, 7, and only recently. So we assume that these definitions are now going to be used.

So slippage is now defined as a clinical failure when it comes completely out of the vagina during intercourse.

So how did we get slippage if we didn't have it on our quota log? We had a question, Question 307: Did the female condom stay in place every time during intercourse? Yes, no, not sure. What we asked to do, if women said it didn't stay in place, we asked them in a open-ended qualitative section to describe exactly what happened. We not only got slippage in this, we had invagination, women talked of breakage, women talked of many things. But this is where we got our slippage. And, obviously, the invagination and other issues we specifically asked in questions later on.

And these are two typical complete slippage responses: Slipped out twice from the vagina during sex. The condom was pulled out during sex and we inserted a new one. So we would check, we would say, "Did that condom come out completely?" And, often, until you probe, you have to say to the woman, "Where

was the condom when you went to take it out? Was it still in your vagina? Had it been pushed inside? Was it hanging out?" So this was often a required probe, which you cannot put on a coital log. You actually have to get the detail because women cannot see what's going on down there during sex, so, often, it's only the removal of the condom that indicates to them what has gone wrong.

So after ten uses of each type of condom, women return to complete a questionnaire, and in that questionnaire, there was problems and questions around the failure modes, whether the device stayed in place. We had insertion, removal, and many acceptability issues. Overall preference for each condom type, and what was the -- and from the women's perspective, what was the partner's experience with the condom.

So moving onto our results. We enrolled 276 women, and 201 completed the study and used both condoms. We had just under 4,000 condoms used altogether and about half/half of each. We recorded 194 failures, which was 5 percent of the total use, and 88 percent of those were recorded within 30 days of use.

The coital log and the questionnaire were

complementary. So the questionnaire was filled in with the coital log in front to clarify issues. It was a one-on-one interview, and the events were clarified. Now, interesting, though there is this recall issue, when women only came back and they had ticked the invagination, we used to probe further and say, "Was it the whole ring or part of the ring that went inside?" And they would actually be able to tell us in almost every event whether it was the whole ring and part of the ring because we would probe, "Where was it when you removed it?"

And tears and breaks, we would ask them specifically where it broke and in what instance it broke and also differentiated between non-clinical and clinical breakage. Then of course there's the, "Did the condom stay in place," which has nearly all the events in there but in a qualitative format.

So these are the results of our study, which are very difficult for you to see, I'm sure. Hang on. There we are. Failure modes are on the left, so breakage was broken down into clinical and non-clinical for FC1 and FC2. And here you can see the results, but they're very, very small, and I will be talking about them later. But you can see the slippage are obviously the lowest in both categories.

And for invagination, we've got total outer ring displacement, which is what we called it at the time, completely and partially displaced, and we had a combined figure for both. So based on the results of our study, we felt that FC1 and FC2 were functionally equivalent. Thank you.

And what I'm going to do now is go onto a short literature review to just discuss the failure modes and definitions that are available for you in your Panel pack. But just to remind you, obviously, the studies we're comparing with are only FC1 because there has only been one -- well, there's a second one I'll mention later, but there's -- most of the literature is obviously on FC1.

So if we look at breakage, we can see there on the screen, our breakage was less than 1 percent, and it falls very well within the range here. Now, we've only quoted four studies. What we're doing is we're quoting the studies that have used at least 1,000 condoms, which is the WHO recommendation. But there are other studies which we'll talk about later.

Now, invagination rates, if you see there, our partial and complete invagination totals 3.14 for FC1 and 2.97, and that also falls well into the range here. And you see this third study, it's combined

slippage in and out, and that has also -- the confusion about slippage is the -- in and out is the one thing. So you can see that this figure is combining both.

Now, going on to slippage now, you can see our rates are much lower than the other studies. There's no doubt about it. Many of these studies have not said, except for Macaluso, whether it's complete or partial slippage. But on discussion and talking to one of the researchers in these studies, I said, "Well, what did you use as partial," and they said, "Any single movement of that condom." Any movement was included as a slippage. So women will come back and they'll say, yes, it moved a little bit. That, in most studies, is included as a slippage. We did not include that, and that is why our rates are lower. We also didn't include if the man put the female condom on his penis, and, of course, it was used as a male condom. We also didn't count that as slippage. And, also, with the PMA study, we see it was one figure here with 2 and 2.7.

So misdirection, our rates were 1.6 FC1 and 0.64, and it's not been well-reported in other studies. And you can see with these larger studies, only one, Macaluso, has reported it, and it was 2

percent.

Now, when we talk about total clinical failure, if we include our invagination, we have 5 and 4.31 percent. And this is also slightly lower, but still in the range of the two other large studies, and in this study, it wasn't determined. But if I show you all of the studies in your Panel packs, except for one that only came out last week which has been added in, you can see that for the three modes, invagination, misdirection, and breakage, we fall within that range for FC1 and FC2. Don't worry about the numbers down here. It's just the way the studies are graphed. But, of course, on slippage, you can see we're low, but not as low as one of the early studies, which was 0.

But, also, just to mention that the second study using FC2, which was done in 2007 and 2008 by FHI, they have reported to me just before this meeting that the analysis is at a stage where they can say the FC2 failure rates are almost identical to the ones in our study. And that work will be published in the next year, but they just wanted us to know that.

