FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY

DEVICES PANEL

OPEN MEETING

TUESDAY
DECEMBER 7, 1999

The meeting was held at 9:00 a.m. in Salons F and G of the Gaithersburg Marriott Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, MD, Dr. Henry C. Nipper, Chairperson, presiding.

PRESENT:

HENRY C. NIPPER, Ph.D.            Chairperson
MICHAEL P. DIAMOND, M.D.          Consultant
JAMES EVERETT, M.D., Ph.D.        Consultant
BEVERLY HARRINGTON-FALLS, M.D.    Member
ROBERT L. HABIG, Ph.D.            Industry Rep.
JANINE E. JANOSKY, Ph.D.          Consultant
EMILY KOUMANS, M.D., M.P.H.       Consultant
DAVIDA F. KRUGER, M.S.N.          Consumer Rep.
BARBARA R. MANNO, Ph.D.           Member
NADER RIFAI, Ph.D.                Consultant
ARLAN L. ROSENBLOOM, M.D.         Member
THOMAS V. SEDLACEK, M.D.          Consultant
CARMELITA U. TUAZON, M.D.         Consultant
ALSO PRESENT:

VERONICA J. CALVIN, M.A.          Executive Secretary
STEVEN I. GUTMAN, M.D., M.B.A.    Division Director

FDA PRESENTER:

JEAN M. COOPER, M.S., D.V.M       FDA Presenter

PUBLIC ATTENDEES:

JAMES C. CAILLOTTE, M.D., FACOG, FACS
JOEL FADEN, Ph.D.
JANICE I. FRENCH, C.N.M, M.S.
SUBIR ROY, M.D.
THOMAS M. TSAKERIS

GUEST PRESENTER:

JANE R. SCHWEBKE, M.D., FACP
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CHAIRPERSON NIPPER: Is the FDA staff ready to go here and all the visual and audio people ready to go? Good morning, I'm Henry Nipper and I'm the Chair of this panel and I'd like to welcome you to our panel meeting. In this agenda we'll discuss the recommendations on an over-the-counter process for measuring the vaginal pH. The discussion will include appropriate claims, designs to support claims, performance expectations and labeling.

At this time I'd like to call on Ms. Veronica Calvin, the Executive Secretary to the panel, for opening remarks.

MS. CALVIN: Good morning. For the benefit of those who were not here yesterday, the Committee met and discussed the pre-market approval application for the GlucoWatch Biographer, a device indicated for frequent unmedic and uninvasive monitoring of glucose levels in adults with diabetes. After our very lively discussion, the panel unanimously recommended approval with conditions.

At this time I'd like to formally introduce the Chairman, Dr. Nipper. Dr. Nipper is Assistant Dean for Admissions at Creighton University
School of Medicine, Associate Professor of Pathology at Creighton, and Associate Director of Clinical Chemistry and Toxicology at St. Joseph's Hospital in Omaha, Nebraska. I would also like to acknowledge some guest panelists.

We are pleased to have Dr. Jean Janosky, the Statistician from the Dental Products Panel, and Dr. Michael Diamond from the Obstetrics and Gynecology Devices Panel. Drs. Carmelita Tuazon and Dr. Tom Sedlacek from the Microbiology Devices Panel and Dr. Emily Koumans from our sister agency, the Centers for Disease Control and Prevention. I almost said Centers for Devices.

We were also supposed to have present Dr. Penny Hitchcock from NIH, but she's ill and could not be here today. We will also have a speaker, Dr. Jane Schwebke. We are pleased to have her. She is the Associate Professor of Medicine and Epidemiology in the Department of Medicine and Infectious Diseases and School of Public Health at the University of Alabama at Birmingham. Now I'd like for the panel members to introduce themselves, beginning with Dr. Robert Habig.

DR. HABIG: Hello, good morning. I'm Robert Habig, I'm the Vice President of Clinical Operations at Cytometrics, Inc. and I'm the non-voting
Industry Member of the panel.

MS. KRUGER: Good morning, I'm Davida Kruger, I'm a certified Nurse Practitioner in the area of diabetes at Henry Ford Health Systems in Detroit Michigan. And I'm the Consumer Representative.

DR. EVERETT: I'm James Everett. I'm Medical Director of Medicine, Memorial Health Care.

DR. MANNO: I'm Barbara Manno, I'm Professor of Psychiatry at the Louisiana State University Health Sciences Center in Shreveport, Louisiana. And I'm Professor of Psychiatry and Co-Director of the Clinical Toxicology Laboratory for the hospital.

DR. SEDLACEK: I'm Thomas Sedlacek. I'm a practicing gynecologist. I hold faculty positions at Hanneman University and the Philadelphia College of Osteopathic Medicine.

DR. HARRINGTON-FALLS: Good morning, I'm Beverly Harrington-Falls, practicing Ob/Gyn with Cornerstone Healthcare in High Point, North Carolina.

DR. DIAMOND: My name is Michael Diamond, I'm the Kamran Moghissi Professor of Obstetrics and Gynecology and Director of the Division of Reproductive Endocrinology and Infertility at Wayne State University in Detroit, Michigan.
DR. TUAZON: I'm Carmelita Tuazon from the George Washington University Medical Center. I'm Professor of Medicine and a member of the Division of Infectious Diseases.

DR. KOUMANS: I'm Emily Koumans, Medical Epidemiologist with the Division of STD Prevention in the Epidemiology and Surveillance Branch.

DR. RIFAI: I'm Nader Rifai. I'm Associate Professor of Pathology at Harvard Medical School and Director of Clinical Chemistry at Children's Hospital in Boston.

DR. JANOSKY: Janine Janosky from the University of Pittsburgh School of Medicine, a biostatistician.

DR. ROSENBLOOM: Arlan Rosenbloom, Distinguished Service Professor Emeritus in Pediatrics, University of Florida. I'm Director of Children's Medical Services for the State of Florida.

DR. GUTMAN: I'm Steve Gutman, I'm the Director of the Division of Clinical Laboratory Devices, FDA.

MS. CALVIN: Thank you. I will now read the Conflict of Interest Statement. The following announcement address conflict of interest issues associated with this meeting and is made part of the
record to preclude even the appearance of an
impropriety. To determine if any conflict existed the
Agency reviewed the submitted agenda and all financial
interests reported by the committee participants. The
Conflict of Interest statutes prohibit special
government employees from participating in matters
that could their or their employers financial
interests.

However, the agency has determined that
participation of certain members and consultants, the
need for who's services outweighs the potential
conflict of interest involved, is in the best interest
of the government. A waiver is on file for Dr. Michael Diamond's interest and a waiver has been
granted to Dr. Arlan Rosenbloom for his interest in
any firm at issue that could potentially be affected
by the Committee's deliberations.

The waivers allow these individuals to
participate fully in today's deliberations. Copies of
this waiver may be obtained from the agency's freedom
of information office, Room 12-A-15 of the Parklawn
Building. We would like to note for the record that
Dr. Jane Schwebke, who is a guest speaker today, has
acknowledged previous related interests in the firm at
issue. We would also like to note for the record that
Dr. Koumans, who is a guest, has acknowledged a related interest in the firm at issue.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that all persons making statements of presentations, disclose any current or previous financial involvement with any firm whose products they may wish to comment.

I'll turn the meeting back over to Dr. Nipper.

CHAIRPERSON NIPPER: Thank you. As our first item on the subject matter agenda, we're to hear a presentation from Dr. Jean Cooper, who is the Branch Chief with the Center. Dr. Cooper, welcome.

DR. COOPER: Good morning, as Dr. Nipper stated, I am Dr. Jane Cooper, Chief of Clinical Chemistry and Clinical Toxicology Branch in the Division of Clinical Laboratory Devices. I will present a brief overview of vaginal pH devices, some of the challenges we are facing, pre-market review considerations for home use of in vitro diagnostic
devices and questions for panel consideration. FDA has seen an increased interest to market over-the-counter devices that measure vaginal pH.

These devices have been promoted for a variety of indications such as diagnosing or aiding in the diagnosis of bacterial vaginosis, parasitic infections or trichomoniases, and/or vaginitis. And they would be available for use by pregnant and non-pregnant women, whether symptomatic or asymptomatic. To use these tests, women would add a vaginal specimen to the device or hold the device against their vaginal wall for a few seconds, then compare the color produced on the pH paper to the color chart provided in the kit. Certain colors, such as blue, correlate to optimum pH levels, which could be indicative of some abnormal vaginal condition. FDA to date has cleared two devices for the measurement of vaginal pH as an indication of an abnormal vaginal condition. However, both have been intended for use by health care professionals only.

Testing in this study provides for the interpretation of pH results in the context of medical history, a physical exam and/or other diagnostic procedures. Limitations of the test are well understood, however, diagnosis of vaginal infections,
even in these environments, can often be challenging.

Another issue to consider is that although changes in vaginal pH are associated with a variety of disease conditions, the association between disease states and the pH reported are not strong.

And analysis of three pivotal studies were performed by one sponsor looking at bacterial vaginosis, vaginitis as a diagnostic endpoint. Using a pH cut-off of approximately 4.5 or 4.7, the following performances were observed. Then using conservative values of reported prevalences, the positive predictive values and negative predictive values were recalculated and the results are shown in this table.

Based on the results, there is a 51 percent probability that symptomatic women who test positive with these tests, will actually have some vaginal disease of a bacterial nature. When you look at the asymptomatic population these tests would be an even less strong predictor of bacterial vaginosis. For example, in women who test positive, the results do provide assurance that with a negative vaginal pH test result, say less than 4.5, it is likely that a bacterial or parasitic infection does not exist.

FDA expects that these numbers are a
reasonable reflection of likely device performance in the general population. These are the types of issues that are raised during the pre-market review and special considerations must be given to devices intended for home use. FDA's approach toward regulation of these types of products was first outlined in 1988, put the publication of the guidance document entitled, "Assessing the Safety and Effectiveness of Home-Use In Vitro Diagnostic Devices: Draft Points to Consider Regarding Labeling and Pre-Market Submissions.

The document outlines three key parameters in FDA's review of home-use devices. First, the tests when used in the hands of lay users must produce results equivalent to those expected in the hands of professionals. Secondly, the test results must be interpretable by lay users. Third, the benefits of use must outweigh the risks. Documentation of the first point requires field studies designed to mimic real-world use.

Data sets from lay users are required to demonstrate key performance parameters, such as accuracy. Documentation of the second and third points requires a clinical evaluation of the proposed test and an intense, some might say excessive, review
of proposed labeling. FDA's review of the merit of a
home test takes into account the benefit versus the
risk of having home access to test results.

A major issue in this evaluation is
whether information can be clearly communicated to lay
users and would lead the users to actions that promote
health and minimized harm. Guidance is available.
The guidance document on labeling of home-use devices
has been published by the NCCLS. This document
includes information on techniques for evaluating the
reading level of a package insert. FDA requires these
products to be targeted at a seventh grade reading
level.

The NCCLS document also includes
information on how test reliability can be reported in
a manner understandable by lay users. FDA has also
guidances on labeling of home-use devices, one being
the 1988 Points to Consider, previously mentioned and
the Write it Right manuscript. Although home-use
laboratory tests have been marketed in the United
States for more than 20 years, these represent a
relatively small number of test types.

Until the end of 1996, home-use devices
included only seven categories of tests. We expect
continued growth of the number and scope of products
offered for home use, particularly as technologies improve and with the increase in health consciousness of the general public. However, it is our mission to protect the public health and we must ensure the safety and effectiveness of these in vitro diagnostic products.

You will be hearing from several public speakers and invited guests, Dr. Jane Schwebke. And as you listen to their presentations, please remember the following questions in which we seek your specific input. Question 1, are there sufficient data demonstrating an association between the vaginal pH and various states of vaginal disease to allow use of such a product in an over-the-counter setting? If not, what additional studies would be needed?

Question 2, what intended uses are appropriate for an over-the-counter device for measurement of vaginal pH? Two examples are as follows. To monitor for recurrence in women with a history of documented recurrent vaginal infections. For use in symptomatic women to determine pH to distinguish between alkaline and non-alkaline vaginal infections. If non-alkaline, to direct use of anti-fungal creams, or if either alkaline or non-alkaline, recommend that they see their doctor.
Should the device be used with pregnant women? Would any additional testing be necessary for pregnant women? What labeling is appropriate for such devices? How should the performance be captured in the labeling? What limitations should be included in the labeling? And should the labeling be written similar to an educational brochure? What risks are associated with having these devices available over-the-counter? And do the benefits of over-the-counter use outweigh the risks?

We thank you for your attention to this important matter. The Review Team assigned to this product would be happy to answer any of your questions.

CHAIRPERSON NIPPER: Thank you. I have a brief question that doesn't have to be answered now but I would like to know it a little bit later, if we could. On the slide where you did some recalculation on the analysis of three pivotal studies, you said that there were, you conservatively estimated prevalence. But I thought maybe the staff could, during the day, provide, if you don't have that now, what prevalence you assumed in the populations? Thanks.

DR. COOPER: Let me get back to you.
CHAIRPERSON NIPPER: I just want to see a little bit about how many false positives we deal with in a couple of the cases. Thanks. Thank you very much for your presentation, Dr. Cooper. At this point -- okay, yes. Identify yourself, too.

DR. KOUMANS: Yes, Emily Koumans from CDC. There's, on Question Number 1 it says are there sufficient data demonstrating an association? And I'm wondering if there's any guidance or whether this is something that is formulated as we go in terms of what sufficient data is?

CHAIRPERSON NIPPER: I think we're going to formulate that as we go and that's part of our job as the panel to figure out whether the data are sufficient. I think we'll have plenty of opportunity today to come to that conclusion. I know, I'm sure many of us who are not intimately familiar with this topic are going to be answering the same question. Any other things that the panel would like to remark on before we start the open public hearing?

Okay, I'm a little early on the open public hearing, does that present a problem? Okay. This is the part of the day when we're going to hear from public attendees who contacted Ms. Calvin prior to the meeting. These individuals are going to
address the panel and present information relevant to
the agenda. I will remind you if you don't
voluntarily do it, to tell us whether you have any
financial involvement with the manufacturer of the
product being discussed or with their competitors.

And the first speaker is Thomas Tsakeris.

MR. TSAKERIS: Good morning, Mr. Chairman,
Madame Executive Secretary, Dr. Gutman and Members of
the FDA Panel, and other FDA staff. I am Tom
Tsakeris, a Regulatory Consultant for PhemTek. I am
being paid for my appearance here today, I have no
other financial interest in the company. PhemTek is
of course a company that has developed the vaginal pH
test intended for over-the-counter use.

As a former employee of 18 years with
FDA's Division of Clinical Laboratory Devices, I would
like to speak to you this morning about the scientific
and regulatory criteria FDA has traditionally applied
to the pre-market evaluation of proposed new over-the-
counter in vitro devices or IVDs. And also to relate
this criteria to evaluation of a proposed over-the-
counter vaginal pH test.

Now, like other prescription use IVDs,
over-the-counter home tests can be categorized into
three major groups. They're, of course, diagnostic
tests, such as those for testing urine and pregnancy. Screening tests such as those for testing stool for traces of blood that may be indicative of colon cancer. And finally tests used to monitor an already diagnosed disease or condition, such as the home blood glucose monitors for diabetics which of course this panel is now more than intimately familiar.

A very important consideration to the approval of over-the-counter in vitro diagnostic devices is the prior demonstration of its clinical utility, its prescription or professional use products. This is certainly the case with vaginal pH test devices, which of course you have, Dr. Cooper has mentioned the clearance of already a couple of devices for this purpose.

Vaginal pH is considered to be a key criterion of the established Amsel’s criteria for differential diagnosis of bacterial vaginal infection. May I have the first overhead, please? In their evaluation of an OTC in vitro diagnostic, FDA considers, of course, the risks and benefits of the test in terms of intended use, conditions for use, the target user, the patient population and of course product performance characteristics.

In particular, the FDA considers whether a
product label and other sources of user information fulfill these, fulfill the requirements for adequate instructions for use. In contrast to non-home-use tests, the need to ensure adequate instructions for use has particularly important implications for OTC tests with regard to the target user and target patient population, since these are usually one in the same.

The basic FDA approach then, is to determine whether the benefits of having OTC diagnostic tests significantly outweighs any risk for its use. The next overhead. What then, are the criteria that FDA applies in assessing risks and benefits of over-the-counter tests? As Dr. Cooper mentioned, FDA has published or referenced guidance documents that define requirements they consider in their assessment for both risk benefit and the adequacy of instructions for use.

This morning, I would like to focus the panel's attention on the FDA document to which you've already been introduced, "Assessing the Safety and Effectiveness of Home-use In Vitro Diagnostic Devices: Draft Points to Consider Regarding Labeling and Pre-market Submissions." This document addresses issues about risk benefit, performance and labeling of over-
I would like to focus on the portion of this document that addresses specifically risk benefit issues in the context of a proposed over-the-counter test for vaginal pH. Next overhead. The first benefit question posed by FDA is, what is the clinical benefit of the test to the patient or society in terms of screening, diagnosis or monitoring the particular disease or condition or risk factor? Next overhead.

As the panel is aware, vaginitis is a significant public health concern resulting in ten million office visits among women annually. Often serious vaginal infections go unnoticed as many women with such infections are asymptomatic. The causes of vaginitis may be a result of bacterial, parasitic or yeast infections. Elevated vaginal pH is a risk factor often associated with bacterial or parasitic vaginal infections that cannot be readily recognized by the average women.

While most women associate vaginitis with yeast-based infections, a significant number of infections are of bacterial origin, such as bacterial vaginosis or BV, a particularly serious form of vaginitis that is asymptomatic approximately 50 percent of the time. BV has been found in ten to 25
percent of women in general obstetrical and
gynecological clinics and in up to 64 percent of women
attending STD clinics.

Laymen and consumers can clearly benefit
from use of a home vaginal pH test, as it would serve
as an additional objective aid in presumptively
detecting bacterial or parasitic vaginal infections as
maybe evident from the appearance of other symptoms
associated with such infections. For example, vaginal
pain, itching, malodor and discharge. These symptoms
are commonly recognized by women, due to their overt
physical effects and because they significantly
influence a woman's sense of well-being. Next
overhead, please.

The next question the FDA asks sponsors to
address is, what are the benefit to the consumer or
society of having the test available for home use as
opposed to having the test performed only by health
care professionals. Next overhead.

The benefits of making available a vaginal
pH test as an OTC device is consistent with the
existing public health measures regarding the needs of
women who have vaginitis. As you are aware, the FDA
has approved OTC medications for antifungal vaginal
infections. However, since most women cannot
currently test for any specific cause of their symptoms, for example, infections by yeast or bacteria or parasites, many women inappropriately self-treat with an OTC antifungal medication.

Indeed, the FDA raised this very concern during a June 1990 meeting of the Fertility and Maternal Health Drugs Advisory Panel that reviewed the OTC antifungal medication marketing application. The panel acknowledged that this was a potential risk, but concluded that the benefits of making available the OTC medication outweighed the risks. In the nine years since the approval of these medications, the fact that women will frequently self-treat inappropriately has been reported to be as high as 70 percent.

Making available an OTC vaginal pH test will help reduce inappropriate use of OTC medications for the treatment of non-yeast vaginal infections. Women will be better able to evaluate their vaginitis with regard to the source of infection and make better decisions about the appropriateness of antifungal self-treatment and the necessity to seek advice from their physician. The serious obstetric and gynecological consequences of untreated or unproperly treated vaginal infections reported in the literature
and to be discussed by the speakers to follow, further support the need and benefit of OTC vaginal pH tests.

And now let's turn to the possible risks that may be associated with the use of OTC vaginal pH tests. Next overhead. In their guidance documents, the FDA inquires, what is the impact of the user or to society of a false positive or a false negative test result, for example, in terms of user follow-up or adverse medical conditions? And what are the risks to the user or society in terms of delay in obtaining a professional examination if a proposed home-use IVD that is intended for use on symptomatic subjects gives a false or equivocal result? Next overhead.

Now let's first examine the conditions that may contribute to a false test result. A false-positive result would occur when a vaginal pH test gives a reading suggestive of bacterial or parasitic infection, when in fact no bacterial or parasitic infection exists. A false-negative test result would occur when the OTC vaginal pH test gives a reading not suggestive of bacterial or parasitic infection when in fact a bacterial or parasitic infection exists.

Probable follow-up actions and medical implications would likely be based on whether the woman is inclined to self-treat or not with the OTC
antifungal medication and whether the woman is performing vaginal pH testing because she is symptomatic for vaginitis or she is testing to assess vaginal health.

Time does not permit a detailed discussion of all the various risk-based scenarios. A full risk/benefit analysis was provided in the white paper presented to FDA by PhemTek last year and may have been sent to you as way of background for this meeting. However, I would like to address a few noteworthy scenarios during my remaining time.

A female consumer with signs and symptoms of vaginitis or who has had a history of vaginitis and desires to monitor herself for recurrent infection and who obtains a positive vaginal pH test result, would be directed by product labeling to consult your physician and report the result. The physician might advise re-testing at home or schedule an office visit for a follow-up examination. Given that a positive vaginal pH test could either be a true positive test or a false-positive test, a woman consumer who is inclined to self-treat might take the following actions.

A, she might not self-treat, but instead consult her physician. She could self-treat and
consult her physician. She could self-treat without consulting her physician, or she might not do anything at all. In Case A, the risk of a vaginal pH false-positive test would be that a woman consumer who would otherwise self-treat and benefit from self-treatment might delay this action should the physician decide to schedule an appointment for further examination.

However, given a vaginal pH test with acceptable performance characteristics, this would be minimized. Moreover, the health risk of a false-positive vaginal pH test would be no greater than for women consumers who are not inclined to self-treat, but instead consult their physicians. In Case B, the risk of a false-positive pH test would be minimized as the woman consumer may very well have benefited from the OTC anti-yeast medication, and by consulting her physician as to her health status.

In the unlikely event of Case C, in which the woman consumer would ignore the test result and product labeling and self-treat anyway, a false-positive test would perhaps have little impact. Ironically, self-treating might actually be beneficial as the vaginitis may in fact be due to a fungal infection. Finally, Case D, as with Case C, should be rare if it occurs at all.
Since it is unlikely that an action-oriented woman consumer would invest in the cost and time of an OTC test and then disregard the test result, particularly if the result is positive, suggesting a vaginal abnormality. Next overhead. Now let's look at some of the possible outcomes in the false-negative over-the-counter vaginal pH test. Once again we can look at risk scenarios based on self-treat behavior.