And so the conclusions of the literature review is that breakage and total failure are

consistent across studies, irrespective of investigator or population. The variance in slippage rates has been because of this evolving change in definitions of slippage over the years, and that will come down since the WHO meeting as partial slippage has been removed. Misdirection has either not been reported or not collected, and as with male condoms, female condom failure, we feel, is something that women will remember. Thank you.

DR. LEEPER: So it's my turn now to go through again, and just let's scrub and look at the issues that have been raised by FDA that they would like you to consider. Broadly, first, whether or not a contraceptive study should be included to approve FC2. We believe that the information gained will not be meaningful enough, not additive enough to justify delaying the time to put the protocol together, execute the study, write the study up, submit it to FDA, and get it approved. You're talking somewhere around five years. And we just don't believe that the incremental information justifies that delay in getting this product to women who need it.

Secondly, is FC2 robust enough to do the job? I think Mike showed you why, in terms of the physical characteristics, that it is the same as the

FC1. And the RHRU study shows, the data shows, that FC2 performed comparably to FC1 in terms of tears, in terms of invagination, which are the critical pieces in terms of is it going to rip or is that "softer" outer ring, is that going to be pulled in more frequently than FC1. And the data shows that, no, that the way Mike put together the compensation, that this produce, FC2, does perform physically the same way as FC1.

So now we have to go to the protocol adequacy. And let's just look at the key points and what the data shows for each of the key points. Now, you can say, yes, you know, these points may or may not have caused -- led to underreporting. That's true. You can say that. But we believe that the data suggests something different.

First of all, the FDA is concerned about the coital logs, and we're not relying on the coital logs. We're relying the fact that -- the way we use coital logs and the one-on-one interviews. Our database was the one-on-one interviews. Mags just went through that with you. The coital logs were complementary. They worked both together. The woman had the coital logs to reference, but it was this one-on-one and pulling out what happened, what didn't

happen, and that formed the database for the study.

Next question, recall. In our study, 77 percent of the women reported their first -- reported follow-up within, actually, 29 days, less than 30, 77 percent reported in. If you look at the literature, the studies that Mags and also Colin, because Colin's studies were on Mags' chart, the last four charts, all of those studies, their follow-up visit was four weeks. So 29 days, 30 days, versus four weeks. It's standard.

Now, let's look what did we find. There were 194 failures identified or occurred in 3,800, approximately, 3,800 uses of the female condom. 84 of the 194 female condoms were identified in the interview process, in the one-on-one interview process. 34 of the 84 female condom failures were actually identified in the interview process from women who were using the coital log. So, in essence, even though they were using the coital log, they forgot, didn't put it down, didn't mark it right, and it was the process of the one-on-one interview that identified from those women the additional failures. The one-on-one interviews was a very important aspect to this study in terms of identifying what happened when those women used FC1 and FC2.

I thought another important point you would find interesting, that if you look at the percent of problems identified 30 days -- beyond 30 days, the women came in beyond 30 days, the percent of failures for each mode was similar to the percent of failures that are identified on women who came prior to the 30 days. In other words, they recalled and they remembered what happened regardless of when the interview took place.

Okay. Slippage is not on the coital log. This has been raised as an issue. I think Mags was pretty clear that when this female condom is in your vagina and you are having intimate sex and it gets pulled out, you remember it. First of all, you feel the ring coming out. You feel it. Second of all, you've stopped having sex. I mean, there's this thing that's not where it's supposed to be. I mean, you remember if that happened. And another point, the fact that this happens doesn't -- is so rare. It's a rare occurrence. In our study, there were 12 complete slippages identified, 6 of them complete, 6 partial. And 4 of the 12 were identified beyond 30 days and then, again, recalled, remembered it happened, and it was noted.

Okay. Multiple sex acts on a given day.

There were 1,500 days when a sex act was recorded on the coital log. Approximately 50 percent of those days were multiple sex acts days, so, say, 750 days. 75 multiple sex acts days, a problem was reported, okay? So 75 multiple sex acts days, there was a problem reported.

Now, if we look at the problems that were reported on the coital log, there were a total of 133 problems recorded on the coital log; 47 of those problems were single-sex days. So, in other words, okay, I had invagination, and the slot was there, and I recorded it. But 86 of the 133, or 65 percent of the problems, occurred on multiple sex act days. So if, in fact, the woman experienced two invaginations on that multiple sex acts days, she wrote it down. Women reported what happened to them. They reported it on the coital log whether the slot was there or not.

Now, some women did not, mostly commercial sex workers, did not complete coital logs. Their manager of the hotel, after they had agreed to do the study, forbid them to fill out the coital logs, afraid they were going to scare off the clients. This is, of course, why the one-on-one interviews were really important. They didn't fill out coital

logs, but they sure did report for their interviews, and they sure did remember what happened to them while they reported it. They remembered it, they reported it.

And if you look at the database, and Doug is going to go through this with you in a minute, the coital -- if you look at the database with women with coital logs and you look at the database, women without coital logs, they are the similar findings whether or not they had coital logs.

Commercial sex workers. Commercial sex workers do right now today use the female condom, and they will in the future, and it's really important that they have the female condom as an option for them. And they are a representative group of participants who need to have this product, and we felt that it was important for them to be included in the database to see how they felt about having this -- and how the product performed with them.

FDA suggests that perhaps, you know, because their male condom experience, that that would impact their results of using the female condom, but I think by now you're clear that the use of a male condom and the use of the female condom is completely different. You put it on differently. You take it

off differently, and the failure modes are different. And as, again, no difference between a database with -- that includes commercial sex workers and a database that does not include commercial sex workers.

Blinded. Users and nurses received two sachets. They looked exactly the same, no way to tell. It's not, like, you know, little white pills, however, little white pills in two little packets. They look exactly the same. But FC1 and FC2 don't look exactly the same. FC1 has a seam. FC1 doesn't. So if a woman had been a prior user, she may remember that FC1 had a seam, but of our database, 19 women included had used the female condom at least once prior to this study out of 276, and nine of them did report problems using the female condom. We believe the study was "suitably" blinded. We did the best that we could, given that FC1 had a seam and FC2 doesn't.

So, in summary, we don't believe that a contraceptive study would give meaningful information to justify delaying another five years to get FC2 approved in the United States. FC2 is robust. It's demonstrated by the FC1 comparative study by RHRU. The failure modes and results were comparable. And,

number three, a point that we think, again, is really important, FC1 performed in a similar manner in the RHRU study as it did 16 years ago in terms of failure mode results.

DR. TAYLOR: Good morning, everyone. My name is Doug Taylor. I'm the Director of Biostatistics at Family Health International. FHI has been involved in female condom clinical and epidemiological research for probably about 20 years. It certainly pre-dates the time that I've been there. But, most recently, we were asked to provide some support in the analysis of the clinical failure data from the condom effectiveness study that RHRU conducted.

I don't want to spend too much time on this. I know we've spent a lot of time here already, and Colin Pollard already made a nice description about functionality studies. But, you know, essentially, underlying the concept of a functionality study is that if you had two condoms that had absolutely no difference in their condom failure rates, in terms of modes, that you could get, if not exactly the same, then certainly comparable pregnancy rates.

When we conduct such a study, our interest

lies in assessing what the true differences are in the complete slippage, the failure modes, complete slippage, clinical breakage, invagination, and misdirection rates are between two condom types. Of course, we don't know what those true differences are, so we provide a finite -- we get a finite sample of data, and statisticians compute confidence intervals for those differences, which are simply a plausible range of values for those differences based on the data that were observed in the trial.

One important thing to emphasize is, currently, as well as certainly when the study was conducted, there is no standard for what that acceptable range is. I mean, how close do we -- does the difference in functionality measures have to be in order for us to conclude that a new condom type is not inferior to an existing condom. Hence, so we really are left with making epidemiological and regulatory and procurement decisions based on what we observe in these studies.

You've certainly all seen this before. You're going to see it again. I don't want to spend too much time on it. But these are the primary functionality study results from this crossover functionality trial based on all data in the

database. Key points to notice are these observed -- the observed difference column, column four. Negative values suggest or negative values indicate that the failure rate for the FC2 condom was less than the FC1 condom.

And, of course, more importantly and essential is to look at the confidence intervals for the differences in those rates. And in all instances, we can be highly confident that the true difference in failure rates were no more than, well, in the case of invagination, 1.01 percent. But the take-home message here is that these are all much smaller differences. We have a high degree of confidence that the differences are smaller than anything that's reasonably going to be imposed as a standard in the future, if and when a standard is established. So we really have demonstrated comparable -- the data demonstrated comparable performance in terms of these functionality outcomes.

As Mary Ann mentioned, there's been concern raised about the inclusion of sex workers. Essentially, from my perspective, this boils down to if you enrolled a population of people who are so good at using condoms that they never failed, you wouldn't gain any information in which to assess the

comparability of two condom types.

Of course, if we do observe failures in novice users and we don't observe failures in experienced users, we might jump to the conclusion, and it might be a reasonable conclusion, that experience matters. Hence, enrolling a heterogeneous population, for example, commercial sex workers, is an advantage, so long as we actually obtain some information which we can use to assess the function of the two condom types. It's not a disadvantage.

Nonetheless, if we exclude the commercial sex worker data, what do we see? Well, we see something very comparable. I think you'll find that, overall, the failure rates for FC1 and FC2 are a little bit lower when we exclude the sex workers. In general, the sex workers did have slightly less failure rates, but our conclusions don't change at all. The differences are all about, you know, in the same range, and the confidence intervals are all telling us about the same thing, which is, in this population, excluding the sex workers, we also see a comparable performance of the two condom types.

Another issue, of course, is the accuracy of the condom failure data. The FDA has expressed concern that relying on in-depth interviews rather

than coital logs could have led to misreporting of failure rates. Hopefully, by now we realize that given the complexity of all these failure modes, it really was essential that there be detailed questionnaires/interviews with the participants in order to get an idea of what was really going on with these condom types. Even if misreporting did occur, it seemed unlikely that reports of ever having experienced these types of failures were overly biased.

And, in fact, if we look at the per-woman analysis, instead of looking at the proportion of condoms that failed, we look at the proportion of women who ever experienced types of condom failures, we again see something very consistent, very -- it makes us feel, you know, good about the study, which is we see really no differences, no meaningful differences in the rates of women ever experiencing problems with these two condom types.

I do want to make one little note or comment about effectiveness studies, something to keep in mind, because the FDA has said that they would require a single-arm contraceptive study. We got to keep in mind what such a study would actually provide to us.