In the first situation, a consumer who is inclined to self-treat might do so in the face of a false-negative vaginal pH test result believing that she has a fungal infection for which self-treatment is warranted. The main risk would be similar to that of many women today who are self-treating themselves based solely on symptoms for a non-existent yeast infection.

In the second situation, a consumer who is not inclined to self-treat uses an over-the-counter vaginal pH test and obtains a false-negative test result. An expected outcome is that she would consult her physician as directed in product labeling and the decision to self-treat or be treated by her physician would occur after consultation or follow-up examination in the physician's office.
In either case, the impact of a false negative vaginal pH test, should it occur, is minimized as the consumer would be under physician's care and no delay in treatment would be likely. Next overhead. Finally, I would like to note that the benefit of making pH testing available as an OTC device is consistent with past actions by the FDA, such as their approval of over-the-counter versions of urine tests for common urinary tract infections.

Like UTI, vaginitis is a serious and prevalent disease among women which could have serious consequences. Fortunately, women with concerns about UTI have available simple, objective tests, such as the CHEKSTIX UTI test manufactured by Bayer Corporation. This test can be used to periodically evaluate urine for evidence of UTI. Like the urine dipsticks, pH tests are simple to use, virtually one step, with tests that are easily interpreted by lay consumers for the use of a simpler, of a simple color chart.

I believe there is sufficient scientific, medical, public health and regulatory basis to support the approval of OTC versions of vaginal pH tests as a means to permit female consumers to use an objective, simple and effective tool to better assess vaginitis.
The information you were provided before the meeting, in conjunction with the medical information you will hear from the speakers to follow, provide a strong basis on which to made recommendations concerning the availability of a vaginal pH test. I look forward to the panel's discussion and believe the panel will concur. Thank you.

CHAIRPERSON NIPPER: Thank you. Our next speaker is Dr. Sabir Roy, who is a Professor of Ob/Gynecology at University of Southern California School of Medicine. Is Dr. Roy here? Okay. This is Dr. James C. Caillouette, M.D., FACOG, FACS. Remember our admonition to state whether you have financial involvement with the manufacturer of the product being discussed or with their competitors.

DR. CAILLOUETTE: Yes, sir.

CHAIRPERSON NIPPER: Thank you, welcome.

DR. CAILLOUETTE: Thank you. I'm Jim Caillouette. I've been in a solo practice of Ob/Gyn in Pasadena, California since 1959. I am founder of PhemTek, which is a limited liability partnership. PhemTek holds a number of patents and patent applications having to do with vaginal pH screening devices. I've been an inventor for more than 40 years. I've invented medical devices, I would say
more than 40 years and perhaps the best known device is the instant hot/cold pack. So I have a track record of doing that sort of thing. I am the majority shareholder of PhemTek.

CHAIRPERSON NIPPER: Thank you.

DR. CAILLOUETTE: Is that sufficient?

CHAIRPERSON NIPPER: Whatever you say, sir.

DR. CAILLOUETTE: Thank you. I thank Dr. Nipper and Dr. Gutman, Ms. Calvin and the members of the panel for permitting me to make this presentation. I'm here today with the hope that I can persuade you of the wisdom of permitting a vaginal pH paper screening device to be sold over-the-counter for the protection of women's health and safety.

My interest in vaginal pH as a screening device began after attending an early morning conference on the relationship of bacterial vaginitis to obstetrical complications, held during the American College of Obstetric and Gynecology Annual Clinical Meetings in Denver in 1996. I became determined to do my best to develop a vaginal pH screening device that would be inexpensive, easy to use and would help address the problem of vaginal infection and its consequences. In addition, it would provide women
with a self-determined way to screen for abnormal vaginal pH.

Nitrazine pH indicator paper was chosen for vaginal pH testing for good reason. It's use was first suggested by Dr. Baptisi in 1938, as a simple and reliable method for diagnosis of ruptured membranes and it had been described in every addition of the text book Williams Obstetrics, for the past 50 years. In 1983, Dr. Richard Amsel confirmed the importance of vaginal pH in his paper, "Non-Specific Vaginitis."

He identified a vaginal pH greater than 4.5 as one of his four criteria for diagnosis. You have been provided documents that validate the seriousness of the public health concerns associated with bacterial vaginitis. Over-the-counter use of a vaginal pH paper screening device may help in the detection and proper treatment of vaginitis, particularly non-yeast forms of bacterial infections as well as infections caused by *Trichomonas vaginalis*.

This is important because bacterial vaginitis has been associated with increased risk of serious obstetric and gynecologic complications and disorders. An example of the utility of vaginal pH testing appeared in the November 1, 1999, issue of
Ob/Gyn:News. It was reported that in a non-randomized study of 2,400 women who performed vaginal pH checks twice weekly during pregnancy, there was a 90 percent drop in births before 32 weeks.

This German study was reported at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology. In this study, women with a vaginal pH of 4.7 or higher, were told to see their physicians as soon as possible for diagnosis and treatment. One study estimates that if bacterial vaginitis is not screened for, detected and treated during pregnancy, the annual cost to the United States and the direct consequences of this infection will reach 1.4 billion dollars by the year 2000.

To reduce this heavy economic burden, pregnant women, with their health care providers, must establish an effective screening, diagnosis and treatment program. This program has been shown to result in a significant reduction in the instance of pre-term birth, I'm sorry, pre-term labor, pre-term ruptured membranes and pre-term birth. As has been documented, these obstetrical events have been associated with an increased risk of cerebral palsy.

The annual cost of cerebral palsy in the United States is 2.4 billion dollars, representing
one-third of the cost of the 18 most common birth
defects. As with the risks associated with vaginitis
in pregnancy, the risk for the non-pregnant patient is
also a great concern. More than ten million office
visits per year are due to the signs and symptoms of
vaginitis in the non-pregnant patient.

Making available an over-the-counter
vaginal pH screening device, is consistent with
existing public health policy regarding these women
who have vaginitis. I was reassured about vaginal pH
screening when I recently read an article by Dr. Barry
R. Bloom, Dean of Harvard School of Public Health, and
I quote from his article which appeared in Newsweek,
October 11th, 1999, titled The Wrong Rights. In
discussing what he characterized as the patriotically
named Patients' Bill of Rights, he stated that such
rights would effect only a minority of our citizens.

He said that these are the wrong rights
and that we need rights to prevention, not just a
system of payments. He advocates the right to
information, the right to mother and infant care, the
right to childhood immunization, the right to a
healthy environment. And, finally, the right to
health screening. And I certainly could not agree
more. Because of the impact of vaginitis on our
health care system, I believe that it is imperative that women be provided a safe, self-initiated, self-determined, inexpensive, easy to use, vaginal pH paper device.

In the symposium entitled, Update on the Management of Vaginitis, in the November 1999 issue of the medical journal, Contemporary Ob/Gyn, Dr. Jack Sobel states, and I quote, "I believe that the pH test is the single most important determinate of which direction the clinician goes in terms of differential diagnosis." And on the same page, Dr. David Eschenbach stated, "the pH testing really is key."

510(k)s have been granted for professional pH screening devices and it is my sincere hope that a 510(k) for an over-the-counter vaginal pH paper screening device will be granted.

I submit to you that the benefits of making available a vaginal pH paper screening device for over-the-counter use by women, will far outweigh any conceivable risk. It is believed that over-the-counter use for vaginal pH paper screening device will greatly help in the education about and screening for vaginitis. Further, the over-the-counter use of such a device may reduce the misuse and overuse of over-the-counter antifungal or yeast medications that are
frequently initiated solely on the basis of self-
diagnosis by symptomatic women.

In addition, frequent screening by
asymptomatic women can reveal a presence of a sub-
clinical bacterial vaginitis, alerting the individual
to contact her health care provider for guidance or
some treatment. I believe that this will substantiate
and increase public awareness of bacterial vaginitis
and its associated risks, and may therefore, reduce
the spread and the devastating consequences. Thank
you.

CHAIRPERSON NIPPER: Thank you, Dr.
Caillouette. I think I've finally got the order down
now. The next speaker is Janice French from the
University of Colorado Health Science Center.

MS. FRENCH: Thank you very much. My name
is Janice French. I would like to acknowledge that I
am being, my travel is being reimbursed by PhemTek for
presenting her today. I'd like to thank the panel for
allowing me the opportunity to present this
information. I'm a Nurse Midwife and I've spent a
number of years working with a group of individuals in
Denver, Colorado, and we've primarily been
investigating the role of reproductive tract
infections as risk factors for pre-term birth.
What I'd like to speak with you about today is an analysis of our data to look at the effectiveness of vaginal fluid pH testing as a means of identifying women at high risk for having reproductive tract infections. Next slide. As you well know, there are a variety of microorganisms that have been associated with increased risk for pre-term labor.

And certainly shown here is bacterial vaginosis, which is one of the most commonly studied infections and probably the most consistently associated with increased risk. This is data from a study conducted in Denver and published in 1995, where if you look at the yellow bars, you'll see that women that have bacterial vaginosis present, on the left-hand side of the screen, were twice as likely to deliver pre-term compared to women in the yellow bar on the right-hand side of the screen that did not have bacterial vaginosis.

And there are over 20 prospective cohort studies from around the world that show increased risk for pre-term birth among women who have bacterial vaginosis. Next slide. What we'd like to do is to develop clinical schemes that are easy and cost-effective ways of identifying individuals at low risk.
for having reproductive tract infections and then prevent unnecessary diagnostic testing. And further to identify women who are at increased risk for having reproductive tract infections and identify the women most likely to benefit from screening for infections and treatment during pregnancy. Next slide.

The goals of this particular analysis, which would examine a well-studied cohort of pregnant women who have been examined for reproductive tract infections, we wanted to look at the sensitivity and specificity and predictive values of vaginal fluid pH for detecting women with infections and to begin to explore the potential use of vaginal pH testing among women who are asymptomatic.

And further, to look at the usefulness of pH testing for reassuring women that they are well and also as an aid for women to identify their specific need for further professional diagnostic testing and treatment. Next slide. As I said, this is a cohort of data that's combined from four prospective clinical studies that were conducted between 1984 and 1993. There are over 1,700 women that were receiving publicly supported health care in our Denver system.

Microbiological testing was done in the first or second trimester of pregnancy, as was vaginal
fluid pH testing which was conducted using ColorpHast indicator strips. You can see a description of the population and the women are approximately 40 percent white and non-hispanic, 38 percent hispanic, 17 percent African-American, with fewer percentages of women of Asian and Native American descent. Next slide.

You can see here that reproductive tract infections were very common in this population. On the left-hand side of the screen, bacterial vaginosis was present among 34 percent of women, and I'd like to point out that 80 percent of these women were asymptomatic. Eighty percent of the women with bacterial vaginosis did not complain of symptoms. Approximately 6.5 percent of women had culture findings of trichomonas and nearly 8 percent with chlamydia.

Less than one percent of women who were positive for gonorrhea and certainly the genital mycoplasmas, *Mycoplasma hominis* and *Ureaplasma urealyticum*, were very common and Group B Strep bacteria was present among three percent of these women. Next slide. Now the vaginal fluid pH was elevated or greater than 4.5 among 42 percent of the women in this cohort. Shown here in the red bars,
reflect the percent of women who had an elevated vaginal pH for each one of these conditions. You'll see that bacterial vaginosis, trichomonas, chlamydia, gonorrhea, each of those conditions women were significantly more unlikely to have high vaginal pH.

Conversely, among women with a clinical yeast vaginitis were less likely to have a high vaginal pH. Or women with yeast vaginitis most often had normal vaginal pH. Next slide. It's also important that a number, many of these women had multiple infections. And in this situation, the high vaginal pH indicated that a woman was 56 times more likely to have multiple infections with BV, trichomonas or chlamydia.

She was 26 times more likely to have an infection, a single infection with bacterial vaginosis. Seven times more likely to have trichomonas, and three times more likely to have chlamydia. Next slide. In considering the sensitivity and specificity of these vaginal fluid pH and, again, I'd like to stress that 80 percent of the women with bacterial vaginosis were asymptomatic. You can see that a high vaginal fluid pH detected nearly 93 percent of the women with bacterial vaginosis and 71 percent of women with trichomonas.
The specificities are somewhat reduced and this is consistent with other data from the study. And positive predictive value is 74 percent for a high vaginal pH for bacterial vaginosis. The next slide. What is key and this is the same information just highlighting the negative predictive value, you will see that having a normal pH or a negative test for high pH, 95 percent of the women were -- excuse me, accurately predicted 95 percent of the women not to have BV.

The probability of not having trichomonas was 96 percent. The probability of not having chlamydia, 94. And the probability of not having gonorrhea is more than 99 percent. Next slide. So in summary, having a normal vaginal fluid pH predicts the absence of the studied conditions in this population. It enhanced the identification of women less likely to be infected and it allowed the elimination of routine diagnostic testing for these selected conditions. And of course, this would be a function of the prevalence of these conditions within the population.

A high vaginal fluid pH predicted women that were at increased risk for having these selected infections and would identify them. And most likely
to benefit from a routine diagnostic testing, the high pH prompts focus testing of individuals at the highest risk and allowed focused use of more accurate and expensive diagnostic tests. Next slide.

And finally, a normal vaginal pH is reassuring for individual asymptomatic women and their care providers and would reduce unnecessary testing. And with education, pH testing could prompt symptomatic individuals to appropriately seek effective, diagnostic testing and treatment from their care providers. Thank you.

CHAIRPERSON NIPPER: Thank you very much. We'll hold questions until the last person has spoken and then we'll ask questions. Dr. Roy.

DR. ROY: Thank you. I'm Subir Roy. I'm currently a member of the FDA Advisory Panel for Ob/Gyn Devices and have formally served on the Maternal Drugs Health Advisory Committee. I am here as an individual, receiving no financial support because I think this is a very important issue before us. Next slide, please. The types of vaginitis that are generally -- and what I'd like to do is just to give a sort of gynecological overview of this issue and I'll quickly go over some of the slides which I didn't know that Dr. Cooper was going to use, just to
reinforce some aspects.

In terms of bacterial vaginosis and *Trichomonas vaginalis*, they account for more than 50 percent of the types of vaginitis, while *Candida albicans* is less than 50 percent. This, in the top portion you see among Amsel's criteria, pH greater than four and a half, these conditions have previously been cultured and we've had a variety of different opinions. Martius has said that cultures of the vagina are unreliable.

Eschenbach says even *Gardnerella vaginalis*, which used to be mnemonic for the diagnosis of non-specific vaginitis, had no role because it was found in up to 60 percent of the normals. And in a paper that Dr. Caillouette published in 1997, he noted that the presence of *Gardnerella vaginalis*, which was associated with an increased vaginal pH, could be a harbor of, if left untreated, of succeeding bacterial vaginosis.

This was the slide from Dr. Caillouette's paper indicating that for normal flora or for yeast you have essentially normal vaginal pH, while for Beta strep, *Gardnerella vaginalis* and other mixed organisms you have materially elevated pH. Next slide. This is a simple predictive value table. Next slide. It
indicates one of the three reports that Dr. Cooper showed you before showing non-specific vaginitis. The sensitivity and specificity being 81 and 67 percent, with the break point being a pH of 4.5. Next slide.

This is Dr. Caillouette's paper, wherein he studied asymptomatic individuals and had extraordinary sensitivity of 100 percent, specificity of 92 percent. Next slide. This is a report from Seattle by Dave Eschenbach using slightly elevated pH as a cutoff, sensitivity being 96 percent, specificity 53 percent. And, this didn't turn out, that's what happens with these sorts of presentations. I'm sorry, but if you go back to what Dr. Cooper said, and it's probably good that she showed those slides because this is her summary of the pivotal studies. And next slide, let's see if it's the same.

That's okay. I think that this --

CHAIRPERSON NIPPER: It won't help me, I'm color-blind, I can't see the difference.

DR. ROY: It will be okay. These are just copies or the same information as what Dr. Cooper showed you in terms of her tabulation of the summary. And this is the -- next slide. This is the tabulated positive and negative predictive values. Next slide.
CHAIRPERSON NIPPER: That's the one I needed.

DR. ROY: That's the one? Well --

CHAIRPERSON NIPPER: We'll go back and get it later.

DR. ROY: I can, we can print this out and have it for you after the break. And this is also the summary of the predictive values where she gave you the information on, so we will print this out. I'm sorry, I didn't realize this was what was going to happen. The only thing that showed up is white, is the white paper. Now, basically, I think a vaginal pH of greater than four and a half in pre-menopausal women is strongly suggestive of those two conditions noted previously; namely *Trichomonas vaginalis* and bacterial vaginosis, while with *Candida albicans*, the pH was less than four and a half. And in addition to Dr. Caillouette's paper was the study of menopausal women where in the absence of bacterial pathogens, the vaginal pH in excess or in the realm of six to seven and a half, this is strongly suggestive of menopause or lack of compliance with or adequate estrogen replacement therapy. Next slide.

If you look at BV, why is it that we're interested in it. As you can see, the non-pregnancy
conditions with which it is associated include pelvic inflammatory disease or upper genital tract infections, post-abortion PID or post-hysterectomy infections. These studies are done all over the country and world and there's a consistency of finding in this realm. Next slide.

And for pregnancy complications, you just heard from the previous speaker their experience and they are cited there as well. You see that it's associated with pre-term delivery, premature rupture of membranes, amniotic fluid infections, and subsequently with chorioamnionitis and post-partum endometritis. And the frustrating thing about this, being a clinician, is that so many of these people have this condition asymptptomatically and they suffer these consequences.

Those case control studies are supported by Gravett's report as a prospective cohort study and you see the link with BV with premature ruptured membranes, pre-term labor and with amniotic fluid infections. Next slide. I was on the FDA Advisory Panel back in '90, when we approved OTC vaginal Candidal therapy because we were persuaded it would in essence be beneficial to patients. Since then it's been somewhat disturbing to note, as this slide
indicates, the numbers of individuals who use these preparations inappropriately.

And it seems to me that absent having some way to test for whether they should or shouldn't use it, this sort of a misuse will continue and it would be highly more effective if an OTC-type of vaginal pH test were available that these people could use it more appropriately. Next slide. Consequences of having the development of asymptomatic conditions leading to more serious conditions are listed here.

We have increased likelihood of STDs or salpingitis. You, therefore, may increase pelvic pain, injury to the fallopian tube can lead to increased ectopic pregnancies, or indeed even to infertility as Westrom has shown and others as well.

Another aspect to this issue that we don't generally talk about is it may alter the risk of genital tract cancers; namely, HPV is more apt to occur with individuals who have vaginitis, as is HIV. As a matter of fact there are four new studies that indicate a link with that.

Delayed first full-term pregnancy is linked with breast cancer and there's controversy about whether it's just that reproductive technology is associated with ovarian cancer. We don't really
believe so, but at least it's in the literature. And adverse pregnancy outcomes, habitual abortion with *Ureaplasma urealyticum*, and then prematurity post-partum endomyoperimetritis with BV, Group B Strep, GC and *Chlamydia trachomatis*, all with conditions that Ms. French just showed you. Next slide.

Conclusions. I believe vaginal pH is an important factor in assessing the status of a woman's health. It's not to be considered as a diagnostic test, rather as an aid to diagnosis, like a thermometer. Symptomatic women may utilize the test to self-medicate, again, if the pH was less than four and a half. While if the pH is greater than four and a half, further medical workup is indicated.

Asymptomatic women may be reassured if the pH is less than four and a half, while if greater than four and a half, medical consultation should be considered. Next slide. The test has minimal risk, potential of great benefit. And should patients be able to follow directions and be able to obtain the same results as professionals, this product I believe should be made available for OTC use. I thank you very much for your time.

CHAIRPERSON NIPPER: Thank you, Dr. Roy. At this time, we can entertain a couple of questions
if we have some for the previous speakers and my colleague on the right, Dr. Harrington-Falls had a question, I believe, for Ms. French, if you'd be willing to answer a question. You can just sit right there. There's a microphone right there for you.

DR. HARRINGTON-FALLS: This is Beverly Harrington-Falls. Ms. French, can you briefly describe what your current practice is with use of pH assessment in obstetric patients?

MS. FRENCH: Right now we are actually screening everybody routinely for bacterial vaginosis using the full clinical Amsel criteria, so vaginal fluid pH testing is part of that.

DR. HARRINGTON-FALLS: By your slides you gave the impression that if a patient had a normal pH on vaginal secretions, you would omit gonorrhea and chlamydia screening.

MS. FRENCH: I thank you for bringing that up because I don't want to leave that impression. Gonorrhea and chlamydia testing is separate from the analysis of vaginal pH. That's very important that for those women, especially in populations, inner-city, impoverished populations and others, young women, et cetera there are criteria for women who need to be specifically tested for gonorrhea and chlamydia.
Thank you.

CHAIRPERSON NIPPER: Dr. Habig had his hand up.

DR. HABIG: Yeah, I have a definitions question, not being -- I'm a chemist. I think I understand vaginitis as an inflammation. I would like to hear a definition for vaginosis and vaginalis, just so I have them all straight. Can somebody help me with that?

CHAIRPERSON NIPPER: Dr. Roy, you can go to the table or the podium, whichever is easier.

MS. FRENCH: The condition bacterial vaginosis, as you know, has gone through a number of name changes. Generally vaginitis does imply an inflammatory response, and in 1984, the name bacterial vaginosis was chosen because there's a characteristic absence or a decrease in the numbers of white cells in the vaginal fluid of women who have this overgrowth of bacterial vaginosis or bacteria in the vagina.

DR. HABIG: And vaginalis is associated with --

CHAIRPERSON NIPPER: Go to the microphone, Bob.

DR. HABIG: I'm sorry. This is Bob Habig again. There was a term with vaginalis --
DR. ROY: Yes. *Trichomonas vaginalis* is the term used for indicating infection with trichomoniasis or trichomonads, which is the parasitic organism. And of course others would argue that the term bacterial vaginosis implies that bacteria have gender and it's the female bacteria that have a problem. And so the correct term should be bacterial vaginosis, I mean vaginal bacteriosis. But we don't need to redefine it beyond the difficulties which I think you've correctly indicated exist in the field, just trying to talk about this condition.