As I've said, a functionality study, which was what RHRU did, evaluates the rates of condom failure during actual use. All right. Were the rates of exposure to semen comparable between the two condom types when the condoms were actually used? Effectiveness studies don't do that. Effectiveness studies evaluate pregnancy rates over many months or cycles of what is no doubt typical use. I emphasize typical because the observed pregnancy rates in effectiveness studies are going to be highly impacted by non-use of the condom.

In fact, if you look at the pivotal study for FC1, you can see in the U.S. sites, the perfect-use pregnancy rates, the estimated rate was 2 1/2 percent. Probability pregnancy was 2 1/2 percent at six months, a typical use rate of 12 1/2 percent, all right? So I think if you look at those data objectively, you're going to conclude that the bulk of the pregnancies are not because the condom failed during use but because the condom wasn't used or wasn't used perfectly.

And if you look at the sites from South America, the perfect-use rate estimate was 5 percent at six months and I think 20 percent, or so, at six -- for typical use. So, again, you get this wide

range of results.

In addition, if you do an effectiveness study, these days if we did an effectiveness study, we would have to counsel for the use of emergency contraception if a condom failed or if someone didn't use a condom for sex. And that's going to further shrink any apparent differences in pregnancy rates that you might otherwise observe.

So I think it's unreasonable to think that we could expect true differences in condom failure to translate into detectable differences in pregnancy rates. That's not the same thing as saying are the typical-use failure rates comparable between two arms, or is the typical-use pregnancy rate comparable to an historical control. But if we want to get at the idea of is the condom failing more often and that resulting into more pregnancies, it's highly unlikely that an effectiveness study is going to answer that question.

So, in summary, there is strong statistical evidence that FC2 and FC1 are comparable in clinical performance. Multiple subgroup analyses, for example, excluding commercial sex workers, or if you just look at the first-use period of condoms or just the second-use period of condoms leads to consistent

findings. That makes us feel good about the study. The proportion of women who ever reported clinical failure was also comparable for the two condom types. And, finally, an effectiveness study is unlikely to identify important differences in condom function and their impact on pregnancy rates between FC2 and FC1. Thank you.

DR. LEEPER: So it's my turn to sum up for the Female Health Company and for its product, FC2 PMA. Basically, I think the data -- we believe that the data shows that FC2 is safe and biocompatible, that the failure rates of FC2 in our study are equivalent to the failure rates of FC1, that FC1 performed the same way in this study as it did in the PMA that approved it. And, in summary, we really do believe that the studies that we have submitted in our dossier, in our PMA, are adequate to establish that FC2 is safe and effective.

FC2 already is playing an important role in STI prevention, HIV/AIDS prevention outside of the United States. If FC2 -- if FDA approves FC2, it will increase the access of this product, a woman's method to protect herself, obviously, in the United States and in the rest of the world. And we truly do not believe that an effectiveness study will likely

add to our understanding of the basic performance of the FC2 female condom.

We thank you for listening to our presentation this morning. We look forward to answering any additional questions that you may have now or later, and we thank you greatly for the deliberation that you'll be doing over the next hours on behalf of FC2 and women who need it. Thank you.

DR. CEDARS: Thank you. I'd like to thank the Sponsor for their presentation and ask if members of the Panel have questions. If I could just ask if you have fairly simple questions, that we'll answer them at this time. If they're more complex or extensive, you can go ahead and ask the question, but we may ask the Sponsor to respond after lunch. So if we can start with Dr. Hillard?

DR. GILLIAM: So I appreciated hearing the answers to the questions that the FDA has asked, and we will talk about those sorts of things. I have some questions that I hope there will be data to answer that are not related to the specific questions that are asked but may well be relevant; in particular, issues that might be answered by the questionnaires or the interviews.

So when I talk to my patients about the

female condom, the biggest concern that they have when they try it once is that it's noisy. And so my question is related to any data that might answer the issue of the snap, crackle, pop from the Female Condom 1 --

DR. LEEPER: Right.

DR. GILLIAM: -- that might suggest that Female Condom 2 is preferable to women, and if it is preferable, then would it be used more frequently, more likely to be used. And so I'd just like to ask are there data to answer that particular question?

DR. LEEPER: Yes. Is this -- can you hear me? Is this mike on?

DR. GILLIAM: Yes.

DR. LEEPER: I'm going to ask Mags to completely answer that question, but right off the top, the snap, crackle, and pop that some women report on FC1 use is not reported on FC2. And Mags is going to tell you they have done a whole acceptability aspect that we did not report on today about FC2. Mags, do you want to tell about that?

MS. BEKSINSKA: Yes. Just in the acceptability paper on the study, the noise was mentioned by 2 percent of women using FC1 and 1 percent of women using FC2. And I understand from

them that the material may be -- just the material, what it's made of, may make it less likely to be noisy.

DR. GILLIAM: Thank you.

DR. LEEPER: They also felt that the -- they liked the acceptability of FC2 because it felt more, looks more like a male condom, and they're used to more male condom, and so just psychologically they liked it better.

DR. CEDARS: Okay. Dr. D'Agostino?

DR. D'AGOSTINO: Yeah, I have two quick questions. I enjoyed your presentation, found it very informative. One of the issues that I don't believe you covered was the dropout rate. Depending on how you count it, it's 27 percent. In most clinical trials, a dropout rate of that would be a fatal flaw. Can you talk about why we shouldn't worry about dropout rates here?

And then the other is the per-woman analysis. Do the confidence intervals rule out the 2 percent?

DR. LEEPER: Okay. Mags, why don't you answer the first question, and, Doug, will you answer the second?

MS. BEKSINSKA: Okay. I think our dropout

rate was higher than we normally actually have in studies. In many cases, you know, for the women like commercial sex workers who lived in a hotel, they moved from hotel to hotel. And some of them, I think, were slightly distracted by the fact that they weren't allowed to fill in their quota log in their hotel rooms and then didn't come back to the study.

The students were -- there was one part -- there was the holiday period, but also because we wanted to make sure it was going to be short study. We, obviously, there were women who actually came back once we completed the study, but we felt that they had come back far too long to recall properly the events they had with their condoms. So some women came back after three months, and we actually said, no, it's too late now. So towards the end of the study when we finished, some women came back later than that, and we didn't include them.

DR. D'AGOSTINO: That explains why you might have dropout but doesn't explain the impact on your analysis and conclusions.

MS. BEKSINSKA: I think we did some analysis looking -- we compared the baseline characteristics of those who dropped out and those who continued, and they were fairly similar. I don't

know if Doug wants to make a comment on that.

DR. D'AGOSTINO: Yeah, that's usually not considered adequate.

MS. BEKSINSKA: Yeah, but, otherwise, no, I can't really comment on that.

DR. TAYLOR: Thanks. It's a big -- a very good question. Unfortunately, these studies do tend to suffer from, or oftentimes suffer from high discontinuation rates. The problem in pregnancy studies is really even worse. It's extremely challenging. But in terms of did it impact the results, I believe -- I'm not sure, so I'm not saying absolutely here -- that an analysis was done that restricted -- restricted the analysis to the 201 women who completed both cycles, and you got consistent findings among at least those people who definitely completed both. That, I realize, doesn't fully answer the question, but at least would provide some --

DR. D'AGOSTINO: There were a lot who didn't -- who dropped out right away, never came back even for the first --

DR. TAYLOR: I'm really not hand waving the issue. I realize it's very important.

DR. CEDARS: Is that something that you

could check during lunch? Do you have that data available?

DR. TAYLOR: I could check to see if it is available. If it's not available, it would take a little while for that to be provided.

DR. CEDARS: If it's available, it would be helpful if you could look at that, please.

DR. TAYLOR: Okay. All right. And the second question, in terms of was the difference in proportions of women ever experiencing failures, could we rule out that difference -- be more than 2 percent. Well, one is the 2 percent isn't really -- it may be relative, it may not be relative, because the delta of two percent relates to condom failures, the denominator being the condom.

DR. D'AGOSTINO: I understand that. I'm just --

DR. TAYLOR: Okay. The answer is I don't know because those are correlated, paired data, and I haven't analyzed the data at that level of detail to tell you whether that -- if you analyze it appropriately, accounting for the paired data nature whether it would be less --

DR. D'AGOSTINO: Every other table gives confidence intervals and that one didn't so --

DR. TAYLOR: No, absolutely. The primary outcome was the rate of condom failure, appropriately accounting for the correlation, but we didn't do that analysis for comparing the proportion of women who ever experienced them. So maybe you could do a binomial proportion and assume they're independent because that variance should be higher, and if you found that it was equivalent in that --

DR. D'AGOSTINO: Well, you can -- there's simple test to do it --

DR. TAYLOR: Sure. No, I know it's simple. I don't -- the analysis wasn't done, so I can't give you the answer.

DR. CEDARS: Dr. Padian?

DR. PADIAN: A super-quick question about follow-up, I mean, loss to follow-up. Was it differential by arm? And that's one. And then two other questions. One, I just want to make sure I understand the protocol correctly. When they used ten, got ten, and then they were supposed to come in, was that ten consecutive acts of intercourse, or did you somehow account for the fact that it might have been dispersed over a larger denominator of intercourse?

MS. BEKSINSKA: Yes, it could have been.

So sometimes they didn't use the condom. So we asked them to come back as soon as they had used all of their condoms.

DR. PADIAN: But it didn't have to be consecutively?

MS. BEKSINSKA: No, no.

DR. PADIAN: And did you look at whether that might have made a difference in --

MS. BEKSINSKA: No, I haven't looked at that.

DR. PADIAN: And then my final question is reuse. I mean reuse of the female condom in general, but in particular, for the women that had multiple acts of intercourse on the same day. Do you have any idea whether they might have left the same one in or do they always have a new one?

MS. BEKSINSKA: No, we told them not to reuse it.

DR. PADIAN: Oh, okay.

MS. BEKSINSKA: And in the South African Female Condom Program, which is very extensive, women are told they should not reuse a female condom.

DR. PADIAN: Okay.

MS. BEKSINSKA: It hasn't been an issue in our country. I mean, we tell them not to do that

because there are enough female condoms available to use a new one.

DR. PADIAN: Right. Okay. Thanks.

DR. CEDARS: Dr. Warner?

DR. WARNER: I also have two questions. The first one is the results were presented overall and without the sex workers and were shown to be comparable between the FC1 and the FC2. My question is if you look at it by each population type, so I think it was students, Family Planning Clinic clients, I don't remember what else, did you observe the same thing?