DR. ROSENBLOOM: Mr. Chairman, I think, there's a semantic error here.

CHAIRPERSON NIPPER: Yeah.

DR. ROSENBLOOM: *Trichomonas vaginalis* is an organism. *Trichomonas vaginitis* is the disease. You indicated that *Trichomonas vaginalis* is the disease. All right, I think that was a mistake, but *vaginalis* just refers to where it comes from, not to a disease statement. Is that correct?

CHAIRPERSON NIPPER: Dr. Sedlacek, do you want to clarify something?

DR. SEDLACEK: That's my understanding as well that that's the genus and species of the infecting protozoan. I have a question for Ms. French
and then for Tom Tsakeris. For Ms. French, how did you collect your pH specimen? And, I'm not familiar with the device you used to measure it. How is it similar or dissimilar to the device in question today?

MS. FRENCH: The vaginal fluid pH was collected by placing a swab in the lower lateral vaginal sidewall and collecting some of the vaginal fluid and then placing that on an indicator strip. The ColorpHast indicator strips are commercially available through scientific supply catalogs. And the range of pH that we test for is between 4.0 to 7.0 and it changes in approximately two to three to four point increments.

DR. SEDLACEK: I didn't ask my question properly, I guess. From which part of the vagina, upper, middle or lower?

MS. FRENCH: The mid lateral sidewall, away from cervical mucus but it's on the lateral sidewall of the vagina.

DR. SEDLACEK: And how does this differ from the proposed measuring technique before us today?

MS. FRENCH: Probably not very different at all.

DR. SEDLACEK: Okay. Thank you. And, Tom, one of the possible outcomes of a false positive,
was the patient might self-treat without consulting or self-treat and consult the physician. Now a false-positive means an elevated pH would suggest that she has a BV or one of the other infectious problems. With what drug could she self-treat?

   MR. TSAKERIS: Well, the point there was that if you're going to look at risk/benefits you're going to have to look at all the possibilities. A woman who may be inclined to self-treat, who has perhaps had a past history of self-treating, has now available a test, even though in the face of a positive, a so-called positive pH test, you can't rule out the possibility that the woman would still self-treat.

   And there are test scenarios. Either she self-treats and ignores the test results, which I point out is very unlikely. Or she could perhaps self-treat and also consult her physician.

   DR. SEDLACEK: So you mean self-treat for yeast?

   MR. TSAKERIS: Yeast, yes.

   DR. SEDLACEK: In spite of a positive test?

   MR. TSAKERIS: In spite of a positive -- and you can't rule out the possibility that could
occur. We didn't want to make -- we want to make sure we get all possible scenarios addressed.

    CHAIRPERSON NIPPER: Does the panel have other questions? Yes.

    DR. TUAZON: With regards to the false-positive, are there studies or have there been studies to show the correlation between the increasing colony count of Gardnerella and the positivity of the pH? Maybe the false-positive is related to the number of the colonies of the organism? Has that been done?

    DR. ROY: That's a very interesting question. I'm not sure that it's specifically been done in terms of whether there's a certain number of colonies beyond which it would turn positive or not. The study that Dr. Caillouette did, did pick up individuals who had Gardnerella and, as you saw on that graph, they had substantially increased numbers of, or the pH was elevated. But I don't believe it was quantified as to how many.

    DR. TUAZON: Right. Because that may be a possibility to explain the false negatives in patients who have symptoms but yet have negative pH. Do we know exactly what causes the elevation in the pH? Are the Gardnerella organisms producing a certain chemical that causes the elevated pH?
DR. KOUMANS: From my understanding of bacterial vaginosis, it's an abundant overgrowth of Gardnerella vaginalis plus other microorganisms and an absence of lactobacilli. And the lactobacilli are the bacteria that produce acids and hydrogen peroxide in the vagina. So they are usually considered the bacteria that maintain a low vaginal pH. And their absence is typical in bacterial vaginosis.

So it's not clear whether it's the abundance of bacteria creating a high pH, or the lack of lactobacilli. But it's probably the relationship of the two.

DR. TUAZON: And the other question I have is what's the standard procedure in terms of use of this vaginal pH in pregnant and non-pregnant women? Do you do routinely, do this in women who come for routine pelvic exam or routine Gyn visits? Or how often do you do this in pregnant women?

DR. ROY: Well, in my practice I do use it routinely because it's so simple to do and it's such a useful adjunct to the algorithm leading to diagnosis and/or treatment. And Dr. Caillouette can speak to it as well. He's been in practice a great deal longer than probably anyone in this room. And why don't you describe how you --
CHAIRPERSON NIPPER: Dr. Caillouette, you can go to the podium or stay at the table, whichever is more convenient.

DR. CAILLOUETTE: Since developing an interest in this area, I now do a vaginal pH on every patient who has a pelvic examination in my office. Initially, when I was doing the early work for the study, I only did women in the childbearing age. And one day I sat down with myself and I said, you know, you're not being a very good scientist. You better check all of the women who come into your practice because you might learn something.

And the thing I learned was that it's related to serum estradiol in the menopausal group. I had no clue that serum estradiol played a factor in all of this. But it certainly does. And they have to be well estrogenized and that helps support the lactobacillus and the lactobacillus puts out the lactic acid and hydrogen peroxide and then you get the acidic environment.

DR. TUAZON: Thank you.

CHAIRPERSON NIPPER: Ms. French, did you want to comment on how you use vaginal pH's in the patients you see?

MS. FRENCH: Similar to Dr. Roy, we
basically test all women coming for annual exams with a vaginal pH, as well as a wet prep. And certainly during pregnancy, all of our women are being examined with pH as part of that.

CHAIRPERSON NIPPER: Thank you. I think, Dr. Tuazon, was that the last question you had? Dr. Diamond had his hand up and then we'll go to our friend from CDC.

DR. DIAMOND: I guess the question that I have, in thinking about this, is that -- I'm trying to find a happy medium -- each of the presentations today have talked about testing for vaginal pH and then utilizing that as an endpoint by which either to self-medicate or using that as an endpoint to see a physician. But the responses to the questions that were just given, talking about using this as one step in the paradigm of turning, an approach to treating a patient, as well as leafing through these articles in here.

I was just given this morning. I don't know if you've had access to them or not. But they're basically about diagnosis of vaginitis. Virtually all of them talk about using pH in combination with either a wet prep or with a gram stain. And so the question is, what do we know or what studies do we have that
look at sensitivity or specificity of, or positive and
negative predictive value of pH independent of these
other markers as opposed to in combination with them?

Do we have data on that?

MS. FRENCH: Well, I think I presented
some of that data. Looking at -- we have a clinical
diagnosis of bacterial vaginosis from the women I
presented. And we looked, compared the vaginal fluid
pH as a predictor for the diagnosis of bacterial
vaginosis as well as trichomonas. And I think the
information that Dr. Cooper presented, as well as Dr.
Roy, the summary information, that's vaginal fluid pH
as a predictive value for the presence of bacterial
vaginosis. So there is information.

DR. DIAMOND: Well, maybe I didn't
understand your presentations well enough then. The
data that you presented was purely pH, independent of
these other parameters? Or is one of the things you
were doing included as part of your evaluation?

MS. FRENCH: The clinical diagnosis of BV
includes pH as one of the criteria. It's three out of
four clinical criteria including an abnormal vaginal
discharge or high pH. The presence of any odor when
you add potassium hydroxide, and the observation of
what are called clue cells under the microscope, which
are epithelial cells that are covered with bacteria.

DR. DIAMOND: Right.

MS. FRENCH: So the clinical diagnosis of BV does include pH, but what we did was look at the pH as a predictor of that diagnosis. So you can also -- I also have data, which I didn't show you, looking at pH as a predictor of BV by gram stain, where the pH is not a part of that criteria.

DR. DIAMOND: All right. So maybe I'm being dense, but the data you presented was purely pH as opposed to all those others in combination? Okay.

CHAIRPERSON NIPPER: Dr. Roy.

DR. ROY: I think, Mike, it's important to recognize that in order to understand how any one factor fits in, you've got to have your gold standard to compare it to. So the gold standard is looking at the entire criteria, the culture data, things like that, depending on which study you're looking at. But then you back off and see how predictive is just this single test with respect to having everything. Because you obviously have to get to your diagnosis somehow.

CHAIRPERSON NIPPER: Dr. Koumans.

DR. KOUMANS: Yeah, thanks, Janice, for a very nice presentation. I was wondering whether you
or any of the presenters could address other possible reasons that you found in your research for an elevated pH?

MS. FRENCH: In this data set we focused on the reproductive tract infections. In other work and in the literature, they talk about certainly recent intercourse and it has to be actually very recent intercourse would cause an elevated pH. Certainly blood in the vagina or cervical mucus will cause elevated pH's. So there are other factors, as you know.

CHAIRPERSON NIPPER: Okay. If there are no further questions or comments from the panel for these speakers, I will declare the open public hearing closed. And in the interest of panel comfort and maybe that of the audience, I hope that our next speaker won't mind if we take a brief break before we come back to hear her speak. Let's reconvene at 20 of 11:00. Will that be all right with you, Dr. Schwebke?

DR. SCHWEBKE: Yeah, that's fine.

CHAIRPERSON NIPPER: Okay.

(Whereupon, the foregoing matter went off the record at 10:26 a.m. and went back on the record at 10:43 a.m.)

CHAIRPERSON NIPPER: Okay. The moment
we've been waiting for. Dr. Schwebke. I was worried, I didn't see you.

DR. SCHWEBKE: No, I'm here, I'm here.

CHAIRPERSON NIPPER: Great.

DR. SCHWEBKE: And Emily and I were talking, this presentation might have been a little, timed a little better to come before what we just heard. So some of what I'm going to say is going to be a review.

CHAIRPERSON NIPPER: There's some of us who need to hear it again and again and again.

DR. SCHWEBKE: Good. Well, I thought the chemist might benefit so I was really --

CHAIRPERSON NIPPER: Well, I'm a chemist, too, so thanks.

DR. SCHWEBKE: -- happy to hear that. And as I go along I'll try to, also, put a little bit of, sort or reality into what's going on as well, I think. So, let's see if we can do this. I was asked to give an overview of vaginal infections as part of my presentation. We're going to start with some slides and then move to some crude overheads. But I think, they were helpful to me in trying to think through some of these issues.

As you've already heard, there are three
major causes of vaginal infections. And that is candida or yeast infections, trichomonas -- 
*Trichomonas vaginalis* is the full name and this is a parasitic infection -- and bacterial vaginosis. And of these three, bacterial vaginosis is definitely the most prevalent. A few words about the normal vaginal ecosystem and Emily already alluded to some of this.

But this is a gram stain preparation of vaginal fluid. And what you see here are these large, purple gram positive rod organisms which are the lactobacilli. And the lactobacilli are felt to be the, sort of the key players in maintaining a healthy vagina. The lactobacilli are, as you can see from this smear, would seem to represent the predominant organisms in the healthy vagina.

They are also important in terms of their protective role against some of the pathogens that were mentioned, like *Trichomonas* and other organisms that are involved in bacterial vaginosis. The lactobacilli maintain the vaginal pH at an acidic level less than 4.5. They use the glycogen and lactic acid is one of their by-products and this is what maintains the normal vaginal pH.

They also produced anti-bacterial factors such as hydrogen peroxide. They have other affects on
the local immune system of the vagina, so they are thought to be key. This is just some data that looks at whether or not lactobacilli are there all the time in large numbers and in healthy women. This is a slide where you see these little boxes represent the lactobacilli. The little triangles represent Gardnerella and Bacteroides, which are organisms that often are increased in bacterial vaginosis.

And what we did here is we took normal volunteers, they had no pathology, they were very low risk women and we asked them to collect daily self-obtained gram stains, where we can look at these different types of bacteria. And you can see on the left, the x's there, that this particular woman had four plus or lots of lactobacilli virtually everyday throughout her cycle. Except for that one blip, where it was just that there wasn't enough quantity on the slide to make a judgement.

But in reality, even though this is what we might expect would occur in all healthy women without vaginal pathology, this pattern occurred in only about 20 to 25 percent of women that we looked at. And the other women, the majority of women had a fair amount of variability, day-to-day variability in their vaginal bacteria.
So they had some days where they had four plus lactobacilli, but interspersed were days where the lactobacillus population fell. And the Gardnerella population rose. And I show this just to sort of re-emphasize that even though the lactobacilli are important and we feel that they are there to maintain a healthy vagina, they don't seem to be there in large numbers in all women at all times.

Now, I would have been very interested, I wish I could stand here and show you pH data that match each of these days. I don't have that. But I think it is a consideration as we talk about some of these tests. Okay, I'm going to very briefly go through the three ideologies of vaginal infections, just so we're all up to speed. Candidiasis or yeast infections is thought to be an overgrowth of a normal inhabitant of the vagina. Many women are colonized with low levels of yeast and for whatever reason, whatever trigger, these organisms increase in numbers and become invasive.

They cause symptoms such as itching, irritation, some discharge. Treatments are, as you see here, and I think the key point is that availability, as you all know, of over-the-counter medications for yeast infections. This is the only
vaginal infection for which we have OTC products. And just some pictures for you. Here's a typical discharge of candida. Now as I go through these, in terms of the clinician's perspective, there was a question earlier about standard of practice in terms of utilizing diagnostic tests for vaginitis.

And although I, I confess, I also do pH's on all women I see, I would submit that we are in the minority. And that most clinicians make empiric diagnoses. And they do this either by speaking to the woman about her symptoms or putting the speculum in and taking a look and saying, oh, obviously that's yeast. Obviously, they are going to be wrong if they don't pursue a full diagnostic work up. But nonetheless, I think that this is more likely the standard of care that exists.

And then the good clinician will take some of that fluid and look under the microscope in addition to checking the pH and some other tests that we'll talk about in a minute, and they will confirm the diagnosis of this particular infection by seeing the yeast forms under the microscope.

The next infection is *Trichomonas vaginalis*. This is a protozoal infection. Interestingly, it was originally regarded as a
commensal, but indeed it is a pathogen.

It is the only one of the three that's been proven to be a sexually transmitted disease. So partner treatment issues become important here. This a very busy slide, don't try to even go there. It just reminds me to tell you that women who are symptomatic with trichomonas generally complain of discharge, irritation and some itching. Now, having said that, about a third of women who have trichomonas have no symptoms.

And here is a picture of a typical discharge. Again, a clinician might just look at this and say, oh, that's trichomonas. They might not follow through and do the other testing that would be recommended. And to confirm it again, look under the microscope and actually see the motile trichomonads swimming around in the vaginal fluid. They are those pear-shaped organisms that have flagellae coming off the end.

Okay, in terms of treatment, this is not OTC. There is only one medication in the U.S., and that's metronidazole. It's usually given at a single dose and because it is a sexually-transmitted disease, it is recommended that the partners be treated as well. I don't think I included a slide, but I should
mention that trichomonas has been associated in one cross-sectional study with pre-term birth. There are no prospective studies, these would be very difficult to do to confirm that association. Trichomonas has also been associated with apposition of HIV.

And then finally bacterial vaginosis or BV. This is again just to reiterate. It's called vaginosis instead of it is because there is not an obvious inflammatory component to this condition. The prevalence of BV varies by the population that you look at. In the general population, I would say 20 to 25 percent. In our STD clinic where I practice, it's about 50 to 60 percent.

This is a disease that's never been proven to be sexually transmitted but it certainly is sexually associated. It is most frequently seen in women who are sexually active. The etiology of bacterial vaginosis is unknown. All we can do is describe what happens. And what happens, microbiologically, is that those lactobacilli that I showed you early on, tend to fall in numbers, particularly those that produce hydrogen peroxide. And instead seem to be replaced by large numbers of organisms, such as Gardnerella vaginalis and anaerobic organisms such as, lots of names, Prevotella,
Mobiluncus and others.

And these changes, these microbiological changes then lead to the changes in pH, that we talked about earlier, and in some women lead to symptoms. And the primary symptoms of women with BV are odor and discharge. So they'll notice a fishy odor, sometimes more noticeable after intercourse and during menses, a difference in their usual discharge. Sometimes irritation and itching, but this is usually not a prominent complaint.

However, 50 percent of women who meet the clinical criteria for BV are asymptomatic. And here's a picture of the, what they describe as a homogenous discharge. Again, a physician might look at this and say, oh, BV. This is a clue cell. This is one of the criteria that Amsel described. And this is, we look under the microscope again at the vaginal fluid and we see this epithelial cell that's covered with bacteria. And particularly the edges are obscured. And so this is one of the diagnostic criteria that we use for making the clinical diagnosis of BV.

Treatment of BV. I wanted to just spend a minute on this, not to really get into specifics but to make a comment about the efficacy of treatment. The two drugs that we rely on the most, and these are,
by the way, this is taken right from the CDC STD
Treatment Guidelines. And so this is what is in the
current guidelines. But the two drugs that we rely on
are metronidazole and clindamycin. And these are
actually, rather empirically chosen because they are
very effective against anaerobes, and we see a lot of
anaerobic organisms in bacterial vaginosis.

All of the recommended therapies are
equally efficacious. The problem is that the efficacy
rates are only about 80 to 85 percent. And the
recurrence rates with this condition are very high.
So we have a couple of dilemmas with this disease in
that we don't know the etiology. And the treatments
that we have aren't nearly as effective as we would
like them to be.

Okay, just to go back a little bit and
then talk about the diagnostic work up of vaginitis.
These are the things that we encourage clinicians to
do. Obviously, they want to take a history, they want
to look at the patient, describe the discharge. The
vaginal pH, we've certainly heard about. The whiff
test is another ancillary test that's part of the
Amsel criteria, where the clinician actually takes
some of the vaginal secretions and mixes it with
potassium hydroxide and smells it.
And they are trying to detect a fishy odor which would be indicative of increased amine production by anaerobic organisms. And then looking under the microscope, and I've already showed you examples from the specific infections. I do think it's important. It's important for the clinician and maybe for you to understand as well, that it's vital in terms of where the specimen is collected. Here's a diagram that shows the speculum in the vagina and you see the swabs there.

One of the swabs is right at the opening to the cervix, the os of the cervix. And then the other is positioned against the lateral wall of the vagina. And cervical mucous is certainly a factor that can interfere with the interpretation of vaginal pH. The cervix naturally has a more alkaline pH. So it is important for the clinician and for the woman, in the case of self-collection, to make sure that she is sampling the vaginal area.

It's not hard to do, but it's just a caveat that we need to remember. Oops, upside down pH paper. But this is the pH paper that we generally use in the clinic and these are individual, I mean there are different things out there, but I think this is probably the most widely used, individual strips with
the pH paper on the end. And you apply the vaginal fluid and then match it up to your color chart. There are other things besides cervical mucous that interfere with pH.

We've already heard about semen. Semen is more alkaline. Blood will also interfere with this test. This is just a diagrammatic representation of the whiff test, where we mix the secretions with potassium hydroxide. And then, of course, we need to look under the microscope. Having done all this, the astute clinician should come up with the correct diagnosis. And this is just a little chart that helps us out. One think I'll say is that women can certainly have mixed infections which can affect some of the results, particularly the pH.

For example, they can have mixed infections with candida and bacterial vaginosis, which is not, it's not common but it's not all that uncommon. And in any event, this, you know, the use of these diagnostic tests does lead to a more specific diagnosis and hopefully specific therapy. Okay. Just to say a few more words about the diagnosis of BV, to remind you this is the clinical criteria of Amsel, et al. He reminds us there's no single marker for BV because we don't know what causes it.
And so if you have three of these four criteria, an elevated vaginal pH, presence of clue cells, a homogenous of milky discharge and a positive whiff test, any of those three, then you can make the clinical diagnosis of BV. This is probably the most common, next to empiric diagnoses, this would be the most commonly used criteria for diagnosing BV. Because it can all be done at the bedside very rapidly and cheaply.

I just wanted to make sure that you were aware of another criteria. This is a gram stain criteria that can be used for BV. And here, I mentioned this before, we can look at the different types of organisms and grade the presence or absence of these and come up with a scoring system of zero to ten. And I'm not going to go into detail about this except to say that actually these scores were derived, the break points were derived by comparing it to the Amsel criteria.

So there is pretty good agreement between the two methods, although not perfect agreement. These are examples of women with normal bacteria. Scores of zero to three are normal. Then there is a class of women that are intermediate. And if you'll think back to those first couple black and white
slides I showed you where that one woman had a lot of variation in her vaginal bacteria. If you'd done a gram stain of her, on those days when she had quite a bit of variability, this is what you would see. It's this intermediate flora, where you see some decrease in the lactobacilli and some increases in the other organisms, but not enough to be --

CHAIRPERSON NIPPER: Dr. Schwebke?

DR. SCHWEBKE: Yes.

CHAIRPERSON NIPPER: I wonder if we need a little bit better light. Maybe just put something on top -- yeah, that's good.

DR. SCHWEBKE: Okay.

CHAIRPERSON NIPPER: Yeah, we can still leave the overhead on, but put something on top of it. And I don't know whether anybody on the panel would like to see your previous slide with the --

DR. SCHWEBKE: There we go.

CHAIRPERSON NIPPER: Yeah.

DR. SCHWEBKE: So this is very similar to that first gram stain I showed you where you see lots of these large gram positive rods which represent the lactobacilli. This is what, you know, ideally we would want to have in terms of vaginal flora.

CHAIRPERSON NIPPER: Okay.
DR. SCHWEBKE: And then this intermediate category which is in between. It's not normal, it's not BV. And what you can appreciate, I think, is that those large gram positive rods have decreased in numbers. And instead you see these tiny bacteria which represents, for the most part, Gardnerella, an organism that has certainly been associated with BV. And you're also starting to appreciate an increase in the number of bacteria that are there. A total increase in the concentration.

And then lastly, scores of seven to ten using this particular criteria, represent BV. And again you see increased numbers of bacteria here. You tend not to see lactobacilli and you see these large numbers of organisms which represent the anaerobes and facultative anaerobes, such as Gardnerella vaginalis.

This was just to reiterate my point that the, these sort of fed off each other, because the break points were derived from comparing these gram stain scores to the individual Amsel criteria.

In terms of the Amsel criteria or the clinical diagnosis of BV, what do we know about sensitivity and specificity and I'm not going to dwell on this because we've already heard quite a bit about sensitivity and specificity of pH which is our
interest today. The pH test though does have a fairly high sensitivity for diagnosing BV, but it's specificity is certainly not all that good.

Other, as you've heard, other conditions, particularly trichomoniasis can cause an elevated pH. And I should mention that trichomoniasis and BV very frequently travel together. So you very frequently see these as co-infections and that may be why we see some problems with the pH here. Discharge, looking at the discharge really has very low sensitivity and specificity. The wet mount is a good test. If you see a motile trichomonad, obviously you've made your diagnosis.

So the wet prep, looking under the microscope, is a very good test. The whiff test is not very good and we actually know from scientific studies that people's noses are not all the same. And then this is just some, because you were interested in sensitivity and specificity, again I'm not going to dwell on this, but this was just some data that we, oh, and actually this was higher than I remember, Emily.

This now is looking at sensitivity and specificity of predicted values of Amsel. So the Amsel criteria and other individual diagnostic
criteria, this time compared to vaginal gram stain for
the diagnosis of bacterial vaginosis. So that gram
stain diagnosis that I showed you. And if we look at a
pH greater than 4.5, which is the third one down, you
can see in this particular study, this was a multi-
center study, sensitivity of 89 percent, specificity
of 73 percent.

And lastly, in terms of the slides, and
then I'll move to my overheads, I just wanted to touch
on the issue of self-collection. There are a few
studies out there now that have looked at the ability
of the woman to self-collect vaginal specimens. This
is a study that we looked at where we compared self-
collected versus clinician-obtained specimens for the
diagnosis of *Trichomonas vaginalis*. And what we did
was we had the woman, we instructed her on self-
collecting a vaginal specimen, which she then handed
over to the clinical for inoculation into a
trichomonas culture medium.

And then she had her pelvic exam and the
clinical did her usual thing and also collected a
specimen that was inoculated into a second trichomonas
culture medium. And what we found was that there was
virtually no difference in the results of these tests,
indicating that certainly a woman is capable of
collecting a vaginal specimen.

We've also done it with the vaginal gram stains for bacterial vaginosis and showed no difference. I must say, though, that I think the point here is that, there's a finer point here is that these were specimens that the woman obtained but handed over. There was no interpretation involved in her part. And I'm actually wondering and I have a question for the group. If there have been studies that have looked at the ability of the woman to interpret the ph, self-collected pH plus interpretation versus the clinician's interpretation. I'll put that up for further discussion.

And I think we can move to the overheads. I just have a few overheads and I apologize, they are just handwritten. I was trying to think about some of the issues that Veronica asked me to think about, considering this. And I hope you all can read my scribbles. But I think it is true that the vaginal pH, at least for me, is also a decision point. When I approach a woman and in the STD clinic because we're dealing with such a high, high prevalence population for many things, we do full screening. And if the pH is less than or equal to 4.5, I'm somewhat reassured, from an STD point of view.
I start thinking, well either there's nothing going on here or perhaps she has a yeast infection. Whereas if the pH is greater than 4.5, my antennae go up and I start thinking about BV and trichomonas. Now a couple of caveats. Mixed infections can occur, we've already mentioned that. Trichomonas can have a normal pH and actually I was struck by Janice's data of 29 percent. So that would have even been higher than I would have thought.

But we certainly do see cases where women with trichomonas have a normal pH. And then again, let's not forget interfering factors of blood, semen, cervical secretions. I think douching is a question. It's mentioned out there in the literature, but frankly I've never seen a study that showed resulting changes in pH or interference with pH measurement as a result of douching. Next overhead.

You know, I should have put these slides in and as I was listening to people talk, I thought it might be helpful just to, I hope I'm not using up all my time here. But I thought it might be helpful to say a few words about some of the complications of BV, just to bring everybody up to speed here. Obstetrical complications, certainly the major one is pre-term birth and there is no doubt that this association has
been shown in study, after study, after study, from the U.S., from Scandinavia, from wherever.

However, I must say that what we are lacking is data, prospective data on the role of treatment for BV in preventing pre-term births. There is some good data on the effectiveness of this approach in a select group of women. That is women who have had a prior pre-term birth. But there was conflicting data that was recently released when it came to the general population of pregnant women. A study that was done that compared treatment of BV in pregnancy with metronidazole to placebo, did not, in the general population of pregnant women did not find a benefit in treating.

So I put this out on the table that even though there is an association, a very strong association, what we're lacking is the prospective data about what to do with this in some cases. In terms of gynecological complications, this is what made it to my short list. There are certainly others that you will see floating around out there. But I think it is true, from some recent studies, particularly some of the recent African studies, that STD and in particularly HIV apposition is linked to bacterial vaginosis.
And that BV may actually be a biological risk factor for apposition of HIV. And I think this is important. Again, though, we don't have prospective treatment studies, of course, and we're left with the dilemma that our treatments are sub-optimal, if you will, and that recurrence rates are high. Pelvic inflammatory disease. Again, some very good associations but prospective data on this is lacking. And I don't think is coming anytime soon.

Surgical infections certainly important and here we do have some very good data, particularly on post-abortal PID. Hysterectomy infections related to the presence of BV and recurrent urinary tract infections. There has been some recent information about the role of abnormal vaginal flora in the ideology of this problem. But again I don't think, I may have missed it, but I don't think there's any prospective treatment data. Next overhead.

So what are the risks and benefits of OTC pH? This is just me thinking about this. The benefit is it's simple. It should be inexpensive. It certainly may increase the correct diagnosis and treatment of vaginal infections. And I have this scenario of the patient coming armed with this information which I've already suggested that the
doctors often don't bother to collect.

So I think that could be powerful. You know, I have this discharge and I checked the pH and it's alkaline. So don't treat me for a yeast infection. So I think it is empowering for the patients to potentially have this information. The increased pH should alert women that yeast is less likely and perhaps, and I think this was mentioned before, avert inappropriate use of OTC antifungals. And this could certainly be a good thing.

Risks. I wondered if this might give women a false sense of security. So that if I checked my vaginal pH and it was normal, I might say, I'm fine. And what I want to make sure and I think this could be handled in labeling, is that the woman is not mistakenly equating vaginal infections with cervical infections such as gonorrhea and chlamydia. And I think that needs to be very, I think there needs to be an education piece there.

And also, and I think this is important to think about also. I think that this could lead to, and depending on the indication for the test, whether it's screening or diagnostic for the OTC use, this could lead to an increased number of office visits for asymptomatic BV. And currently, although there will
be some in the crowd who disagree, currently the
treatment of this condition, asymptomatic BV, is
controversial and it is currently not recommended by
the CDC. Next.

So labeling issues, I just mentioned, is
screening versus diagnostic. Is this something that's
going to be for asymptomatic women as well as
symptomatic women or purely for symptomatic women.
Education, I mentioned, I think it's very important
that there be a strong educational piece and that is
includes sexually-transmitted disease information.
Interfering factors would certainly have to be
mentioned and then whatever else we come up with. And
I think that's it, is that right? Thank you.

CHAIRPERSON NIPPER: Thank you. Hang
around for a minute, I'm sure the panel is going to
have some questions. If you'd be more comfortable at
the table, you can do that.

DR. SCHWEBKE: No, I'm fine.

CHAIRPERSON NIPPER: Okay. Does anybody
on the panel have questions or comments on Dr.
Schwebke's presentation. I know I'm never going to
think of cottage cheese the same way again.

(Laughter.)

CHAIRPERSON NIPPER: I don't mind clinics,
I just don't want to cross up the two things. Dr. Habig.

DR. HABIG: In the data you presented and also in, I suppose data from other presenters, I wonder what kind of instruction has been available for the women who have done the self-testing? What kind of specimen collection instruction is typical, if any?

DR. SCHWEBKE: Well, in the studies that we've done where we've compared the self-collection for diagnosis for BV and trich, it's simply been the clinician, it's pretty, it's been pretty straightforward. It's been them handing them the swab and saying we want you to swab the inside of your vagina, along the wall, with this cotton swab and then pass it on to us. So it's been very straightforward.

And I should also mention, because this was an issue, we, we were proposing to use this technique in a study of, oh, I don't even, it's been a while now, I don't even remember exactly what the thing of the study was, but it was among a cohort of pregnant women. And a concern came up about pregnant women inserting these swabs into the vagina and could they inadvertently snag the cervix and, you know, cause complications or whatever. And we sort of felt that that was highly unlikely and that with some
simple instructions that that wouldn't be a problem.

And in fact the study went forward, it was under the auspices of the Navy. And the study went forward and I'm totally unaware of any problems that they've had with this cohort of pregnant women as well. So I think it's a pretty safe and relatively easy procedure. I'm just concerned about the interpretations out of it.

DR. KOUMANS: Can I add something that, when we instruct adolescents to take a vaginal sample, we often give them a limitation of how deeply they should be inserting it. So it, you know, this is how far your finger goes and that's it. So that's something that I would consider an important component of the product.

DR. HABIG: And actually, this is Dr. Habig again. That answered my second question. But you're talking about health care practitioner providing instructions. When we look at OTC labeling it won't be by a health care practitioner, it will need to be graphically or in good language provide that kind of instruction. And I, it sounds like it could be important. You guys discussed where on the vaginal wall the swab should be and should not be at the cervix, etcetera. So that would be something I
want -- think the panel should be careful about --

   DR. SCHWEBKE:  I agree.

   DR. HABIG:   -- in ensuring it's done well.

   DR. SCHWEBKE:  Umm hmm, I agree.

   CHAIRPERSON NIPPER:  Thanks.  Ms. Kruger, do you have anything?  Dr. Everett.

   DR. EVERETT:  Just one.  What are you proposing to tell the female the indications for the use of this device?

   DR. SCHWEBKE:  What am I proposing?  I'm neutral about this whole issue.  The indications, I guess if it, from the thought that I've given to this issue thus far, if I'm understanding your question correctly, I would favor it being used for diagnostic purposes rather than screening purposes.  So I would favor this being available for a woman who has an abnormal discharge or odor and it being a tool that's available to her for, for that decision point that we've talked about.

   So that if she does have symptoms and if this is a normal pH, then somewhere in the text it's saying this is highly suggestive that you're problems are from a yeast infection or are not due to bacterial vaginosis.  Some language around that point.  I'm really not extremely enthusiastic, personally, about
it being used as a screening test, for the reasons that I mentioned before. Is that getting at what, is that your question?

DR. EVERETT: Yes, it does. And what would you tell them for those who are asymptomatic? Without running the list of symptoms.

DR. SCHWEBKE: Yeah, see, that's where I think you get into some muddy water and that's why I'm, I would ask, I would suggest that it be very carefully considered if it's to be licensed for an asymptomatic population. Because it, I mean I think we saw data before that the predictive values become less, less well interpreted for an asymptomatic population. And you know, if you were to say something like, well, here you are asymptomatic, check your pH, if it's elevated, see your doctor.

And she ends up going to the doctor and maybe has asymptomatic BV. That may put some health care professionals in an awkward position because the formal guidelines are not to treat asymptomatic BV.

So there is some dilemma there. There is some tension there about our current state of knowledge about some of these conditions and the information that we would be empowering the asymptomatic woman with in that case. So I have some concerns about that.
CHAIRPERSON NIPPER: Do you mind if I open
the floor to some of our presenters from the public
hearing, if you'd like to comment on that particular
question, because the question went to what would the
intended use be.

DR. ROY: Well, I guess I take a different
approach in terms of the asymptomatic individuals. I
think we just heard that half of the BV is
asymptomatic and that the current guidelines say that
you don't treat that. But what's that based on. CDC
nor anyone else to my knowledge has information that
says that not treating those individuals leads to no
consequences. And I think part of what disturbs me is
that an agency like CDC will make a statement based on
lack of data and people go away from that with the
notion that it's based on established studies.

And I don't think that's necessarily true.
So I am concerned about sort of ignoring the
asymptomatic person who may have BV and not treat that
individual.

CHAIRPERSON NIPPER: What about the
question that Dr. Everett asked about what the
intended use of this device would be. Can you answer
that question?

DR. ROY: I think it comes down to the
reassurance factor, recognizing there will be a small proportion who will have a normal pH and still have some sort of disease process. But I think that will develop over time. I think one of the key aspects to this whole issue is, as was brought up, and that is education. I think as women become more informed about the subtle presentations of a variety of these vaginal conditions and what they then may be linked to in terms of associated disease, then they will be in a better position to seek assistance or make decisions in terms of managing their conditions.

CHAIRPERSON NIPPER: I'm still not sure we're at the intended use issue. I don't want to take your question away from you, Dr. Everett, but --

DR. EVERETT: No, I'm not sure either --

CHAIRPERSON NIPPER: Maybe we'll get to this in more detail later. Dr. Koumans, would you have any comments at this point?

DR. KOUMANS: I'd just like reaffirm that asymptomatic women may have other conditions in addition to BV, which Dr. Schwebke, Jane, presented. It might not only be BV, it might also be trichomonas. There might be other conditions that have led to an elevated pH which need to be evaluated.

DR. SCHWEBKE: That's true, yeah, I agree
with that.

MR. TSAKERIS: I'd like to --

CHAIRPERSON NIPPER: Yes.

MR. TSAKERIS: -- add something here. I sometimes think that when you talk about screening, you have to also define what you mean by screening, because there's different flavors of screening. There's, you can talk about screening the general population of women who are apparently healthy for the purpose of trying to determine whether or not there's a vaginal abnormality, that's one thing. Another context would be to look at selective screening. Women, in women perhaps who have had a history of vaginitis who are concerned about that or looking for some way to, now we're getting in, we're mixing terms, monitoring for their condition or monitoring their health status. That sort of mixes screening with monitoring and you're still dealing with an asymptomatic issue. It's my understanding, I haven't read the labeling lately for the over-the-counter antifungal medication anti-use medications, but it's my understanding, please correct me if I'm wrong, but I think initially the labeling for those products advised that these medications were not intended for first time episode vaginitis.
That they were intended only for recurrent infections. And so if you look at it, if you look at a so-called screening test for OTC vaginal pH in the same context that you would use the medication. In other words, it would be for screening/monitoring for recurrent infections. I think it would be consistent with how the medication is being used.

CHAIRPERSON NIPPER: Okay. Thank you very much. Let's resume questioning for Dr. Schwebke and we'll call you back if we need to ask further questions. Dr. Manno, do you have questions for Dr. Schwebke?

DR. MANNO: What would you say the likelihood would be for an asymptomatic individual to decide to go do this?

DR. SCHWEBKE: Oh, that's a very good question. I think it depends on what the advertisements say. And I think a good example of this is douching. Why is it that so many American women douche? Well, it's probably because there's been, well for one reason it's been handed down from generation to generation. Another has to do with commercialization of the product. So why would asymptomatic women do it?

I think they would probably end up doing
it as a result of whatever, you know, if there were commercials for the product or this sort of thing. That would be my guess.

CHAIRPERSON NIPPER: Dr. Sedlacek, do you have questions?

DR. SEDLACEK: No, not really, thanks.

CHAIRPERSON NIPPER: Okay.

DR. HARRINGTON-FALLS: I have no questions, thank you.

CHAIRPERSON NIPPER: Dr. Diamond, do you have any?

DR. DIAMOND: No.

CHAIRPERSON NIPPER: Dr. Tuazon.

DR. TUAZON: How would you envision the use of this in symptomatic women in terms of advantage of doing the pH? Because if they have a high pH, they will consult the physician anyway. So the utility of this is in those people with suspected candida infections where they can self-medicate, is that correct?

DR. SCHWEBKE: Yeah. I envision it, if, you know, I can envision a symptomatic woman using the product and then either, particularly if she's had a history of prior yeast infections and now has a normal pH with the product, feeling assured that, oops, this
is my yeast infection again and I need to do OTC. But
if it's not a normal pH, if it's an elevated pH
saying, or you know, that woman or another woman
saying, I need to consult my physician.

DR. TUAZON: So she goes to the physician
regardless of --

DR. SCHWEBKE: Yeah, well she's going to
have to because if she has an elevated pH, as was
pointed out before, there's no OTC products.

DR. TUAZON: So I think the advantage of
this is in those women, symptomatic women with low pH,
right? And what percent of those people with
vaginitis would have that?

DR. SCHWEBKE: Well, it depends on how you
look at it. I mean I can look at it both ways. To me
it might be beneficial if I noticed I had a high pH to
go to the physician and be diagnosed with trichomonas
and appropriately treat it. So I can look at that
both ways.

DR. HARRINGTON-FALLS: Could I also --
this is Dr. Falls. I'd like to also add in that we've
been presented with several scenarios where some
people will medicate no matter what.

DR. SCHWEBKE: Except the --

DR. HARRINGTON-FALLS: And some people,
even with a diagnostic test will not see health care providers.

DR. TUAZON: I think that's true for the cream, because this may be available to them before. But for the oral preparation they still need a prescription.

DR. SCHWEBKE: Right.

CHAIRPERSON NIPPER: Dr. Diamond, did you have something?

DR. DIAMOND: No, I did not.

CHAIRPERSON NIPPER: Okay. Dr. Koumans, did you have something else to add or to question? Dr. Rifai, any of the other panel members? Dr. Rosenbloom, did you? Okay. Well, we thank you for your presentation.

DR. SCHWEBKE: Sure, thanks.

CHAIRPERSON NIPPER: And I hear from my scuttlebutt about Birmingham that the Vulcan statue is in trouble.

DR. SCHWEBKE: Do you want to send a contribution?

CHAIRPERSON NIPPER: Yeah, I think we ought to, we ought to seriously think hard about that. For those of you who don't know, Vulcan is the statue in Birmingham of the person made of steel or iron and
honoring the ironworks in Birmingham that are now rusty in the rust belt category.

DR. SCHWEBKE: It was falling apart and threatening to fall on people.

CHAIRPERSON NIPPER: Yeah, Vulcan is rusty himself. I used to enjoy going to see Vulcan when I was a kid. At this point we're going to move to open committee discussion. We've already had some discussion already. I put Dr. Cooper on the spot to find some prevalence data for us and I think she's got it. My question was, in the summary data that she showed us, what were the prevalence, what was the prevalence of bacterial disease in all population, the symptomatic population, asymptomatic population in both non-pregnant and pregnant women.

And what I was trying to do was to get an idea about what, what, how many false positives we're going to see if we, if we use this product in broad screening, screening of everybody that came in the general population. We'll get there in a second. Yeah, it's coming out. You just need to turn that overhead thing off. It, the overhead really affects that, what we can see on the screen. Yeah, that's better, Bob, thanks. I think you've got a second career ahead of you.
DR. COOPER: What you're looking at is analysis of the three pivotal studies that were provided to us. The, what the table you're looking at is the recalculated positive prevalence values and negative prevalence values.

DR. TUAZON: No, that's the next table.

DR. COOPER: And the actual prevalence values, not the recalculated ones.

DR. KOUMANS: Those aren't prevalence values.

CHAIRPERSON NIPPER: Those are positive predictive values.

DR. COOPER: Positive predictive, I'm sorry, positive predictive values. The actual prevalence values for, calculated for the positive predictive value and negative predictive value are on all women, whether they are non-pregnant or pregnant, is 12 percent. And that in the non-pregnant population it's based on over six million, an N of over six million, it looks like. And in the pregnant, it's 700, close to 800,000.

And in the symptomatic population for non-pregnant and pregnant, it's 30 percent for both of those, symptomatic. And the asymptomatic population, for non-pregnant, is six percent, and pregnant
population is 12 percent. So the, to sum it up, the
prevalence is 12 percent for all, 30 percent for
symptomatic. The only one that's really different is
the asymptomatic population where non-pregnant is six
percent and pregnant population 12 percent.

CHAIRPERSON NIPPER: And the data I show,
shows that the total number of non-pregnant women
screened was 53 million and some odd, 284,000 and so
six percent of that 53 million would be, would have
disease. Is that, do your figures --

DR. COOPER: I have 63 million, but that's
okay.

CHAIRPERSON NIPPER: No, yeah, it's
probably a typo. But a million here, a million there.

DR. KOUMANS: I'm having trouble with
these figures. I'm having trouble with these figures,
I'm sorry. There's an N on Study One of 311, and an N
in Study Two of 46, and an N is Study Three of 661, to
get a prevalence of 12 to six percent don't need to go
to six million.

DR. COOPER: I don't have an explanation
for the difference in the --

CHAIRPERSON NIPPER: Yeah, they're in
the -- this is a -- there's a group of literature,
this is not this group of N 311.
DR. KOUMANS: Oh, I'm sorry.

CHAIRPERSON NIPPER: Yeah, it's a literature review of one, two, three, it looks like about a dozen papers. And the prevalence ranges from, in the data that I was given, somewhere between six percent and up to 23 or 24 percent, roughly. But I appreciate that. Even though it sounds confusing, I think it helps me a lot to put in perspective what kind of prevalence we're talking about with the disease.

DR. COOPER: Yeah, I think what it is, is the company itself did three different studies. But the summation of all of it, including the literature, is where we're going with it.

CHAIRPERSON NIPPER: Yeah. And I'll be glad to share that with the panel at an appropriate time when we get a xerox machine going. Do I have to get permission? Okay. Well, anyway, I'm just trying to shed a little light here. Thank you. At this point we are open, the meeting is open for committee discussion. And we can proceed in the way that the panel feels we should, whether we have further questions or comments, we can take those ad lib, we don't necessarily need to go around the room formally to do that. We have a little time to develop the
If you have questions for other people who, people who have given this data, now is the time to do that. We have about 45 minutes before the schedule calls for lunch, and we can proceed however you see fit. I think that our assignment, between now and the time we leave, correct me if I'm wrong, Ms. Calvin, is to answer the questions. And of course we're going to have another open public hearing later this afternoon. Does anyone on the panel have comments or questions at this point? Yes, Dr. Falls.

DR. HARRINGTON-FALLS: The use of the pH screening to the public would be very helpful for women that are using the over-the-counter yeast medications. It's almost too bad we can't include that in their packaging at this point, because by the time a woman buys one of those preparations, to be able to determine on her own, particularly if she has not had an examination by a physician, whether it's an appropriate use of the medication is just out of her range to be able to tell.