And then the second question is can you give some type of comment on the timing in which the coital logs were completed? So did you have any type of process or validation to be sure they weren't tick-marked right before they came to the clinic, in which case that would underscore the importance of the interview?

DR. LEEPER: Mags, do you want to answer that, and I'll augment. Go ahead.

MS. BEKSINSKA: Okay. Just can you just -- on the one about the ticking, just say that one again?

DR. WARNER: The question was do you have

any information --

MS. BEKSINSKA: Yeah --

DR. WARNER: -- on when the logs were completed. So I had done some of those studies in the early '90s on male condom use and coital logs --

MS. BEKSINSKA: Right.

DR. WARNER: And one of the concerns is that people would check, or complete the logs right before they came in for the visit.

MS. BEKSINSKA: Right. No. We didn't ask them if they'd completed the log at the time of the visit.

DR. WARNER: Um-hum.

MS. BEKSINSKA: So that's something we didn't do, yeah.

DR. LEEPER: They did on the coital log, obviously it says the day, and we've analyzed each coital log and saw how many reported at so many days, but whether or not that number is accurate, we have no idea. And, Doug, I don't think we looked at it by population, did we?

DR. TAYLOR: No, I did not.

DR. LEEPER: No, we haven't --

DR. CEDARS: Did you --

MS. BEKSINSKA: The STI group was much

lower than we had originally hoped because when a woman was an STI client, she had to be treated and to come back. So we only have 20 -- we had slightly more than 50 in some groups. So we would probably not be able to analyze that small subgroup anyway. So because of the 200 couple, the WHO guidelines, those 200 are actually supposed to be analyzed together, so we haven't actually looked at them by subgroup because we feel they're probably too small.

DR. WARNER: Okay. Thank you.

DR. CEDARS: Dr. Sharp?

DR. SHARP: Yes. I had a question about the mitigating labeling, and I just noticed in the two that we have here, 1 has it and the FC2 doesn't.

DR. LEEPER: Right.

DR. SHARP: Is that because that's not packaged for the U.S. or --

DR. LEEPER: Yes, that's correct. The FC2 that you have is what we distribute outside the United States. However, what we are suggesting in our PMA is we think that the drawings that we use on the ex-U.S. package that you have in your hand, that they are really -- it's really important and to put that onto -- we want -- we are suggesting that we move the mitigating labeling we have still kept on

the, you know, proposed labeling for FC2 for the United States, but we have also added those drawings because we think it's really important women see exactly how to put it on as they're opening up the sachet.

DR. SHARP: Sure. Great. Thank you.

DR. LEEPER: Sure.

DR. CEDARS: Dr. Katz?

DR. KATZ: A couple of technical. Is this on?

DR. CEDARS: Can we make sure his mike is on?

DR. LEEPER: No, I don't think it is.

DR. KATZ: A couple of technical questions having to do with the material in FC2. The thickness of FC2 is about the same as the thickness of a male condom -- thank you. The material has more in common, in terms of its chemical composition and structure, with the latex in a male condom than it does with the polyurethane in FC1. What do we know about the mechanical properties of a sheet of this material versus -- at that thickness compared to a male condom? And can we draw any inferences about shelf life as well?

DR. LEEPER: Mike? Mike and Bill?

MR. POPE: What do we know about the mechanical properties of the sheath -- the male condom?

DR. WARNER: Well, does the FC2 -- how do the tensile properties of FC2 compare with the tensile properties of a latex male condom.

MR. POPE: Frankly, I can't describe that to you. I can tell you FC1 versus FC2, but not FC2 versus a male condom. But I have somebody with me that can.

DR. LEEPER: Hi, Bill.

MR. POPE: Bill, would you like to step up?

DR. POTTER: Thank you. I'm Bill Potter. I'm a consultant to the company. If you look at the film of the two materials, basically, the tensile strength of the nitrile latex film is going to be about the same as the natural rubber latex film, possibly slightly below, say about 2 or 3 percent. Elongation is going to be substantially lower. So we're looking at elongations, from memory, I think about 600 percent versus the latex film, we're looking around 800 to 1,000.

And the reason why nitrile was selected is because those -- the characteristic of elongation was closer to the polyurethane film it was replacing in

FC1.

DR. WARNER: Right, right.

DR. POTTER: On stability, the thing about nitrile latex is it's much more stable than NRL latex. And I think we checked on the stability studies that have been done. We're not seeing any change at all over up to a year at 50 degrees centigrade. We've got one year at room temperature, 30 degrees centigrade, no change, see. The two year results will be coming out very shortly now. We're not expecting to see any difference. So it's much more stable, thermally stable, oxidatively stable than latex films. And, also, it's got much better solvent resistance. So it's compatible with a much wider range of potential lubricants than NRL films.

DR. WARNER: Thank you.

DR. POTTER: Okay.

DR. CEDARS: Dr. Ramin?

DR. RAMIN: I had a couple of questions. Is that all right?

DR. CEDARS: If they're --

DR. RAMIN: Okay. The first one is you had mentioned that you instructed the patients not to use the FC2 again, but I was wondering if at the one-on-one interview, if you specifically asked them if they

used it multiple times?

Okay. The second one is it was mentioned that 22 million FC2s have been distributed. Do you have any data as to whether or not there have been any allergic reactions or is that only seen with the natural rubber latex?