I do have some concerns about it being used as a diagnostic tool, particularly in pregnant women. I feel that there are a lot of issues that the women need to discuss with their doctor and it ends up
putting them in an adversarial position with their obstetric provider.

CHAIRPERSON NIPPER: Thank you. Are there other comments, questions, concerns at this point? Dr. Habig.

DR. HABIG: I think this question would be for Dr. Schwebke. In the presentation of the probably month long study that showed high levels of lactobacillus and low levels, except for the general population, there were excursions where the lactobacillus went way down and other things came up. In those studies, I think that slide you showed was a summary slide that had a lot of different women examinations, it was not a single person.

DR. SCHWEBKE: That was a single person. There were two single people. The first slide was a woman who was very consistent --

DR. HABIG: Okay.

DR. SCHWEBKE: -- and the second woman was a representative of women who have a lot of variability.

DR. HABIG: Okay. And in that, in those excursions though, away from sort of "normal", did you have data from that subject on other factors, so that were you able to say, oh, well that was probably
because of?

DR. SCHWEBKE: Well, not exactly. What we were able to do was, in a study that, a similar study that we did like that where we saw the same distribution of patterns, we looked at correlates of that variable pattern, which I don't think is quite what you're getting at. I think what you're asking is on those days where their lactobacillus population went down, were they symptomatic? Is that kind of where you're going?

DR. HABIG: Actually not symptomatic about vaginal conditions but just could that have happened after intercourse? Would that have happened with a cold or a runny nose or, you know, of those kind of other factors?

DR. SCHWEBKE: Right. We asked questions of the women concerning their, certainly their sexual behavior, douching, use of vaginal medications. And what we found overall was that the women with the variable pattern were more likely to have increased number of sex partners, were more likely to be, have an increased level of sexual activity. So that the variable patterns seemed to behave, if you will, like a sexually-transmitted disease and that it was correlated with, you know, number of partners,
increased episodes of intercourse, these sort of things.

We did not find, one of the things we specifically looked for was, for example, douching. Was there day-to-day variability in the bacteria as a result of douching. We were not able to demonstrate that. That may have been a result of the women, for some reason, deciding not to douche while they were in the study. So we didn't have very many events to look at, but we did not see that correlation. So all I can say is that in general, an increased level of sexual activity was predictive of that variable pattern.

CHAIRPERSON NIPPER: Yes.

MS. FRENCH: I'd just like to share with you, there's another paper that's published by Frances Keane from the UK, which was similar to Dr. Schwebke's study where she followed 21 women daily through their menstrual cycle and actually, in this study, was able to identify three different patterns of vaginal flora for these women. Approximately one-third or 40 percent of the women had normal vaginal flora throughout. And another third or 40 percent had an abnormal pattern throughout.

And then there was a group, approximately 19 percent of women who had the variable pattern. And
what Frances was able to show was the pattern most often changed in the first phase of the menstrual cycle, approximately Day 7 to 9 was when you noticed the shift in vaginal flora towards the abnormal. And she also found that an elevated pH was present among these women prior to the shift in flora. And I can get, leave copies of this for the panel if they like.

DR. SCHWEBKE: Janice, thank you. That was also, we also noted the relationship between a point change or a significant point of change was related to menses.

CHAIRPERSON NIPPER: I'm glad for you to make comments, but let me remind the speakers you need to go to the microphone. I'm not sure our, did you get that at all? Would you like it for the record? I'll need you to go to the microphone. I'm not smart enough to read.

DR. SCHWEBKE: I was thanking Janice for reminding me that in our study we also saw a significant relationship between menses and the timing of these shifts in the bacterial flora.

CHAIRPERSON NIPPER: Thank you for doing that to accommodate the record. Are there any other comments? Yes, Dr. Koumans.

DR. KOUMANS: Yeah. In speaking to some
of my colleagues at CDC, there are a number of questions that have come up regarding the use of a product like this. In particular, something that, it was unfortunate that Janice Rupkey couldn't study this in her prospective study of women, but the risk of douching associated with having a test that's positive or negative on the basis of this pH. And we're concerned that there be some important information in the labeling, if this is, you know, to be approved, that douching will not treat a high pH and that douching may actually lead to a high pH.

So that it may be a reason for a positive test and it's not a good method to treat a high pH. I think both of those things should be in there. There's a lot of literature, similar to the BV literature linking douching to ectopic pregnancy, to pre-term delivery, to a variety of other adverse outcomes among women. So I think that would also be important information.

CHAIRPERSON NIPPER: Good. Dr. Janosky.

DR. JANOSKY: I'm trying to think through the issue of what would be appropriate claims for the product. And I think that either Dr. Schwebke or, let's see, Ms. French, might have presented some data, but I'm not sure whether I remember it correctly or
not. What I'm actually looking for is a two by two table where you look at pH value for the cutoff and then for the other outcome, either for screening or diagnosis, whether a disease process is present or not.

Not which particular one, but just any of the following that you had talked about. Do either of you have data that would show us, just as a general screen or if the pH is a certain level, is something going on? Not particularly what might be going on, but just something. I thought Ms. French had some data presented, no?

CHAIRPERSON NIPPER: Dr. Roy may have --

DR. ROY: I think the paper by Dr. Caillouette in the American Journal. That was a group of asymptomatic individuals who came to his practice and who were screened. And the branch point, the two by two table was comprised of those who had a pH less than or greater than four and a half. And so that was at least a small study looking at that issue of branching it out according to any of the pathogens, not just BV, but Group B strep, Gardnerella vaginalis or a mixture of those anaerobes.

DR. JANOSKY: Do you happen to recall what those values were in terms of sensitivity and
specificity?

CHAIRPERSON NIPPER: Is this the table that you showed?

DR. ROY: Yes.

CHAIRPERSON NIPPER: Would you mind if I read it?

DR. ROY: No, go ahead.

CHAIRPERSON NIPPER: Okay. I got a copy of this over the break and as I'm, I was still grubbing around with prevalence. I wonder if there's a way to put it up on the -- is this one of your red tables or was this a pretty good picture?

DR. ROY: I think it was one of the ones that I was able to show.

CHAIRPERSON NIPPER: But you're not connected up anymore, are you?

DR. ROY: No.

CHAIRPERSON NIPPER: Well, let me just read it and we'll see if that does enough for the panel. If the panel needs the information before. If you make your two by two table with bacterial vaginitis up at the top, and bacterial vaginitis positive with a test positive, that's true positives or 61. I don't know whether Dr. Janosky, that's the one you were talking about?
DR. JANOSKY: No, I was actually looking for any disease process, not just BV.

CHAIRPERSON NIPPER: Okay.

DR. JANOSKY: So if, Janice, I'm just trying to grapple with the issue of what would be the claims.

CHAIRPERSON NIPPER: I've got another one, all right. This was -- okay, disease positive, disease negative, this was a fairly low end? Okay, we're getting there. Thirty-three true positives, 12 true negatives, zero false-positives, pardon me, zero false-negatives and one false positive for a sensitivity of 100 percent, specificity of 92 percent.

DR. JANOSKY: That's helpful.

CHAIRPERSON NIPPER: Yeah. Well, I did my, I did some calculations on the six percent prevalence and if you assume 100,000 population that you're going to do screening of asymptomatic people and you assume the sensitivity and specificity of 75 percent which is, I think I've seen some figures like that. To find, you're in this, 1,500 patients when you do that. And you're going to find 4,500 truly ill people, but you're going to have to wade through 23,500 people who have false-positives. That's the trouble with a low sensitivity test in an asymptomatic
DR. KOUMANS: It's the trouble with a low specificity test.

CHAIRPERSON NIPPER: I'm sorry, thank you for the correction, it's the trouble with a low specificity test in an asymptomatic population. And we can argue about whether the specificity is appropriate or not, but even so, you've got to have fairly high specificity in order to do a screening test. Otherwise you're going to be, you're going to weight down the system with a huge number of people who are not ill. Dr. Rosenbloom, did you have anything to add?

DR. ROSEN BLOOM: No.

CHAIRPERSON NIPPER: Okay.

DR. SEDLACEK: I have a question.

CHAIRPERSON NIPPER: Yes, Dr. Sedlacek.

DR. SEDLACEK: I may have missed this, but in the material that I read prior to today's meeting and today, I couldn't satisfy myself that I understood the frame of reference for the pH measurement. Basically, how accurate is the device before us today? When I look at the, at the, one of the studies in our handout, a study by Sagawa, et al, they used a digital pH meter to measure pH in the population of pregnant
women.

Are there studies that compare the accuracy of this device to a pH meter?

DR. CAILLOUETTE: I have it in this large book, it's Dr. Amsel's study. And Dr. Amsel did use a pH meter along with indicator paper. And I think it's fair in saying he concluded they were very comparable. But I will find that for you.

DR. SEDLACEK: Thank you.

CHAIRPERSON NIPPER: If the panel has no further questions or comments, I think I'd like to break at this point for our lunch break and then let's come back with, in a hyperglycemic state and answer the questions. I don't know whether I'm, I don't know whether other panel members felt as guilty as I did yesterday about eating candy in front of the diabetics, but I've eaten a lot more candy today, so I think that we have, we have our finger on some of the issues about this particular issue, about the vaginal pH.

Maybe questions will occur to us over lunch time that we need to ask. We'll open it up for further questions and then we'll look at the questions the FDA has asked us to consider. There is a distinct chance that we will be finished and ready for the open
public hearing which is scheduled at 2:00. There is a chance we may open up earlier for that.

So if there is anyone in the audience who is presenting, you might want to come back early after lunch. Since we're breaking at a quarter of 12:00 and we're scheduled to reconvene at 1:15, could we reconvene at 1:00? Would that put any pressure on anybody? Okay. That would give us a chance to go pack our bags if we need to and then be ready to do our business this afternoon. Okay, so hearing no dissent, we'll break for lunch.

(Whereupon, the foregoing matter went off the record at 11:48 a.m. and went back on the record at 1:04 p.m.)
CHAIRPERSON NIPPER: Okay. If we can get started. If you'd look over to Steve Gutman's chair, you will notice Steve is not there. And then we've got Dr. Woods in the audience also backing us up, hopefully keeping us straight. All right, predicting that I've stirred up a hornet's nest, maybe not hornets, we've just, we've generated some further comment and our morning presenters would like to clarify some issues regarding prevalence and how the test performs. Who's going to do it? Now we haven't heard from you yet.

DR. FADEN: No, you have not. I'm Joel Faden, Ph.D. I am a Regulatory Consultant and I'm a paid Consultant of this company.

CHAIRPERSON NIPPER: Yes.

DR. FADEN: I am responsible for a number of things that you may have or may not have. One of them is that big binder on, the binder that's sitting in front of him.

CHAIRPERSON NIPPER: Oh, this binder.

DR. FADEN: Which is a generic discussion of vaginitis. I also produced a nine or ten page, it was originally a letter to FDA which reviewed the, the
various studies that existed at that time, and
summarized them and tried to present some idea of what
the worst case scenario would be. And that's one
thing I'd like to correct. Those numbers that were in
there for prevalence were my review of the literature
and then saying what are the ranges that exist in the
various studies?

And then I took the low end of those
ranges and said, this would be the low end and
therefore given this, what would, given this
prevalence, what would be a reasonable estimate of
positive predictive value and negative predictive
value. So it was all theoretical, it was all worst
case scenarios. What I would like to point to today,
at this point in time, however, is studies that were
presented this morning which are really larger studies
and also maybe more accurately reflect those numbers.

The presentation by Janice showed a
positive predictive value of asymptomatic patients in,
I believe, in the 60 some percent range. Also Jane's
presentation, when she showed her numbers, the PPV was
also I think around 70 percent. So I would perhaps
use those, mine is only merely a theoretical
presentation for worst case. Can I clarify a number
of other things too?
CHAIRPERSON NIPPER: Let's don't move off that subject there --

DR. FADEN: Sure.

CHAIRPERSON NIPPER: -- so quickly. When I teach the medical students at Creighton about Bayesian statistics, one of the points that I try to make is that prevalence changes predictive value. And there's no better case to use for that than when you do what I call a well patient screening or asymptomatic patient screening.

So if, what I like to do is look at, I'm looking at this product in a couple of different ways. One is that if you have a situation such as we heard about from Ms. French, who had a high prevalence population, but then I wanted to contrast that without taking anything away from the presenters, from Dr. Schwebke or Ms. French, I'd like to contrast that with an asymptomatic population.

So that's why I was looking for the prevalence in an asymptomatic populations or essentially a population that might walk into a drug store or wherever they pick this product up and say, oh, this looks interesting, I might do this. So that's why, that's why I asked for the numbers because I wasn't trying to distance myself or devalue any of
the presenters' information. But I still think it's valid to look at what the prevalence is, the prevalence of these diseases are in asymptomatic populations that may walk up and buy this test, buy this device to use on themselves.

DR. FADEN: And see that's why I wanted to get the worst case from the literature that I could find, for those numbers. That was the six percent and the 12 percent.

CHAIRPERSON NIPPER: Right.

DR. FADEN: But again, Janice's asymptomatic patients were 80 percent and of those, they had a very high positive predictive value. Maybe we're concentrating a little too high on positive predictive values.

CHAIRPERSON NIPPER: Well, I like to also look at sensitivity and specificity as well, because if we're looking, if we're doing screening we need a high sensitivity test. And if this test is not as highly sensitive as we'd like to have, maybe -- I should state that in a positive way. If this test is, a device is a high sensitivity device, then you can look at, you can look at it as a screening situation.

DR. KOUMANS: Can I, can I correct that again. I don't think the mic is on.
CHAIRPERSON NIPPER: Yeah, it is now.

DR. KOUMANS: This specificity is the criteria that you would like to have be high in a low prevalence population.

CHAIRPERSON NIPPER: In some cases, it is. On the other hand, I respectfully submit that if you're looking for disease in a low prevalence population, you still need a high sensitivity test. Because sensitivity gives you the index in which you find disease. If you have a low sensitivity test, if doesn't matter what the specificity is going to be, you're not going to find the amount of disease you need.

DR. KOUMANS: Actually with a chlamydia culture test, which has a sensitivity of about 50 to 60 percent. With a specificity of 100 percent, you can reduce the prevalence by screening using that test.

CHAIRPERSON NIPPER: Yes, you can. But I would, without meaning to be argumentative, I would cite to you that if you had a better chlamydia test with a higher sensitivity, I bet you'd walk into that and walk away from the test you have with only 50 percent sensitive. If you're looking for disease, you've got to have high sensitivity, as high as
possible. It's not to say you can't take a low sensitivity test and find disease, but you're going to have a lot of overhead doing it.

DR. KOUMANS: Right. I mean, I think in terms of a test that determines disease versus not disease, the best way to determine a sensitivity or specificity cut-off is an ROC test, ROC curve, which in this case you presumably have already done or that's been done in the literature for decades. And that's already been determined to be a certain cut-off. So we're not having a discussion about ROC curve anymore.

CHAIRPERSON NIPPER: We haven't seen an ROC curve, to date.

DR. KOUMANS: No, we haven't. I agree.

CHAIRPERSON NIPPER: Okay, have we clarified the issue?

DR. FADEN: Can I make a couple of other comments while we're on this?

CHAIRPERSON NIPPER: Sure.

DR. FADEN: First of all, this is a generic discussion, so I've made all my product for the panel to be generic. This not a discussion of a particular product at this time. In that vein, we have also in the past provided FDA labeling, proposed
labeling for products like this to complete the product. And some of the points of that I'd just like to make clear. The indication was not to tell somebody to go do a test if they get low value, I mean to a treatment if they got a value less, we did not say that.

We merely said that a value greater than 4.5 is indicative of a bacterial infection, please contact your physician. The other thing was that the labeling warned against doing the test within 24 hours of sex, douching, menses and a couple of other things. I believe we also warned against this test being interpreted in any way to be related to any sexual disease, such as HIV or gonorrhea or any other diseases.

So those were in the labeling to warn against the idea that you should contact your physician whatever your results were, results in the labeling. I just wanted to clarify those points while I was up here.

CHAIRPERSON NIPPER: Okay. Does the panel have any comments or questions about this issue or these issues?

DR. KOUMANS: Yes, I am, I'd like to follow up on Dr. Janosky's question earlier on having
a two-by-two table showing BV -- not BV, pH above the
cut-off, below the cut-off and then disease, yes/no.
And I'm wondering whether Ms. French, Janice, would be
able to pull that together from the data that she has?

MS. FRENCH: I could pull it together from
the data, but unfortunately I don't have that data
here. I can get it and send it to you.

DR. KOUMANS: We could calculate it.

MS. FRENCH: I don't have the raw numbers.

DR. KOUMANS: You have the total --

MS. FRENCH: I don't have the raw numbers

here to make a two-by-two table --

DR. KOUMANS: But you have the total --

MS. FRENCH: -- for any infection versus

no infection.

DR. KOUMANS: But you have total sample

size and you have prevalence of each of the

infections.

MS. FRENCH: Okay. Let me think about it.

CHAIRPERSON NIPPER: Any other comments?

Okay, thank you. At this point we can spend some time
and I'm not sure the panel is ready yet because we're
still asking for data or for information. But I, we
have several questions that have been raised by FDA
staff about these devices. So I guess what I'd like
to do, if the panel is willing to do that now, is to
go through the questions and see what our panel's view
is about this particular device that's in front of us.

Question 1, I'm not sure, yes.

DR. HABIG: Just before you start that, I
wonder if I could ask a question.

CHAIRPERSON NIPPER: Sure.

DR. HABIG: It is not clear to me the
basis of this meeting. That sounds really fundamental
but it is apparently we are not here looking at an
individual device. I'm not sure what FDA wants from
us and I'd like to know that. I mean they want the
answer to these questions but in the context of what?

CHAIRPERSON NIPPER: Dr. Cooper.

DR. COOPER: I'm speaking for Dr. Gutman.

What I think we're trying to obtain is not a vote.
We're trying to get some input so that we have help
with the decision-making process for these types of
products. Does that answer your question?

DR. HABIG: Almost. Would you expect to
write a guidance document on this subject?

DR. COOPER: I think that's something we
could consider. I don't think that was something we
originally intended to do. But it would help give us
some clarifications of input from the panel. I mean
that's what we were hoping to obtain so that we could then get clearer in our mind which direction we're going and that might, down the road, lead to a guidance document. But I don't think that was the original intent.

DR. HABIG: May I continue?

CHAIRPERSON NIPPER: Please, do.

DR. HABIG: Do you have 510(k) submissions that you are looking at from some of these sponsors to put a product, to clear a product to market?

DR. COOPER: That's part of the consideration process, yes.

DR. HABIG: Okay, from an industry perspective, it seems to me there is already guidance about, if products are cleared for professional or prescription use there is a pathway to get to OTC use clearance. So these questions that we answer are going to help you formulate how to allow companies to get through that route?

DR. COOPER: I think there's general guidance for over-the-counter use, but I think the questions we're asking are over and above what's in the guidance. Issues come up periodically in the review process which aren't particularly answered in the guidance. Our guidances are generic as possible.
And sometimes we run into situations, such as we have. These questions represent that we would like some input on so that we have some more information so that when we make a decision, it's the best possible one we can make.

DR. HABIG: Thank you.

CHAIRPERSON NIPPER: Thanks. Does any other member of the panel have questions, further questions in this regard? Okay. Before we start to answer Question 1, I'm reminded, when we started talking about Dr. Gutman, I'm reminded that during the lunch break Dr. Gutman asked me to further refine Question Number 2. So I'd like to tell you about that further refinement so that you can be thinking about your answer as we work on Question 1.

Question 2 deals with intended use for an OTC product or measurement of vaginal pH. He would like that, to break it down by four groups. In other words, to consider Question 2 as having four parts. And what you'll do is pan to the sentence or the question such that the first part would read, what intended uses are appropriate for an OTC product for measurement of vaginal pH in an asymptomatic, non-pregnant population. And then we'll take the same prefix and add, in asymptomatic pregnant population.
Third, in a symptomatic non-pregnant population, in a symptomatic pregnant population. So, that we'll actually ask, have four sub-parts to Question 2. Then, if you think about it, Question 3 then changes because Question 3 deals with should the device be used with pregnant women? Obviously we're going to be dealing with intended uses in pregnant women in Question 2, now. So let's line through the first question there, the first part of Question 3.

And that leaves, would any additional testing be necessary for pregnant women? Then Question 4, deals with labeling. And the labeling question, also Dr. Gutman would like us to try to break down our answers in the four categories that Question 2 is broken down into. In other words, should we have a labeling different for an asymptomatic population, either pregnant or non-pregnant versus a symptomatic population, pregnant or non-pregnant.

So he's interested in the four subcategories of women that would be using, potentially would be using this test. So I guess we're back, does anyone have any questions about the changes to the FDA questions? Yes, Dr. Habig.

DR. HABIG: I do. Is, is there reason to
suspect a difference in performance with pregnancy versus non-pregnancy?

DR. HARRINGTON-FALLS: This is Dr. Falls. Intuitively I think there are the potential for more pH changes in the pregnant woman due to different secretions.

DR. HABIG: Intuitive is pretty good, but --

DR. KOUMANS: There is data.

DR. HABIG: -- based on what?

DR. KOUMANS: There is data on pregnant women that pH tends to, BV prevalence goes down during pregnancy and I don't know what pH does.

CHAIRPERSON NIPPER: Did you say PV or BV?

DR. KOUMANS: BV, bacterial vaginosis prevalence during pregnancy goes down.

CHAIRPERSON NIPPER: Thanks, I'm just thinking of the transcribers.

DR. KOUMANS: And I believe --

CHAIRPERSON NIPPER: Okay, I'm sorry, I didn't mean to interrupt you further. Yes, Dr. Rosenbloom.

DR. ROSENBLOOM: Certainly one reason for decreasing pH would be the high estrogen levels associated with pregnancy as a mechanism.
DR. KOUMANS: Right.

DR. HABIG: Okay, that, the performance, the technical performance is what I was interested in. Is there any reason to believe that the ability to, of these devices to test accurately the pH, would change. I want to subcategorize this, because my fundamental question is, what's different about pregnancy? So it's not the actual performance? If you get the pH, it's going to be the pH. It's the why would pH be different in pregnancy and, then I presume also, the differential decision making that would occur after you get the result.

CHAIRPERSON NIPPER: The ROC curve may change.

DR. HABIG: Okay.

CHAIRPERSON NIPPER: Okay?

DR. HABIG: Yup.

CHAIRPERSON NIPPER: Did I get that right?

DR. MITCHELL: Excuse me, hi, I'm Diane Mitchell and I'm an Obstetrician/Gynecologist with the FDA. I think one of the reasons why we wanted to separate out pregnant versus non-pregnant individuals, is because the potential for having to use the device in pregnant versus non-pregnant individuals was, would change. So it was the use of the device as opposed to
the performance of it.

CHAIRPERSON NIPPER: The medical reason for using the device?

DR. MITCHELL: How we would label it in terms of what we could tell women about what the information would mean.

CHAIRPERSON NIPPER: You see use of the device to an analytical chemist means how you perform the test. Use of the device to you, as an M.D., maybe the medical use of the device. So that's why we need to, I don't want to put too fine a point on it, but I think it's important that we clarify this. And I think that's what Dr. Habig is getting at. Is that we're, we're, we need to just make sure why we're differentiating.

DR. MITCHELL: Well, for example, screening populations for pregnant versus non-pregnant individuals to recommend that you -- if you're going to recommend that you use the test for screening in patients, just to examine them, to see whether or not they have the disease, you might behave, the physician might react differently to an asymptomatic woman who has, who's not pregnant, who has a alkaline pH as opposed to a pregnant woman who has, who's asymptomatic, who has an alkaline pH.
So it would be in terms of the labeling and the way you treat the person if the tests were examined and if the test comes back with an alkaline pH.

CHAIRPERSON NIPPER: Playing devil's advocate here, hadn't we already figured that out with the current device that's on the market that's not over-the-counter?

DR. MITCHELL: Well, current, no, I think, well the issues are different because of the fact that it's a physician who's handling it and making a decision versus the patient who's examining themselves or making the choice to use the device to examine her own vaginal fluids.

CHAIRPERSON NIPPER: But I'm thoroughly --

DR. MITCHELL: I mean part of --

CHAIRPERSON NIPPER: I'm thoroughly confused.

DR. MITCHELL: You may be right, but that's why we're asking you the question. In other words --

CHAIRPERSON NIPPER: We need to focus on the, we need to really fine tune this question. And I think Dr. Habig is right. I'll get to you in a minute. Okay. I thought you said, when you answered
this question was that there may be a difference in labeling because the physician may use the data differently.

DR. MITCHELL: That, okay.

CHAIRPERSON NIPPER: Okay? Now, we're talking about an over-the-counter device here. So when I came back at you and said, but we should have already answered that question about how the physician uses data because you already have a device that's in the hands of a physician, okay? Or we already have a test that's in the hands of the physician.

DR. MITCHELL: No, you're right, you're right.

CHAIRPERSON NIPPER: Okay, so, okay. So I don't mean to harass you but if we're, are we talking really about differences in labeling because the woman herself may use the data differently? Am I putting words in your mouth?

DR. MITCHELL: No, you're not.

CHAIRPERSON NIPPER: Okay.

DR. MITCHELL: I skipped the step which was an assumption, which is part of what you're going to talk about today. That regardless of the results of the study or the test, you contact the physician. So that's where the confusion lay.
CHAIRPERSON NIPPER: But there may not be such a contact, as people have presented this morning.

DR. MITCHELL: That's correct. That's correct, and that's part of what --

CHAIRPERSON NIPPER: And that may be part of the problem.

DR. MITCHELL: Yes.

CHAIRPERSON NIPPER: Okay, Ms. Kruger, you had your hand up next.

MS. KRUGER: Just a point of clarification. In diabetes in pregnancy or gestational diabetes, we might ask, we do ask all of our patients to check their ketones every morning. And we're not looking for ketosis necessarily in gestational diabetes, we're looking at nutritional therapy and adjustments we might need to make on their diet and insulin. And my question would be, in a typical Type 2 situation, we wouldn't use ketone sticks for the most part.

Would a physician recommend, is there an indication to recommend using a pH on a weekly basis or a monthly basis during pregnancy that might help the physician decrease the risk of a negative outcome to that pregnancy and hence that might affect how recommendations are labeled?
DR. DIAMOND: Those are all the questions we don't have answers to. And that's actually my biggest fear of having this available over-the-counter for pregnant women to use is someone will use it, will get a response and then will call their obstetrician and what do I do? And in the litigious environment in which we live and the physicians are going to feel compelled to respond in certain ways for the result of a lab test, the consequences of which we do know, which they may never have performed if it was something they were themselves doing in their office with something that was approved for physician use.

MS. KRUGER: So what you're basically saying, as an obstetrician you don't see the value of a regular basis, to have all the, once you get pregnant we should do the testing?

DR. DIAMOND: I don't if there is or there is not. I don't know, I don't think there is data now to say that we ought to be doing it on a routine, regular basis such as that every month. There are some data that we were given showing that it's helpful in identifying certain obstetrical problems, but none of them that I've read talk about using it in a systematic fashion periodically, week after week or month after month.
CHAIRPERSON NIPPER: Okay, do we have other questions of concerns before we start working on Question 1? Yes, Dr. Diamond.

DR. DIAMOND: This goes, perhaps, back to the same sort of issue. Do we know enough about, we've heard comments about various things that can affect vaginal pH, whether it's menstrual flow, semen, douching. Do we know enough about how long after these events those changes persist. We've seen some anecdotal examples in individual patients where perhaps the changes that we saw in flora were due to those sorts of events.

It would help me a great deal if we had good data to show that these changes were gone in six hours, 12 hours, 24 hours. What's the average for individuals and is it a function of estrogen in different phases of the menstrual cycle. How long are these changes going to persist for? And that also would be important if patients are going to be utilizing these on their own to make these determinations.

CHAIRPERSON NIPPER: That sounds like a suggestion for an intended, additional study.

MS. FRENCH: I'd like to address that.

CHAIRPERSON NIPPER: Yes.
MS. FRENCH: There is information from a study from Giles Monif, I think he's from Nebraska.

CHAIRPERSON NIPPER: He's at Creighton.

MS. FRENCH: Creighton, okay. Who looked at vaginal pH after douching and showed that within an hour, the pH was back to the level that it had been prior to the douching episode. And in, there's other information --

DR. DIAMOND: And, I'm sorry, what kind of douching was that? What was it being done with? Was it a basic solution, was it a neutral solution? Because all those things, I would envision, could influence the results greatly.

MS. FRENCH: You're right, that's a very good point. If it's an alkaline solution it may make a difference. So we would certainly ask women, when we talk with women scheduling their appointments we ask them not to douche prior to coming in. So that would be reasonably something to put in the labeling, reservations about douching. There's also information about changes in vaginal pH following intercourse, and I believe that also is a very short time.

It's older information from the '70's. Also after sexual intercourse the pH remains elevated for a short time. Not days, but more like one to two
hours. Does that help? I'm sorry, I'm Jan French, I'm a Nurse Midwife.

DR. MITCHELL: It helps a little bit, but if, referencing the data is from the '70's, not knowing it or being able to review it, still leaves me a little bit uncomfortable as to number of subjects. I would have to envision things like seminal fluid volume would have a big influence on that and the number of episodes of intercourse. And again, if we have this in the hands of the public to use, I'd like to know if those parameters are going to affect the results if it's within six hours or 24 hours or 48 hours, or whatever the time interval might be.

MS. FRENCH: I would think that, or I would hope that that would be something that we could address on the instruction sheet to the woman. That if she should delay testing after, for a certain amount of time after those, those incidents. And also that could be a question since we're, we would like to have them call if their pH measurement were high. That could be a question that the physician's office or the clinician's office would ask.

DR. MITCHELL: But, but, how, if we in this room don't have the answer and if you as the experts who have done these studies don't have the
answer, how is the physician's office going to respond when Mrs. Smith calls and says, "I've got this response." We have no guidance to give the physician's office on how to respond. That's what it sounds like.

MS. FRENCH: I think from my perspective as a practitioner, if a person is calling you with this information and I would, I would enlist her, her information and her desires in the decision to be made. I would recommend that if she had symptoms, certainly she should come and be examined. Certainly in pregnancy, anybody with symptoms needs to be seen by a care provider and have definitive diagnostic testing done. And I would recommend that to women when they call.

CHAIRPERSON NIPPER: But the question, the follow-up question I would have for you is that if -- and I'm certainly not an expert in this area -- but in general, in any medical issue, if you don't have data on which you recommend that a person access the health system, and you don't base that on information that's well developed by studies, have you used anecdotal or intuitive information? I'm sure that this is not a unique situation and I certainly understand why Dr. Diamond is saying this is not
different information to develop, for the most part of it.

I can envision these studies could be done. If Monif did them I know they are easy to do. But I know that he's a busy man and he has a busy practice and he was able to do these studies, you know, reasonably well. So, you know, it doesn't take big-time NIH funding to it, is my point. It can be done in a clinical setting in a clinical research setting. So I would think that it might seem wise to say these studies might be needed.

They might help both the over-the-counter market as well as the medical practice market, it would seem to me.

DR. DIAMOND: I think so.

CHAIRPERSON NIPPER: Do we have other comments? Yes, Dr. Sedlacek.

DR. SEDLACEK: Yes. During the discussions today I've had sort of a recurring nightmare about the patients with vestibulitis or vulvodynia, many of whom present to our offices with the complaint of a mild discharge and burning and itching of the vulva. Are you aware of any studies or is anyone aware of any studies looking at pH with this?
And when you start off with such a subjective issue as burning or itching vulva, isn't that a little bit shaky to start a scientific study on?

CHAIRPERSON NIPPER: It's a good question. Does anybody want to comment on that, either from the panel or from the presenters this morning?

DR. CAILLOUETTE: Caillouette. I would certainly agree with that. It's so subjective, I don't know how you would ever get parameters to work on a study such as that. You're absolutely right.

CHAIRPERSON NIPPER: Thank you. Well, are we ready to discuss Question 1? I'll read the question. Are there sufficient data demonstrating the association between vaginal pH and various states of vaginal disease to allow use of such an over, such a product in an OTC setting? If not, what additional studies would be needed? Dr. Rosenbloom, would you like to start?

DR. ROSENBLOOM: No. Well, that was an answer to your question. I would like the option of saying something, if I have anything to say, after I hear from the more expert people around the table.

CHAIRPERSON NIPPER: Is there someone who would volunteer an answer to start? Dr. Diamond.
DR. DIAMOND: I'll say something. I think the majority of the data I've seen today indicates that there looks like there's a very close relationship between pH and states of vaginal disease. And would lead me to believe that it would probably in the long run be a very good marker. I think there are, though, additional things that could be done and should be done and actually should be relatively easy to do, as you were indicating which would provide some important information for patients as well as for health care providers as to what are the influence of acute changes in the vaginal milieu, which may affect the pH readings. And are these changes that will last, over how long a period of time will they change? And I can envision that being tested relatively easy with initiating some of these events and then serially checking pH at hour intervals, two-hour intervals for six hours, 12 hours, however long it takes to get back to a steady state.

I think that would help me a great deal ultimately. But as I said, I think in the long run, I think once we have defined those issues more, I think the answer to Question 1 would be that there is sufficient data.

CHAIRPERSON NIPPER: Dr. Falls.
DR. HARRINGTON-FALLS: The answer to Question 1 I agree would be yes. And in light of the fact that we already have over-the-counter yeast medications available, I think this would be a very useful adjunct in that setting.

CHAIRPERSON NIPPER: Do you think any additional studies are needed?

DR. HARRINGTON-FALLS: Regarding the four populations that we're discussing, the asymptomatic and symptomatic, pregnant and non-pregnant, definitely. But just in terms of, you know, being able to say, yes, the test can determine the pH value, I would say no.

CHAIRPERSON NIPPER: Thank you. Do we have other panelists? Yes.

DR. KOUMANS: Yes, thank you. I agree that there does appear to be sufficient data demonstrating an association. And to follow up on the previous comment discussing asymptomatic versus symptomatic women, I think there are currently studies going on that may help address some of the questions that the presenters have had and I'm sure the panelists also have on asymptomatic vaginal infections.

At this point, we don't have those
answers. And on the other hand, we do have some data that shows, hopefully we'll get a little bit more before the end of the afternoon, but showing how good the pH is in distinguishing disease versus non-disease. I think the question in my mind is how much more data do we need?

CHAIRPERSON NIPPER: Dr. Tuazon, do you have a comment on Question 1?

DR. TUAZON: No, I think, I think as the previous comments. I think we have enough studies.

CHAIRPERSON NIPPER: Okay. Any of the panelists here, Dr. Rafai, Dr. Janosky, Dr. Rosenbloom, Dr. Sedlacek.

DR. SEDLACEK: I'm convinced on the basis of the reading I did before and today that there's a good association between vaginal pH and vaginal disease in the professional setting. I'm not convinced that we've really seen enough data to tell us that patient testing, to make that same correlation. I'd like to see the data I requested before lunch about the correlation between the pH paper and a more scientific way of measuring pH.

We've had different methods described. One is measuring in the distal third of the vagina. One is measuring in the middle third. It seems to me...
that there ought to be some kind of a more specific way to get the test done. I'd like to see a double blind study with the patient testing herself in a fashion that you would expect to be consistent with the labeling, in the doctor's office. And then have the doctor repeat the test.

And then you'd have some idea that the intended use, there will be some data to support the intended use. Absent that, we're making a jump from a to d and we're skipping b and c.

CHAIRPERSON NIPPER: Thank you. Dr. Manno, do you have an answer for Question 1 at this time? I'll speak into the microphone for you. She said she would go along with the previous comments. Okay. Dr. Everett, do you have comments, answers to Question 1.

DR. EVERETT: Yeah, I agree that there appears to be sufficient data for that association to be made between pH and various states of vaginal disease. My difficulty is trying to pull that association closer to the pH changes. That is, as you mentioned earlier about the menstrual cycle, that is a few days or, she didn't state exactly how many days, but there is a time period prior to the menstrual flow where pH begins to change.
But that itself didn't appear to be characterized as it relates to performing this test in a home environment. Nor was the incidence of having sexual intercourse. And it was mentioned that within a few hours it should return back to normal. But there was no data presented, in essence, as to what can I expect with the general population. So there are a number of variables that, in some instances, appear to pull that association between pH and vaginitis further apart.

And whereas, I would assume in an asymptomatic woman, if she developed vaginitis, that association between a pH change and the actual presence of vaginitis would be closer. And I guess what I'm saying is some of those variables, I think, should be pulled closer together or at least clarified in terms of what could I really expect if a patient called me up the morning after sexual intercourse and told me they had a positive pH change.

And I would not have, at this point, a good idea as to how long she should wait or if it occurred just prior to her menstrual flow, again, how long should she wait or how long should I tell her to repeat the test, wait and repeat the test? Or should she come into my office? And in a general sense, with
all of that, it sounds as though if one of my patients
called me up and said I had symptoms of vaginitis,
would I really have her do the test?

        Or would I just have her come in? So
again, there seems to be quite a few variables that
pull the association. Even though there is a real
association here, but in some instances that
association is far about and then in other instances
it's pretty close. And as we move to symptomatic
patients, the association should be really close, as
opposed to those that are asymptomatic.

        So what I'm suggesting is that more work
be done to pull the instances where there should be a
stronger association close together.

CHAIRPERSON NIPPER: Ms. Kruger, do you
have comments? Dr. Habig.

        DR. HABIG: I do have some. I think the
simple answer to Question 1 is yes, there is
sufficient data. I think the issue here is, ought to
be focused on can the test be done adequately by lay
people with instruction and can it be interpreted
correctly by lay people with instruction? Some of the
testing referred to earlier is probably useful, but
shouldn't be, isn't typically the criteria that FDA
uses to clear over-the-counter products.
This is a test known useful under the conditions already being used by practicing health care folks. And the issue is can it be used successfully by lay people over-the-counter? Personally, I believe a well-informed populous, a well-informed set of patients are their best health care advocates. And I think this would add to that.

The labeling has to be careful, but I don't think we should need to do extensive studies that would be required in order to get this product on the market as an over-the-counter product.

CHAIRPERSON NIPPER: Well, could I ask a follow-up and that's going to slide into Question 2. Do you see that the product is appropriate for all four groups that Dr. Gutman broke them out into? In other words, should this just be made available and that its, the intended uses should be the same in all four of the groups? Or do you think this should be, the intended use should be for symptomatic, non-pregnant women and that others should be told to come to the doctor? In other words, how do you think this should be labeled?

DR. HABIG: I've got to go back to the question I asked when we started this afternoon or the fact that we clarified we're not talking about a
product here. We're talking about how is FDA going to look at some series of products and typically the sponsor of a product makes claims and argues them through the process of clearance to the market with FDA. Intended use being the principle of them and typically the resolution of that is a negotiation about labeling with FDA.

It's a little hard to give generic advice when there's not a product, in fact, in front of us about intended use, because that tends to presume that FDA is going to tell the sponsor what their intended use needs to be before a sponsor brings a product to them. It should be the other way around. Sponsors describe intended use, which FDA chooses to clear or not. And then typically, as I said, that's done based on negotiation about the labeling, of which intended use is part.

Having said all that, I don't see a reason to differentiate the intended use. I see a reason to differentiate labeling. What do you do when you get a positive, an elevated or a non-elevated pH? But I don't see the necessity to break intended use out for the four categories that Dr. Gutman proposed.

CHAIRPERSON NIPPER: Okay, thank you. Ms. Kruger do you have any comments on Question 2?
MS. KRUGER: I would agree. The thing that still confuses me is why a woman who is totally asymptomatic would reach for this and pay cash for this? So, I guess, and then I guess if she were that symptomatic, I'm wondering why you wouldn't go in for a Gyn visit? But I guess I don't see the need to split it all out based on the fact that I just don't understand why an asymptomatic person, pregnant or not pregnant would want to be testing.

I haven't seen any information in the questions that I've heard or the information I've asked for that would, unless it was a marketing ploy, like someone said this morning, that would push someone to test for it. So I would not see the need to break it all out.

CHAIRPERSON NIPPER: Dr. Everett, how about you for Question 2, intended uses?

DR. EVERETT: Well, I tend to agree with her. That I don't really see a need to break it out, again, unless we're trying to pull the association between the change in pH and vaginitis closer together in one group. Or if it's expected to be different, let's say in pregnant women versus non-pregnant women, or is it expected to be different in those who are asymptomatic versus those that are symptomatic.
And I would think the test itself, in reality, from what we do in the office, I know it is different. That is when pregnant women come in and I do this test, I generally start thinking of things that might interfere with the test, just because she's pregnant, so I don't make the wrong diagnosis and treat her for something that she really doesn't have. But in the -- go ahead.

CHAIRPERSON NIPPER: I was just trying to tease out from you to tease away from your own personal office situation if you imagine the person in the drug store who had, was symptomatic, do you see, would you direct the intended use that way?

DR. EVERETT: Well, that's what I was coming to.

CHAIRPERSON NIPPER: I apologize for getting ahead of you.

DR. EVERETT: That's okay. But in the home situation I wouldn't expect the lay customer to do what I would do in the office. So I really wouldn't expect them to be, to be separated into those categories. So I would leave it simply the way it is, without breaking it down into pregnant, non-pregnant, symptomatic and non-symptomatic. I just don't think that's necessary.
CHAIRPERSON NIPPER: Okay. How about you, Dr. Manno, do you have a comment?

DR. MANNO: I'll go along with Ms. Kruger's comments.

CHAIRPERSON NIPPER: Okay. How about you, Dr. Sedlacek?

DR. SEDLACEK: To me the most compelling data that we've reviewed were the data relating to symptomatic pregnant women, because there's a great deal of potential outcome on the unborn child. The data that tell us about the controversy about treating the asymptomatic patient make me wonder what's the point of doing the test if we aren't sure the treatment is efficacious.

So that it would seem to me that the two most, the two pieces of evidence most supported in the literature are to use it for symptomatic, non-pregnant patients and symptomatic pregnant patients.

CHAIRPERSON NIPPER: Thank you. Dr. Falls.

DR. HARRINGTON-FALLS: Since pH is only one element of what's involved, we talked about the Amsel criteria which are four. The exam provides so much more of an opportunity to put it into perspective, that I don't think the lay person at home is going to have. In specific answer to Question 2,
one of the examples is if the result is non-alkaline, will that be used to direct use of antifungal cream? And I would say no in an asymptomatic person.

For the second question they had, recommendation that they see their doctor, I do think we need to include in the labeling that the user should be advised to seek a medical exam. Regarding the asymptomatic pregnant and non-pregnant patient, I just really feel strongly against pregnant women self-diagnosing themselves. And as you'll see later in some of the letters for the open session, there are some major causes for concern there as to what the population perceives the test will do as what it actually is meant to do.

CHAIRPERSON NIPPER: Thank you. Dr. Diamond, do you think we need to tease out the different subcategories in Question 2?

DR. DIAMOND: I think we do. I can tell you the question, the question was asked as we were going around the table, why would people pay money for a test if they are asymptomatic, they don't know what it's going to do? I can tell you my patient population, which is infertility patients, many of them would probably utilize these and other sorts of tests. And for sure, once they got pregnant, I think
there would be a high chance that they would try to do it after all they've gone through trying to conceive. They are going to probably try to do anything they can to try to avoid the potential of losing a pregnancy. So I can definitely see my patients reaching for this off the shelf, even if they are asymptomatic.

I would think that for asymptomatic, pregnant or non-pregnant, those would be reasonable groups. I think asymptomatic, non-pregnant would probably be a group that I would have the greatest trouble with. And I'm sort of in between on the asymptomatic pregnant. I share some of the thoughts that were just voiced about the anxiety that this would create in pregnant patients as they started the testing.

On the other hand, reviewing the manuscript that we were provided, not in our yellow folder but our other folder, which is from the Maternal Fetal Medicine Network, they don't come out and recommend routine screening, but they imply that that would have advantages to society and economic as well as far as cost of health care. And so I'm unclear as to whether that group should be screened or not.

CHAIRPERSON NIPPER: Thank you. Dr.
Tuazon.