DR. LEEPER: We have received no reports at all on any problems in terms of irritation or use at all in terms of FC2. UNFPA has told us that they are very pleased with how FC2 is being accepted by the women. They feel comfortable with it. They like it a lot. They're very happy with it. We haven't had a problem.

DR. RAMIN: And I had one other question, and that is it was interesting that you said that commercial sex workers use the FC, but in the report, 88 percent were new users. So I was wondering if you could comment on the acceptability by commercial sex workers and why they're not using it as often as we would think.

DR. LEEPER: Well, I was talking about two different points. When I said that commercial sex workers use FC, I'm talking about FC1. They are currently using FC1. And outside the United States in countries where they're being distributed,

obviously, they're being distributed to commercial sex workers. The 88 percent in our study were new users to FC2. They had -- excuse me, FC1. Sure --

MS. BEKSINSKA: Just to say that in the years of when we conducted the study, the female condom had been introduced into South Africa but only in limited sites, and it was mainly focused on family planning sites. So there was probably no more than ten in the whole of KwaZulu-Natal Province. There was no focus, and some countries have a focus on high-risk groups like sex workers and adolescents, whereas in South Africa, we predominantly have moved towards a general public sector approach. And so the sex workers are often very reluctant to come to a clinic. In fact, even for the study, they wanted to be seen in the hotel because they feel they, you know, they're not being treated correctly. So it definitely hasn't been aimed at any high-risk group in South Africa.

DR. CEDARS: Dr. Davis?

DR. DAVIS: I have some questions about the subgroups. And Table 10 from the FDA executive summary suggests that there was much more breakage in the FC2 if you had more than one coital episode a day. And if I understood right, that was half of

your population. So there were three breaks with the FC1 and 9 breaks with the FC2 with a subgroup of failures greater than one condom a day. And I wondered what your explanation for that was, and does this highly represent one's initial subgroup of your population? That's Table 10 on the executive summary.

DR. CEDARS: Page 43.

DR. TAYLOR: I'm not going to -- to answer all those questions, but I do have one question in response, and it's for the FDA who generated the table. They had nine failures. I'm assuming that has to include partial because the total number of clinical failures observed was only eight.

DR. DAVIS: No, that's breaks, breaks.

DR. TAYLOR: I'm sorry, breaks, yeah. So I'm not sure. I guess I would need clarity as whether the FDA when they generated that table was including non-clinical breaks, and I don't know the answer to that question.

DR. CEDARS: Perhaps the FDA can address that in their presentation this afternoon. Dr. Gilliam, and then I think after that, we may take a break for lunch and then come back if there are additional question. Dr. Gilliam?

DR. GILLIAM: I had a couple of questions about the coital log. If after the demonstration, it looks like you could have misdirection followed by invagination. Would those be counted as two separate events or did you ask people to choose which one? So was it different and how was it analyzed. And --

MS. BEKSINSKA: Okay.

DR. GILLIAM: And I have just one other question.

DR. CEDARS: Yeah.

DR. GILLIAM: On the coital log, if someone had more than one act of intercourse and used more than two condoms that day, would you be able to differentiate between whether they were having problems with each act and each condom or whether they used multiple condoms at one act and had problems at those episodes? I'm having a little trouble figuring out what the denominator is.

MS. BEKSINSKA: Okay. Just on your first one, we did actually record when there was more events, more than one event per condom. Normally, studies historically use a hierarchical system where breakage is worse. And so if someone has an invagination or in male condoms, if there's a slippage and a breakage, they only count the

breakage.

Now, I don't know how many people agree or disagree with that, but I think that all of them should be counted, especially with a female condom, where many events are linked. So we had one invagination followed by a breakage. The break occurred when she was trying to pull the condom out of her vagina. We had a misdirection that turned into an invagination. And I think when you're recording events, often, the woman, it's quite hard to find -- maybe one event started as a misdirection and it turned into something else.

So I personally think it's important to try and record as many events as possible, even if it was the same condom. And women will say that to you. They say, well, this started it and then it broke. So we recorded it in that way.

Onto your second point, we have --

DR. LEEPER: Wait, wait, wait, so the answer is, yes, they recorded both.

MS. BEKSINSKA: Yeah, so we recorded both. And your second point is on the log. So if, for instance, women had two acts of intercourse and two condoms, we would, yes, I think we assume that the -- often a woman would have one act of intercourse and

they would say they used two condoms because one condom, maybe there was a problem and they used a second one. So we would record it like that. And, also, if the woman had used on the same day two condoms and there was two events, we would ask her to write the number down. So we have got coital logs where we've got more than one condom or more than one event written on the same day.

DR. GILLIAM: Well, my question is two acts of intercourse and three condoms, and do you know how -- because some of this is the recall and --

MS. BEKSINSKA: Yeah.

DR. GILLIAM: -- able to interview. But once you enter it as multiple sex acts and multiple condoms, three, four condoms --

MS. BEKSINSKA: Yeah.

DR. GILLIAM: Are women really a month later able to recall those events is my -- is really what I'm getting at, and can you differentiate between those?

MS. BEKSINSKA: I'm not sure if we could have actually --

DR. LEEPER: Well, well --

MS. BEKSINSKA: Sorry.

DR. LEEPER: Well, the answer to that is

recall at that point, whether it's multiple sex acts on a given day, the only way you know if it was multiple -- we know that it was multiple sex acts on a given day is because they have recorded it on the coital log. So all the multiple sex acts information that we got is because they recorded the multiple -- because we have that on the coital log.