DR. TUAZON: The problem I have with the asymptomatic non-pregnant woman is how often do you, do women do this in ordinary routine basis? And what do they do with the test? So I'm not sure that the asymptomatic non-pregnant woman needs it. For the asymptomatic pregnant women, I think these women come regularly to the Ob/Gyn's office, so they will be screened for the purposes of looking, ruling out bacterial vaginosis anyway. For the symptomatic, I think regardless of the, the only utility of the vaginal pH in the symptomatic group is in those with non-alkaline pH where they could use over-the-counter antifungal cream, which does not require any prescription from the physicians.

But the rest of the ones with positive or high pH, would still need to come to the physician for prescription or treatment purposes.

CHAIRPERSON NIPPER: Thank you. Dr. Koumans.

DR. KOUMANS: I have a couple of comments.

In our blue folder that the panelists got is a copy of the most recent STD treatment guidelines from the CDC. And they do distinguish between symptomatic and asymptomatic women who, both pregnant and non-pregnant
women. So I think it's an important distinction to make. In terms of, just to review that, for symptomatic pregnant women we recommend that all women are tested and treated to evaluate the cause of their symptoms. For asymptomatic pregnant women, our recommendation is that for women who have had a prior pre-term birth, physicians may consider screening and treating bacterial vaginosis. For example, to prevent pre-term birth. Now this is only for BV. But it certainly raises a distinction between asymptomatic and symptomatic pregnant women.

The, in terms of all the general population of asymptomatic pregnant women, to get to Dr. Diamond's question about whether or not there is any evidence. And I think a lot of people feel like there is an association between vaginal infections and pre-term birth. We just don't know how to adequately treat it yet.

And having, having a device that women can use at home, while it might be useful in the sense of picking up some infections and ruling out others, there's also the difficulty of practitioners not knowing what to do with the test result of someone done at home who doesn't actually have any symptoms. And we don't actually know what guidance to give
practitioners when, even when they do this test in their own office.

And certainly for asymptomatic non-pregnant women, I think it's even less clear. There is less evidence, although it's starting to emerge, that asymptomatic vaginal infections may lead to complications. But we don't have very much data and we certainly don't have guidance for practitioners on how they should further evaluate these women or whether or not they should be treated. So I think it's an important distinction to make, those four categories.

CHAIRPERSON NIPPER: Just to be clear, Dr. Koumans, the CDC guidelines that you refer to are the ones that are in the MMWR?

DR. KOUMANS: Right, that's in the blue folder. The one that's in our larger, that larger white paper is from a previous guidelines, it's from the '93 guidelines. The one that's in the blue folder is the '98 guidelines.

CHAIRPERSON NIPPER: Right. And these recommendations are, don't have a thing, don't, let me try it differently. These recommendations are for practitioners and management verifications?

DR. KOUMANS: Correct.
CHAIRPERSON NIPPER: So they don't refer to over-the-counter diagnoses or treatment in any way?

DR. KOUMANS: No, they don't. But it, this would, it's guidance for practitioners even if they were to do this test in their own office. It would be a similar situation of a woman coming in and saying, I have an alkaline pH, what do I do? And the practitioner, even with our current guidelines, doesn't have clear, we don't have clear evidence of what to recommend.

CHAIRPERSON NIPPER: And I think that we heard from Dr. Everett that that was particular, it might be, particularly be a problem if you don't know how to deal with a patient who comes in with test results, an asymptomatic person, non-pregnant woman. Did I get your --

DR. EVERETT: That's correct. Essentially they'd be evaluated as though they came in the office with that complaint, not evaluated based on, I got this result at home, and have to start the entire process all over again to determine if you have BV or not.

CHAIRPERSON NIPPER: Right. Dr. Rifai, do you have an answer to Question 2?

DR. RIFAI: No, I don't really have a
direct answer to your question. This is, as was
indicated earlier, is a quite unusual case. We
usually, we are asked about the indication of a device
after having the opportunity to review the performance
of the particular device and the specific questions
and then you'll determine whether it works in a
particular situation and doesn't work in another.

And here we don't have any of this
information and this is not my particular area of
expertise. All I know about it is what I heard from
this morning discussion. And we heard, on one hand,
that the prevalence, for example, in those who are not
symptomatic is relatively small. And then again we
heard even those with alkaline pH are asymptomatic,
there are no clear recommendations about what to do
with them.

So it appears at this point that you just
target those who are symptomatic, whether you do it on
non-pregnant or pregnant, to the other part of your
questions, I don't know really. We didn't see much
data to support one way or another.

CHAIRPERSON NIPPER: Thank you. Dr.
Janosky, do you have an answer for Question 2?

DR. JANOSKY: I actually would concur with
what Dr. Diamond had said earlier.
CHAIRPERSON NIPPER: Thank you. Dr. Rosenbloom?

DR. ROSENBLOOM: It seems to me, from the material we were provided, that there's only one of the four groups where it would make any sense to have home testing in an effort to reduce morbidity, mortality or morbidity. And that would be in the asymptomatic pregnant woman, since the symptomatic pregnant woman should be seeing her obstetrician. The symptomatic non-pregnant woman should be seeing her family practitioner, obstetrician or whoever takes care of her.

And the asymptomatic, we have no idea whether that's of value as a routine. And we have concerns about it being promoted much like the example of douches that are more harmful than they are helpful. So it seems to me that the, certainly in the high risk groups that are described in the New England Journal paper, that this is an additional risk factor that bears consideration, prima gravida. Just this, prima gravida as an independent risk factor is equivalent, is the same relative risk as bacterial vaginosis for being associated with pre-term delivery, 1.4.

And the greatest, most important risk
factor, of course, is previous pre-term delivery. And another risk factor of comparable magnitude to bacterial vaginosis is African-American race and I believe those are the major factors. So I think that the asymptomatic pregnant woman is probably the most, seems to be, to me to be the most important target population.

CHAIRPERSON NIPPER: Thank you. It's dawned on me sitting here looking at Question 3, should the device be used on pregnant women, we've lined that out because we've allegedly dealt with that in Question 2. Would any additional testing be necessary for pregnant women? Perhaps FDA staff could clarify for me whether they mean, whether you mean additional laboratory testing or clinical testing for pregnant women or do you mean additional studies? Do you know what the intent of that question was, anybody?

DR. COOPER: I'm going to defer to the M.D. of this group.

CHAIRPERSON NIPPER: Thank you.

DR. MITCHELL: I think the answer to that question is that we were thinking along the lines of additional clinical investigations.

CHAIRPERSON NIPPER: Yes.
DR. MITCHELL: However, if the panel feels that there also are additional non-clinical investigations that would be warranted, we certainly would like to hear that.

CHAIRPERSON NIPPER: Okay. But you're not talking about testing in the diagnostic situation? You're not talking about diagnostic testing for this? You're talking about clinical studies or clinical investigations that would clarify these issues, right?

DR. MITCHELL: That's correct.

CHAIRPERSON NIPPER: Okay, thank you very much. The people who have come to us and spoken several times are anxious to say something. Is it, is it something that can't wait until after we finish our questioning or do you, or are you trying to clarify a question that the FDA is asking, how are you doing it Mr. Tsakeris?

MR. TSAKERIS: There's something I'd like to bring up now.

CHAIRPERSON NIPPER: Well, come on.

MR. TSAKERIS: It seems to me that you're struggling with, you know, the various use scenarios of a vaginal pH test. I'd like to reflect back on my comments I made this morning and probably, or most of you maybe didn't think about it too much, but I think
it's quite important. And that is I think the model for these questions, at least in terms of how you answer these questions, may have already, the FDA may have already looked at some of these issues and perhaps we could hear from them in the context of the home-use test, you know, the dipsticks for UTI.

We brought this model up to them several months ago and asked that they look into the 510(k) clearance for those strips because, and personally I'm not sure that there's, it's in terms of the clinical utility issues. The clinical utility issues in my mind are very similar, in terms of asymptomatic, symptomatic, pregnancy, not pregnancy. These tests are being, are available and they are being used by women, both asymptomatic and symptomatic, both pregnant and non.

There is no limitations, at least as far as I can see, on that product. And so it seems to me the FDA has already struggled, or at least, maybe not so much struggled, but at least has already come to some evaluation of these issues and so, and I don't believe this panel has had an opportunity really to formally review that, unless maybe individuals on the panel had looked at the 510(k) submission.

But I'd like to hear from the FDA. What
have they, what were there concerns or what were their considerations that led to the clearance of the UTI strips?

CHAIRPERSON NIPPER: Well, I'm more than willing to open the meeting to that, but as I understand the agenda today, that we're not considering UTI strips. We didn't get the clearance information about it to consider. We have questions from us as a panel that we're supposed to discuss. I've invited you to clarify issues regarding the questions and it seems to me that you want to put us back into, into a different situation.

MR. TSAKERIS: No --

CHAIRPERSON NIPPER: I'd like to, at this point I would like to ask you to step back and let us go through the questions and do the best we can with what we've been given and then maybe you can work out those other issues with the FDA outside of the panel. I hope that I'm not stepping on too many toes here and I apologize if I'm cutting you off. But I do think that issue is not directly germane to the question we have in front of us.

I think Dr. Habig has raised the issues about approvability, about guidance documents, about precedents for other over-the-counter devices. It
seems to me that he's eloquently stated those issues and this is information that will be taken back to the FDA. I don't think anybody on the panel chose to argue with him about his particular, in his particular viewpoint about this particular issue. I'm not saying that we all automatically agree with him, but this was not a controversial statement.

So I would like you to take away some positives from that particular issue and let us get on with this. Would additional testing be necessary for pregnant women? Now that we know what testing means, as far as the FDA is concerned, does any of the panel have anything to add on that? In other words, do we need to do additional clinical studies on pregnant women and pH, vaginal pH? Yes, Dr. Habig.

DR. HABIG: The answer, my answer to that is no. Again, the model is there for health care practitioners. To make it over-the-counter should not require additional testing.

CHAIRPERSON NIPPER: Okay, anybody else have a comment? Yes, Dr. Diamond?

DR. DIAMOND: My comment is more from the point of view of logistics and while I would think it would be probably very unusual that someone would do something to disrupt the cervix or disrupt the
cervical mucus plug, or if someone had prematurely
dilated and was not aware of it, potentially could
even rupture membranes. So I think there may need to
be greater clarifications of the mechanism, how far
into the vagina it would be placed and depending on
how much is known about and what is defined by what
would be done in a non-pregnant patient.

There may need to be additional testing to
validate the methodology in a pregnant individual as
well.

CHAIRPERSON NIPPER: Any other comments
from the left side? Yes.

DR. KOUMANS: Yes, I have a question. I
have a question for Dr. Cooper. If I have, if I'm
aware of information that's unpublished that might be
pertinent to the discussion.

CHAIRPERSON NIPPER: What's your question?

DR. KOUMANS: Should I --

DR. COOPER: Can you divulge information
that you know --

DR. KOUMANS: Yeah.

DR. COOPER: -- that's unpublished? Is it
your personal information?

DR. KOUMANS: It's not my personal
information, it's done by other people.
DR. COOPER: I think you would need permission from those people before you provide that information.

DR. KOUMANS: Okay.

DR. COOPER: I'm deferring to Dr. Richter.

DR. RICHTER: Kimber Richter, in the Office of Device Evaluation. I think if you're aware in your professional capacities of other information and you want to share something generally, even as your expert opinion or as research you're familiar with, you could feel free to do that. I think we wouldn't want you to do anything that would be so specific as to jeopardize someone's publication opportunities or anything like that.

But if you're aware in general or even if it's a matter of your personal, professional experience and beliefs, that's why you're on the panel to share that kind of thing.

DR. KOUMANS: Okay. I've been recently reviewing a lot of the evidence specifically around bacterial vaginosis and pregnancy. And while it's clear that some women benefit from screening and treatment in certain circumstances, there may be other circumstances where treatment may be harmful. And it's, we don't, I don't think we completely understand
what those situations are and it's certainly not something that I think all practitioners, certainly not the general public, is aware of.

But it's not something we've actually begun to address in our treatment guidelines yet. Although we do say that the use of inter-vaginal clindamycin is not, not recommended because of the potential for adverse outcomes, which has been shown now in almost three, it's not totally statistically significant, but three studies have shown a similar trend that the use of inter-vaginal therapy may be doing more harm than good.

And, you know, I'm concerned that that kind of information, we don't have a good handle on what is actually going on there.

DR. DIAMOND: Do you mean from the point of view of drug reactions or physical disruption to the pregnancy?

DR. KOUMANS: No, I'm talking about increased neonatal infections and increased pre-term delivery with the treatment of bacterial vaginosis with inter-vaginal clindamycin cream.

DR. HABIG: Dr. Nipper.

CHAIRPERSON NIPPER: Yes.

DR. HABIG: I think that you jumped from,
is this a good test to the treatment paradigm. And I think you should be careful about what the panel is trying to consider, which is could this test be an over-the-counter test? And then go back to my, the informed patient is his own best health care advocate. The patient isn't going to treat, the patient would take information to their health care provider and then your guidelines and that thought process would come into play.

So I didn't, I'm trying to sort of counter the negative aspect of what you just presented because it's an aspect to the information part, point of view.

CHAIRPERSON NIPPER: Dr. Falls.

DR. HARRINGTON-FALLS: In terms of labeling, though, it does bring out a very good point, because if you do have a pregnant patient, you would want her to check with her provider before using an inter-vaginal substance and there are over-the-counter substances already available. So that is a good labeling point.

DR. KOUMANS: Right, right.

CHAIRPERSON NIPPER: Others who have something to offer on Question 3? Okay, well let's move to Question 4 and again remember that Dr. Gutman asked us to break it down about asymptomatic or
symptomatic and pregnant versus non-pregnant. And now he's asking us or the FDA is asking us to comment on what labeling may be appropriate for these devices. How should the performance be captured? What limitations should be included in the labeling? Should the labeling be written similar to an educational brochure?

Anybody like to tackle that question first? This is a quiet panel today. Dr. Falls, you've got stuff written down, and you're sitting next to me, and I can see it. Would like to tell us what you've got written down?

DR. HARINGTON-FALLS: I'd be happy to. I was just thinking of some ideas in terms of labeling. Educationally I want patients, the lay public to understand that the vagina does have a normal acidic pH, so that they don't overuse over-the-counter medications, douches and creams and so forth that might not be appropriate for their situation. That they understand that the pH test is just diagnostic, it's not, it doesn't tell them what's causing the change.

It doesn't tell them anything that they may need to be cultured for. So the importance of seeing a health care provider is so important. So I'm
not sure if an educational component to the label, like an educational brochure describing different causes of vaginitis, if it would be more helpful or more confusing.

CHAIRPERSON NIPPER: Dr. Habig.

DR. HABIG: I think I'll take these C, B, A in reverse order. I think an educational brochure is important. I see two aspects. One is the specimen collection. I think that needs to be done very carefully to prevent some of the problems, especially in pregnant women, to avoid negative outcomes of just the sampling technique and to get the correct sample from the correct spot.

The labeling limitations probably ought to address what to do with the result. And then obviously that's, I think, the symptomatic patients with the elevated pH ought to go see a health care provider. It seems to me, from the data seems to show that a symptomatic patient with an acidic pH is a candidate for the over-the-counter medication that already exists for yeast infections.

So, you know, that seems to be the right way to go with that particular circumstance. But typical labeling in this case would probably say if symptoms persist. I mean there's over-the-counter
labeling for a lot of medications that say take this for three days, but if symptoms exist, if your temperature doesn't go down, see your health care provider, would be appropriate.

I don't think the labeling specifically on the package but perhaps advertising, and now I'm going to get out of my expertise in terms of regulation, but advertising for over-the-counter products are regulated by a different agency, I believe, by the Federal Trade Commission instead of the FDA. But the advertising for this product ought to be careful on not encouraging asymptomatic nonpregnant women to simply go buy this thing.

I think there's not much return. Now FDA doesn't normally look at the economics or economic outcomes of tests, but it would seem to me people wouldn't likely use and spend money for something the outcome of which wouldn't tell them much. Avoiding advertising that would say, go get this in any case, is probably okay, but I don't know how FDA deals with it.

Having confused that issue sufficiently, the performance captured in the labeling should be, I believe, part of the educational brochure kind of approach. It ought to say what pH measures. It ought
to say what pH is normally and what acidic versus alkaline pH typically means.

CHAIRPERSON NIPPER: Okay. I'm being advised by my Executive Secretary not to postpone the open public comments too much longer. We're sort of in the middle of the panel's deliberations on Question 4. We are, we still have a Question 5 to do. It's 2:15 and we have several items in the open public hearing to deal with. So I'd like to suspend open committee discussion at this point and let's deal with the items in the open public hearing.

I don't believe we have any people to testify or to speak at the open public hearing. We have information and input to the panel in the form of letters and video tapes. The first letter, I think I have the right one. Okay, this is to Ms. Veronica Calvin and it's addressed to Ms. Calvin and me.

"Please enter this letter and video as supporting the over-the-counter vaginal pH screening devices. I have made the enclosed video in regards to the still-birth experience of my baby girl, Julia "Rose".

I went into my Ob's on three separate visits complaining of external vaginal burning. I was never cultured but prescribed medication for a yeast
infection. On the last visit, the afternoon prior to my daughter's death, I was given a forceful cervical exam that caused Group B strep to cross my intact placenta and cause her to be still-born. I was so particular and careful about all aspects of my pregnancy but, unfortunately, trusted my Ob's judgement call about treating my symptoms as a yeast infection without culturing me.

If I could have easily tested myself with the screening device when my symptoms first started, I could have protected my unborn child as then I would have been cultured and treated with oral antibiotics for symptomatic Group B strep prior to the cervical exam. Since then, I have had two occasions with similar symptoms and my primary care physician balked at culturing me and prescribed yeast infection medication which did not work because, once again, it was not a yeast infection, but Group B strep.

I don't know if doctors don't culture because of the expense or the time it takes to do a pelvic exam or what. I was very irritated, not only because of my symptoms, which were not treated properly, but because I wasted my time waiting forever in the doctor's office to be seen at multiple offices and then wasted my money on my insurance co-pays and
useless prescriptions. This was even after telling my primary care provider of the reason why my daughter was still-born.

It would have made life so much easier if I could have tested myself and then gone to the doctor's office to be cultured for the specific bacteria, knowing that it was not a yeast infection and then been prescribed an appropriate medication on the first visit. I hope you will listen carefully to my video of "Our Baby, Julia Rose". I was fortunate in that I found out why my baby died only because I insisted on having her autopsied against the recommendations of several doctors.

Many women have lost their babies and will continue to lose babies, some without even knowing why because both symptomatic and asymptomatic bacterial vaginosis can cross placentas and cause miscarriages and still-births. Women should have the right to monitor their own health care, especially with frequency during pregnancy and before cervical exams. Because, unfortunately, no one has as much concern for their babies or unborn children as they do.

Most sincerely, Marti Perhach."

I hope I pronounced that correctly,

"11 El Dorado Court, Pomona, California.
Enclosed, "Our Baby, Julia Rose", with copyright credit from "Time Stand Still", Lee/Lifeson, Peart, copyright 1987, Core Music, SOCAN, all rights reserved. Performed by RUSH.

(Whereupon, the video is shown.)

VIDEO: In October of 1997, at 38 years of age, I became pregnant with my fourth child. We were all so excited and looked forward to welcoming the new baby to our family around July 4th of '98. Except for one incident in my first trimester, my pregnancy was healthy, or so I thought. I cultured positive for Group B strep in early June of 1998, at 37 weeks gestation.

I had never heard of it, and when questioned, each of my ob's gave me evasive answers about it having to do with intestinal bacteria --

CHAIRPERSON NIPPER: If you want to stop that and adjust it, go ahead.

VIDEO: -- I asked them about taking oral antibiotics prior, but I was told that the IV antibiotics killed the bacteria instantly. During the last two weeks of my pregnancy I had external vaginal burning, so was prescribed yeast mediation without being cultured. The symptoms did not go away after taking the medication, so my prescription was
refilled, again with culturing.

On June 30th, 1998, at 4:45 p.m., I had my routine ob check up. I still had the same external vaginal burning, but was told to continue using an external vaginal cream which I had also been prescribed. I then recorded the sound of my baby's healthy heart beat, thinking it may be the last time I got to hear it in utero. (Sound of heart beat.)

Then my doctor checked me very forcefully to see how far I was dilated by bearing down on my uterus and inserting his fingers as far as he could into my cervix.

He told me I was three centimeters dilated and could have the baby the next day or next week. I did not have any bleeding afterwards, but even commented to my sister-in-law over an hour later, that I could still feel the forcefulness of his exam. At this point, I was due in four days and had everything ready to welcome our new baby home. The next morning, July 1st, I lost my mucus plug at 3:57 a.m. At 5:00 a.m. my labor started with contractions ten minutes apart.

Then at 5:50 a.m. contractions went to one to three minutes apart and I had the chills and shakes until 6:10 a.m. At this point I started to wretch for
a few minutes. Due to morning rush-hour traffic, we arrived at the hospital at 7:05 a.m. While waiting for a room I distinctly felt my baby kicking at about 7:20 a.m. I handed the desk nurse my IV antibiotic request while waiting. Once a monitor was put around me at 7:28 a.m. in the labor and delivery room, the nurse told my husband and me that there was a weak fetal heartbeat, probably because the baby was already down so far in my pelvis. That seemed logical to me because I had just felt her kick me.

However, later the records show no fetal heartbeat. I was never given any antibiotics, although they put an IV in for ptosin. During the next three or four minutes, the nurse broke my membrane to try to get a fetal head electrode reading and had an ultrasound done to try to find the fetal heartbeat. But at that point, there was none. The nurses had my husband take out my earrings to be ready for C-section, but then I was ready to push.

As none of my Obs were there, the nurse delivered our baby girl after I pushed once, but the neonatal team could not revive our baby daughter. I was not encouraged to have an autopsy done on my baby and no one thought to have a bacterial culture done from the placenta. We decided to have our baby's
heart and lungs examined by the pathologist and have a tissue sample taken for examination.

The autopsy showed pneumonia and chorioamnionitis as a result of Group B strep. Approximately ten months later, I've had the same vaginal burning symptoms, except that sometimes one and sometimes both ovaries also burn. I was found to be heavily colonized with Group B strep. I believe that I had a healthy baby girl up until my last cervical exam, just 15 hours before her stillbirth.

Most likely I was heavily colonized with Group B strep and the exam caused the bacteria to pass my cervix and then invade the placental membranes. I was not told that GBS is the leading infectious killer of newborns, even when I specifically questioned my Obs. I asked them what would happen if I couldn't make it to the hospital in time to get the IV and I was told that they might have to keep the baby in the hospital for a few days to watch for signs of infection.

Never was pneumonia or meningitis or death mentioned to me. I was told that the IV killed the bacteria instantly, whereas it actually needs a minimum of four hours to be effective. I was not cultured for my vaginal burning, even after my third
office visit complaining of my symptoms. There was no
literature available in the office regarding GBS and I
was not told that a fever was a symptom of GBS
infection.

If I had known that when I had the chills
that morning, I could have gone to a hospital five
minutes away from my home. From even just a logical
viewpoint, my Ob should not have inserted his fingers
into my cervix knowing that I had cultured positive
for Group B strep. My heart is always filled with
sorrow from losing my baby daughter, Julia Rose. I
hope that sharing my experience can prevent this from
happening to another family.

CHAIRPERSON NIPPER: Thank you. The
second video is by the Arnolds. The resolution on the
projector is pretty bad. I wonder if we could adjust
the contrast a little bit with that. Well, let's see
if this tape if any better. Okay. Ms. Calvin says it
was like that on her TV, so let's see if this video is
any better.

(Whereupon, the video is shown.)

VIDEO: Hi, my name is Verna Arnold and
this my husband, Steven Arnold. And we are here today
to talk to you about Group B strep and what it has
done to change our lives. I became pregnant earlier
this year of 1999, with twins, I had identical twin girls and I had, because I was going to have twin girls I had my regular Ob/Gyn visit every two weeks and I was also seeing a perinatologist every two weeks to monitor my high risk pregnancy.

I am 35 years old and at 35 years of age they consider twins a high risk and I was also having identical, so there was only one placenta, so it's also considered high risk. I was tested for a full culture of the Group B strep, yeast infection, any other sort of test that they could have possible ran on me because I was going to have a CES or a sampling to have genetics testing done to make sure we have no Downs or any other sort of problems with the twins, partly due to my age and also the fact that they were identical twins.

So I was tested at three and a half weeks of pregnancy for GBS or Group B strep. My test came, my first test came back a false-negative. My doctor had the lab retest me or redo my test after he reswabbed me and cultured me and the second test came back a negative. My feeling was is that the first test was probably a strong indication of it being a positive result and not a negative result.

I went to five and a half months of
pregnancy. I was seeing, like I said before, an Ob/Gyn and a perinatologist every two weeks. Between the two of them I saw enough doctors and specialist to be on top of me at all times and to monitor my pregnancy, that everything was fine. At five and a half months of pregnancy, I went to my doctor, my ob on Monday, everything was fine, I heard the twins' heartbeats, I saw them on the ultrasound, everything was fine.

Tuesday morning I woke up feeling a little bit achy, I wasn't, I just wasn't feeling great. I thought maybe it was pregnancy achiness which was bound to occur at some point because I was having a perfect pregnancy with no morning sickness, no nausea, no body aches to really speak of other than just being 35 years of age and pregnant. So I woke up on that Tuesday morning feeling a little bit achy.

I went and did my daily routine of things that I do. At noon time I wasn't feeling any better. I thought, gee, this is really a bummer of a day. I'll go home and lay down, which I did. By 4:00 I decided to call my doctor's office because I still wasn't feeling well. My doctor's office said for me to get into the office immediately. I had my next-door neighbor take me to the doctor's office and subsequently I found out that the twins had died.
It's not a pleasant thing to have to hear, I actually did not believe the doctor, even though I could see on the ultrasound nothing moving or anything going on. But I was convinced I felt movement because of the fact that the twins were, had already been deceased, deceased since noon when I wasn't feeling well, at the worst point, which was noon time, and they were just bouncing around in the amniotic fluid which I thought was movement.

I was admitted to the hospital where I naturally delivered the twins and it was a terrible experience, I don't even want to discuss what it is to deliver two deceased gorgeous little girls. But the worst part of all of this was the Group B strep and how it infected so quickly and took the twins so rapidly. I mean to see them and hear them and feel them on a Monday and then to be at a doctor's office on a Tuesday at 4:00 and be told they're dead, it's a very numbing, very shocking experience to have to go through. You don't believe it. I didn't believe the doctor. I insisted that I have the doppler, even though I had had ultrasound. I just didn't believe it. It couldn't happen to me.

I couldn't have this happen. By 9:00 that night I had delivered the twins and I became deathly
ill with Group B strep. I was so ill and they had me on everything they could possibly give me for antibiotics, for fever reducers, for, you know, everything that the medical community could give a person who's deathly ill. And the doctors had told my husband and my mother, who had arrived at the hospital by now, that basically if I had waited another hour or two or didn't go to the doctor when I did on that Tuesday, I would have been dead. And that was because of Group B strep. But not only that, they still weren't sure if I'd make it through the next 12 hours because I was so deathly ill and so septic myself.

To be on fever reducers and to go from 101 fever to 103.7 in a matter of 30 minutes, you know there's something wrong. And to be given IV antibiotics and they can't control the bacteria that's spreading through my body, you know there's something wrong. And the reason why we're sitting here today is to tell you that there is something wrong about Group B strep and I'm thankful for medical society and the way it is today, that I'm here to at least try again to have another child or twins as it may happen.

But more importantly, I'm also here to testify and to ask that the FDA approve the test for women to test at home and to also, and to test at home...
for Group B strep and any other sort of vaginal or bacterial infections. But also to test more frequently and to make it a mandatory test that women are tested before they deliver and to test earlier. And also to have more routine testing, so that the labs, when doctors submit tests, the labs don't use chicken broth or lamb broth and another culture differently in different labs.

Or have a urine test by one doctor and another test by another doctor saying we need to swab you. It needs to be a uniform situation. We need to know what will work to identify the levels of Group B strep and also what will work for the future as far as preventing this horrible bacteria. It didn't just take my twins, it took a chunk of my life.

There's something wrong with a test when both of them are incorrect. It also, it rather irritated us that there's no type of mandatory reporting to think that my twin girls weren't recorded. We don't know, they might have been recorded because her culture had to go in because of the condition of her health and try to figure out what was going on there that night that no one was sure what was going on with her fever climbing and her white blood cell count going through the roof, up to
50,000.

You know it's ridiculous when we found out over the last six to eight weeks, and we've done quite a bit of research, but to find out that there's no mandatory reporting about it. Through the CDC, there's no mandatory reporting when a woman has a miscarriage, what the reason is. To know that the maternity wards and hospitals aren't told when a baby has gone home and 15 days later it dies from GBS, the maternity ward isn't told, nor the CDC.

To find out that no one is keeping track of this and no one is telling each other, I think it absolutely ridiculous. I sit there and I know in my heart that one of my best friends and his wife lost their baby at 19 and a half weeks. And when we had our situation, they were completely distraught. And symptoms sounded so close to ours that I know it was GBS, but their doctors just took care of the lost pregnancy and never did an autopsy. They never found out specifically because they weren't required to.

They never swabbed the babies to check. They never swabbed the babies. Our babies were swabbed so that way we definitely know it was GBS. We didn't have an autopsy because we were positive it was Group B strep that took the babies.
But they didn't send it to the CDC. We went to, we've been to two functions in the last eight weeks to try to educate the women out there. And there was a lady that came up and said her sister had a baby that was infected by GBS and it was at the hospital for an extra eight weeks. So that means we know of four babies that have been infected, and that's just us. So when we hear that there's 20 to 30 percent of the women that have it or are carriers and there's three million births a year.

That's what, 600,000 to a million. If you actually look at the true numbers of pregnancies that are infected, it has to be far, far greater. And when, our research has, the minimal amount that we have done, talking about Germany. Germany has already identified that it was a problem, already quantified the numbers, already came up with a reporting requirement, already came up with a solution, already implemented the solution, and quantified the results of the solution to a 90 percent --

CHAIRPERSON NIPPER: At the FDA's suggestion, we've stopped the tape because as compelling as their case is and as tragic as it is, it is off the topic for the day. If anyone on the panel, I assume that if anyone on the panel wishes to see the
rest of the tape, we can do it afterwards? Yes. I do have three other letters to read and I hope we can do this quickly, but to get them in the record and to make them available for the panel.

"Dear Ms. Calvin, I would like to have this letter presented in support of the vaginal pH screening devices being available as an over-the-counter product. I am currently 20 weeks pregnant with my first child. My Ob had down played my concerns about vaginal and/or cervical exams causing miscarriage or still birth in the case of asymptomatic bacteria being present.

I feel my concerns are valid as my sister-in-law lost her baby full term from Group B strep due to such an exam and medical literature supports my concerns. I would feel so much more comfortable having access to an over-the-counter vaginal pH screening device so that I can monitor myself prior to having a vaginal and/or cervical exam during pregnancy.

Recently I've had some symptoms of which I was unsure if they were related to pregnancy or a bacterial vaginal infection. Since I work during normal business hours in a non-private setting, it is very awkward to call my ob's office during their
business hours and describe my symptoms. A product I could use at home would certainly give me some peace of mind.

Please approve vaginal pH screenings as over-the-counter products. Women need to be able to monitor their own health, especially when even experienced obstetricians refuse to take their valid concerns seriously. Yours truly, Geni Sprigg, Pomona, California."

DR. HARRINGTON-FALLS: Just for the record, I'd like to mention that this is a neighbor of the first video that we saw.

CHAIRPERSON NIPPER: The second letter is to Veronica Calvin.

"Thank you so much for looking at this important issue of the vaginal pH screening home test on December 7th. I would like this letter submitted as an exhibit. The Jesse Cause, spelled C-a-u-s-e Foundation is in favor of the vaginal pH screening. As mother of a Group B strep survivor, I believe this test could of prevented my son from becoming so sick with GBS, sepsis, meningitis and hydrocephalus.

If only I had this test before I delivered, I would of known that something was wrong and the doctor would of been able to test me further
because the bacteria would of shown up in my home test. I believe this test could of saved our family from all the horror we had to go through. Please support home vaginal pH screening.

I believe it will save many lives in the future. It will also arm and warn parents and doctors alike that something is terribly wrong in the mother before delivery, before it is too late. Thank you so much for hearing this issue and considering these invaluable tests to be in the market place.

Sincerely, Shelene Keith-Enerle",
E-n-e-r-l-e, GBS survivor, 7-17-97, The Jesse Cause Foundation, saving the babies from Group B strep.

The final letter is from Santa Clara, California, from Litmus Concepts, Incorporated.

"I respectfully submit this written testimony for consideration by the Clinical Chemistry and Clinical Toxicology Devices Panel at its December 7th, 1999, meeting regarding consumer-use devices for measuring vaginal fluid pH. Litmus Concepts, Inc., LCI, is dedicated to improving women's health by providing simply, easy to use, accurate, on-site tests for common vaginal infections.

We have developed and commercialized two professional use products for infectious vaginitis,
the FemExam, registered, pH and Amines TestCard, trademark, and the FemExam, registered, Gardnerella vaginalis PIP Activity Test Card, trademark. As a result of our development efforts in clinical studies, we have extensive experience in evaluating the clinical significance of elevated vaginal fluid pH.

Our data clearly indicate that elevated vaginal fluid pH alone is frequently not a sign of disease or abnormal vaginal condition. We have conducted two clinical studies, enrolling over 1,200 women, with and without symptoms at geographically five separate clinical sites. Clinical investigators performed the four Amsel criteria (including vaginal fluid pH) and the Nugent gram stain with vaginal fluid specimens from each study participant.

A large number of women with elevated vaginal fluid pH had no indication of disease whatsoever. In fact, it is well documented that elevated vaginal fluid pH is the most sensitive but least specific of the four Amsel criteria. Elevated vaginal fluid pH can be caused by too many factors to make it of any significance as a stand alone test. Providing women with a non-specific test for elevated vaginal fluid pH will cause needless concern among women and may thereby increase overall health care
costs.

Elevated vaginal fluid pH, when used in conjunction with other clinical criteria by a professional, provides important and useful information. However, elevated vaginal fluid pH alone is of little use to a consumer. LCI is strongly in favor of women self-testing for vaginitis, but only with test that provide information that does more good than harm.

Key clinical investigators and regulatory consultants contacted by LCI, agree with the LCI position. It is important that women be provided with the tools to assist them in monitoring their reproductive health, however these tools must be clinically useful and serve the purpose of improving health care. A stand alone consumer test for elevated vaginal fluid pH serves no useful function and may cause unnecessary confusion.

We hope that you will take these views under advisement in your consideration of this issue.

Thank you.

Sincerely, Paul J. Lawrence, Ph.D., Chief Technology Officer, Litmus Concepts, Incorporated."

That brings us to the end of the statements from the open public hearing. The open
public hearing is now closed and we will continue open committee discussion.

At our, when we suspended open committee discussion, we were discussing labeling, the potential for additional information in labeling. How would performance be captured? What limitations should be included? And should labeling be written similar to an educational brochure? And I can't remember whether I got through to Ms. Kruger or not. Okay. Dr. Everett, do you have any comments?

DR. EVERETT: Only that if the test is to be used in pregnant females, then of course whether we suggest that that goes into the labeling should be based on the facts. And that is if there's, if the data is there that says that the test works, then it should be in the labeling. But if the test does not work, at least as well in non-pregnant females, than that should be there as well.

To give the consumer some idea as to how well the tests work. I wouldn't expect them to understand the tools that we use, such as precision, accuracy, sensitivity, specificity. But in essence, it should indicate, particularly with pregnant females, that if the test works as well as it does in non-pregnant females, then that be put there. But if
it doesn't, then that should be there as well.

CHAIRPERSON NIPPER: Thank you. Dr. Manno.

DR. MANNO: I have no additional comments.

CHAIRPERSON NIPPER: Thank you. Dr. Sedlacek.

DR. SEDLACEK: Yeah, I think it should be differentially labeled. I just reread the article from the New England Journal by the Perinatal Task Force. They point out that they don't even test in the asymptomatic pregnant woman and don't treat the asymptomatic pregnant woman who has got an elevated pH. I think we have a semantic issue that we need to straighten out. All of these tests are basic, there are no -- sorry, are acidic, they are not basic.

So when we talk about basic versus acidic, it's a misnomer. They are all below seven, therefore they're all acidic. So I would suggest that the, that the label be very specific and educational and that it be multi-lingual. I just bought a hedge trimmer and it's in three languages in the operations manual. So we ought to have at least English and Spanish. And I would label it for the intended use, which in my view is symptomatic patients, pregnant and non-pregnant.

CHAIRPERSON NIPPER: Thank you. Dr.
Falls.

DR. HARRINGTON-FALLS: I answered before.

CHAIRPERSON NIPPER: You already answered before. I started off with you. I apologize. Dr. Diamond.

DR. DIAMOND: I had a couple of comments, but if I could just ask also. The last letter that you read, they referenced a paper, but do they give you the reference in their letter that we can look it up?

CHAIRPERSON NIPPER: No, I read the whole letter verbatim.

DR. DIAMOND: So they don't give us a reference?

CHAIRPERSON NIPPER: No.

DR. DIAMOND: Okay.

CHAIRPERSON NIPPER: I think you might have a copy of that letter under the paper clip there in front of you.

DR. DIAMOND: Okay.

CHAIRPERSON NIPPER: It's probably the last page, the last one.

DR. DIAMOND: Okay. Things that I think ought to be included in the label? We sort of skipped over Number 2-A, up above, there ought to be some
indication of whether it's for recurring, b is for recurring, or monitor or recurrence in women with a history of vaginal infection. I think that would probably be a reasonable use. We've discussed who it's indicated for, whoever that ends up trying to be, ought to be very clearly identified.

And similarly, I think it needs to be very clear on the label what this will not test for. We heard a number of very tragic stories just now during the open public forum, but, and these are individuals who say they've gone to the medical literature, they've reviewed the medial literature, they're very knowledgeable about the medical literature now.

They've talked to lots of people, but they think this test is going to do something for Group B strep and I don't know that we have any evidence to suggest that's the case. And so I think we need to be very clear and the public is informed what this test will not test for. And so people don't put a lot of faith in the test and have a sense of well-being which ends up to be false.

If the results of the test are that it's acidic, less acidic, more basic, than the individual should, sorry, the other way around. If it's more acidic, on the testing and the individual is going to
use an antifungal agent, it ought to be very clearly
specified at what point they should, if it's not
working, see a physician. I think it would be very
helpful to have actual diagrams of the testing
methods, where in the vagina the device is to be
placed and step-by-step diagrams of how the analysis
is to be done.

And I think it ought to be clear, there
ought to be a list of items or events, such as
intercourse, douching, which can alter results or we
think may alter results. So that patient, the public
knows to avoid those prior to utilizing the testing.

CHAIRPERSON NIPPER: Thank you. Dr.
Tuazon.

DR. TUAZON: I have nothing further to add
in terms of the utility of this test regarding vaginal
infections. But I want to raise the question of the
utility of this pH in terms of menopausal women.
Should that be included in the labeling as well,
because I think in one of the articles it was raised
as a useful parameter to monitor hormonal replacement.

CHAIRPERSON NIPPER: Dr. Koumans.

DR. KOUMANS: Thanks. I'd like to support
the previous comments about post-menopausal women and
the differences that might be seen in the results. I
think the key issues for labeling that I've heard and
would also like to add is to, that it should include
what a pH is, what does it mean, what is normal and
what is not. That it is not a test for sexually-
transmitted diseases. How it differs. How the
results may differ and in different kinds of women,
pre-menarcheal, pre-menopausal and post-menopausal.

What might change the results of the test.
All of the things that we've mentioned so far and
anything else that we know of that comes forward
later. And that there is currently no treatment over-
the-counter available for women if they have more
positive, a higher pH.

CHAIRPERSON NIPPER: Thank you. Dr. Rifai.

DR. RIFAI: Nothing to add.

CHAIRPERSON NIPPER: Dr. Janosky.

DR. JANOSKY: Nothing to add.

CHAIRPERSON NIPPER: Dr. Rosenbloom.

DR. ROSENBLOOM: I think that the labeling
for menopause, if I'm not mistaken, there is not, this
is not something that's routinely used in the
physician's office to monitor estrogen status so that
it would be premature to consider it in an over-the-
counter preparation.
CHAIRPERSON NIPPER: Okay. How about Question 5? Risks versus benefits. What risks are associated with having this test available over-the-counter. Anybody want to start? Dr. Falls is willing to start.

DR. HARRINGTON-FALLS: The risk associated with having this test available over-the-counter is inappropriate patient self-diagnosis and treatment.

CHAIRPERSON NIPPER: How about risks versus benefits? Do any benefits outweigh the risk?

DR. HARRINGTON-FALLS: Well, I felt it was a pretty innocuous test until these testimonials were put up, but now I'm concerned that the risk to the practicing physician and the patient that's misinformed as to what the test is meant to interpret might be greater than the benefit.

CHAIRPERSON NIPPER: Anybody else care to comment on Question 5? Yes, Dr. Sedlacek.

DR. SEDLACEK: I had trouble, if that one slide that was shown of the pH strip was an example of a positive, I had trouble interpreting it because it seemed to me like it should have been moved about three strips to the left. So I don't know if that was just an example of the strip or if that was the correct answer. If it was the correct answer, I got
it wrong. And I'm afraid patients might as well.

CHAIRPERSON NIPPER: Any other comments answering Question 5? Dr. Tuazon.

DR. TUAZON: The only other benefit is avoid overusing antifungals with the use of the pH.

CHAIRPERSON NIPPER: Yes. I saw Dr. Koumans nodding.

DR. KOUMANS: I agree with that. I think it would be good to minimize inappropriate use of over-the-counter antifungals in the cases of more serious infections. I think there would also be a benefit in having women become more aware of conditions that they may not be aware of that may need treatment, that they may not know that symptoms are actually symptoms of a condition that needs treatment and may have, may have dismissed these things in the past.

So I think there's a benefit in terms of education for women that can occur and treatment for serious conditions that we have treatments for.

CHAIRPERSON NIPPER: I saw Dr. Rosenbloom's hand go up.

DR. ROSENBLOOM: Well, I was actually going to address the same thing. One of the benefits might be it would address the issues that were brought
up in the testimonials. A broader education about infectious risk during pregnancy that may have alerted such well-read or highly motivated individuals to be even more insistent with their health care providers.

CHAIRPERSON NIPPER: Any other comments?

DR. DIAMOND: I have a brief comment. One other thought perhaps is that as more agents become available over-the-counter, the likelihood that, there's an increasing likelihood that some individuals will not come into see their gynecologist or their family practitioner or their health care provider. And some routine screening test that we have, such as pap smears, which might get done at the same time individuals are in for evaluations of vaginitis or other issues, may get overlooked.

And, you know, with the hectic lifestyle people are leading, there may be other good screening tests that we have which just might end up not being done as things get more and more to being able to be done on their own. And that's not a reason specifically for this type of device to be negative about it, but something perhaps also considered for the labeling, that routine screening tests still need to be done.

CHAIRPERSON NIPPER: Well, at this point
we've reached the end of the numbers of questions. Unless someone has other things to add. I hope we've done some good for the FDA and for the public today. Are there any closing comments that any of the panel would have before I close off the meeting? Yes, Dr. Habig.

DR. HABIG: I have one. I guess it will be my final comment as a member of this panel. This topic today reminds me, I guess, to remind our FDA colleagues that Congress has written a mission for the FDA that includes promotion of public health, not only protection of public health. And I would hope that our FDA colleagues keep both of those aspects of their mission in mind as they proceed forward with their consideration of this over-the-counter test. Thank you.

CHAIRPERSON NIPPER: Are there any other comments that the panel would have? Well, at, I would like to thank the people who participated in the meeting. Not everyone who participated is still here, but I was particularly appreciative of the high quality of the presentations. I'm particularly appreciative also of the participation of members of the panel who are temporary members. Even those Husker fans that are leaving, we were glad to meet
another Husker fan.

I also would like to thank the FDA for preparing this well here and I hope that what we've done has been worth the price of admission. Thank you very much. Unless I hear further business, I think we're adjourned.

(Whereupon, the foregoing matter adjourned at 2:59 p.m.)