DR. GILLIAM: Right.

MS. BEKSINSKA: But we would check -- so, for instance, if a woman had one act of sex and she used two condoms, we would ask her then, "Have you missed an act of sex or did you use the two condoms?" So if the two figures didn't match, especially if there was more condom than acts of sex, we used to say, "You have three here and two here." So we would ask about the discrepancy. And, in some cases, a woman would say, "Well, this condom, I pulled it out and we used another one." And so that was --

DR. GILLIAM: But it's conceivable that a woman is trying to remember what happened with multiple condoms --

MS. BEKSINSKA: Yeah.

DR. GILLIAM: -- over multiple events and whether more than one thing happened with a single condom.

MS. BEKSINSKA: Yes, so that could be, yeah. There's definitely a recall issue.

DR. GILLIAM: Yeah.

MS. BEKSINSKA: Could be for some people.

DR. CEDARS: So for those of you who weren't able to ask questions this morning of the Sponsor, if you could, please note those. After lunch, we'll do the FDA presentation, and then prior to the deliberation, we'll come back for questions for the Sponsor.

I just wanted to note that our consumer representative, Diana Romero, was unable to be here because of unforeseen circumstances and that just to remind everyone that we will reconvene in this room, and I would like to say in 45 minutes. So at about 1:05.

Please take any personal belongings you may want at this time because the room will be secured by FDA staff during the break, and you will not be able to come back in until the room is open and we reconvene. And I want to remind all Panel members that there should be no discussion of the PMA during the break. And there is a separate room reserved for lunch for the Panel members in the restaurant, in the hotel restaurant.

(Whereupon, a lunch recess was taken.)

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

(1:05 p.m.)

DR. CEDARS: 1:05, and I'd like to call this meeting to order, and we will now hear the FDA's presentation. And the first FDA presenter is Ms. Elaine Blyskun, the team leader for this PMA. All right. We're having a little computer problem, so --

MS. BLYSKUN: While we're waiting for the computer, Dr. Corrado could address the one question that was posed for FDA.

DR. CEDARS: Okay. Thank you. And this was about your Table 10 on Page 43?

DR. CAREY-CORRADO: Right. That's correct. So as I understand it, there was a question raised as to what was the source of the numbers on the failure modes in Table 10, and it is a great question. It reflects close examination of the numbers that are appearing throughout the PMA.

So here is how this table was constructed. We had identified the issue of the potential that if more than one event, sexual event, had happened on a particular day, more than one condom was used, that the coital log wouldn't be able to reflect all of the failures that could potentially have happened. And

so the left-hand column on this Table 10 indicates the minimal number of failures. We say minimal number of breaks, minimal number of invaginations and misdirection, and, also, the last item is the minimal number of combination failures.

Okay. These data are all derived from coital logs. So whereas the study data and the conclusions from the study are based on what was reported in the questionnaires, this is not that same database. This is the coital logs, per se.

So under the minimal number of breaks, we calculated that by -- we gave the Sponsor a question, and they told us, provided a lengthy list of subject numbers and the types of failure events that occurred on particular days. For breaks, if you do not count breaks that occurred as part of a combination failure with another event, you got the numbers that you see here. So, number one, these data are based on just outcomes as reported on the coital logs and only for days where more than one event, coital event, took place. And, number two, for the first three type of failures where you see minimal number, that does not include failures when more than one failure occurred on the same day. That is reflected in the bottom line.

So the minimal number of breaks for FC1 was three. That's the minimal number. There were two breaks that occurred as part of combination failures. Those are reflected in the bottom line.

And, so, again, this is probably symptomatic of I guess the extent to which FDA refused data and really were picking apart data in the study to try to get comfortable with the fact of how the coital logs were designed. And so that's the best explanation I can give you in terms of where those numbers came from.

DR. TAYLOR: Thank you very much. I just have one -- my question was --

Sorry. The trouble I had was understanding whether that included just clinical breaks or also non-clinical breaks?

DR. CAREY-CORRADO: That is a great question. This is the data sheet that I got from the Sponsor, and breaks are identified as during use. And so I am guessing that those are clinical breaks. And I can only go from --

DR. TAYLOR: That's fine.

DR. CAREY-CORRADO: -- what we, yeah, what we received.

DR. TAYLOR: Thank you.

DR. CEDARS: Okay. Dr. Whang, is the FDA now ready?

DR. WHANG: Yes.

MS. BLYSKUN: Okay. So, good afternoon. My name is Elaine Blyskun, and I'm the lead reviewer for this PMA. I'd like to begin by introducing the PMA review team. The individuals on this slide contributed to the review of the device and will be speaking to you today.

These team members conducted reviews in areas such as chemistry, biocompatibility, microbiology, and prostate-specific antigen. These individuals contributed to the review of the labeling and the inspection of the study and manufacturing sites.

This is an outline of FDA's presentation. I will begin with an introduction and the pre-clinical review. This will include a discussion on the physical differences between FC1 and FC2. Julia Corrado will discuss the clinical review, which includes FC1 contraceptive effectiveness studies, and the RHRU study, the clinical study for this PMA. Statistics will be covered by Zhiwei Zhang, and Hesha Duggirala will discuss epidemiology review of FC1 STI studies and the purpose of a PMA post-approval study.