

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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. CAILLOUTTE, 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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

I-N-D-E-X

	<u>PAGE</u>
1. Call to Order Henry C. Nipper, Ph.D., Chairperson	28
2. Opening Remarks Introductions Conflict of Interest Statement Veronica J. Calvin, M.A. Executive Secretary	28
3. FDA Presentation Jean M. Cooper, M.S., D.V.M.	33
4. Open Public Hearing Thomas M. Tsakeris, President, Devices and Diagnostics Consulting Group, Inc.	41
James C. Caillouette, M.D., FACOG, FACS	52
Janice I. French, CNM, MS, University of Colorado Health Science Center	58
Subir Roy, M.D., Professor Ob/Gyn, USC School of Medicine	64
5. Presentation Jane R. Schwebke, M.D., FACP University of Alabama at Birmingham	83
6. Open Committee Discussion	104
7. Presentation Joel Faden, Ph.D, Regulatory Consultant	132
8. Open Public Hearing Marti Perhach, letter and video	188
Steven and Verna Arnold, video	195
Geni Sprigg, letter	203
Shelene Keith-Enerle The Jesse Cause Foundation, letter	204

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

I-N-D-E-X (Continued)

	<u>PAGE</u>
8. (Continued)	
Paul J. Lawrence, Ph.D. Chief Technology Officer Litmus Corporation, letter	205
9. Open Committee Discussion	208
10. Adjourned	218

P-R-O-C-E-E-D-I-N-G-S

(9:11 a.m.)

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 School of Medicine, Associate Professor of Pathology
2 at Creighton, and Associate Director of Clinical
3 Chemistry and Toxicology at St. Joseph's Hospital in
4 Omaha, Nebraska. I would also like to acknowledge
5 some guest panelists.

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

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Industry Member of the panel.

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

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

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

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

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

21 DR. DIAMOND: My name is Michael Diamond,
22 I'm the Kamran Moghissi Professor of Obstetrics and
23 Gynecology and Director of the Division of
24 Reproductive Endocrinology and Infertility at Wayne
25 State University in Detroit, Michigan.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. TUAZON: I'm Carmelita Tuazon from the
2 George Washington University Medical Center. I'm
3 Professor of Medicine and a member of the Division of
4 Infectious Diseases.

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

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

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

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

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

22 MS. CALVIN: Thank you. I will now read
23 the Conflict of Interest Statement. The following
24 announcement address conflict of interest issues
25 associated with this meeting and is made part of the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 record to preclude even the appearance of an
2 impropriety. To determine if any conflict existed the
3 Agency reviewed the submitted agenda and all financial
4 interests reported by the committee participants. The
5 Conflict of Interest statutes prohibit special
6 government employees from participating in matters
7 that could their or their employers financial
8 interests.

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Dr. Koumans, who is a guest, has acknowledged a
2 related interest in the firm at issue.

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

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

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

19 DR. COOPER: Good morning, as Dr. Nipper
20 stated, I am Dr. Jane Cooper, Chief of Clinical
21 Chemistry and Clinical Toxicology Branch in the
22 Division of Clinical Laboratory Devices. I will
23 present a brief overview of vaginal pH devices, some
24 of the challenges we are facing, pre-market review
25 considerations for home use of in vitro diagnostic

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 devices and questions for panel consideration. FDA
2 has seen an increased interest to market over-the-
3 counter devices that measure vaginal pH.

4 These devices have been promoted for a
5 variety of indications such as diagnosing or aiding in
6 the diagnosis of bacterial vaginosis, parasitic
7 infections or trichomoniasis, and/or vaginitis. And
8 they would be available for use by pregnant and non-
9 pregnant women, whether symptomatic or asymptomatic.

10 To use these tests, women would add a vaginal specimen
11 to the device or hold the device against their vaginal
12 wall for a few seconds, then compare the color
13 produced on the pH paper to the color chart provided
14 in the kit. Certain colors, such as blue, correlate
15 to optimum pH levels, which could be indicative of
16 some abnormal vaginal condition. FDA to date has
17 cleared two devices for the measurement of vaginal pH
18 as an indication of an abnormal vaginal condition.
19 However, both have been intended for use by health
20 care professionals only.

21 Testing in this study provides for the
22 interpretation of pH results in the context of medical
23 history, a physical exam and/or other diagnostic
24 procedures. Limitations of the test are well
25 understood, however, diagnosis of vaginal infections,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 even in these environments, can often be challenging.

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

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

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

25 FDA expects that these numbers are a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

21 Data sets from lay users are required to
22 demonstrate key performance parameters, such as
23 accuracy. Documentation of the second and third
24 points requires a clinical evaluation of the proposed
25 test and an intense, some might say excessive, review

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 of proposed labeling. FDA's review of the merit of a
2 home test takes into account the benefit versus the
3 risk of having home access to test results.

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

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

23 Until the end of 1996, home-use devices
24 included only seven categories of tests. We expect
25 continued growth of the number and scope of products

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 offered for home use, particularly as technologies
2 improve and with the increase in health consciousness
3 of the general public. However, it is our mission to
4 protect the public health and we must ensure the
5 safety and effectiveness of these in vitro diagnostic
6 products.

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

16 Question 2, what intended uses are
17 appropriate for an over-the-counter device for
18 measurement of vaginal pH? Two examples are as
19 follows. To monitor for recurrence in women with a
20 history of documented recurrent vaginal infections.
21 For use in symptomatic women to determine pH to
22 distinguish between alkaline and non-alkaline vaginal
23 infections. If non-alkaline, to direct use of anti-
24 fungal creams, or if either alkaline or non-alkaline,
25 recommend that they see their doctor.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Should the device be used with pregnant
2 women? Would any additional testing be necessary for
3 pregnant women? What labeling is appropriate for such
4 devices? How should the performance be captured in
5 the labeling? What limitations should be included in
6 the labeling? And should the labeling be written
7 similar to an educational brochure? What risks are
8 associated with having these devices available over-
9 the-counter? And do the benefits of over-the-counter
10 use outweigh the risks?

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

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

25 DR. COOPER: Let me get back to you.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

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

21 Okay, I'm a little early on the open
22 public hearing, does that present a problem? Okay.
23 This is the part of the day when we're going to hear
24 from public attendees who contacted Ms. Calvin prior
25 to the meeting. These individuals are going to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 address the panel and present information relevant to
2 the agenda. I will remind you if you don't
3 voluntarily do it, to tell us whether you have any
4 financial involvement with the manufacturer of the
5 product being discussed or with their competitors.

6 And the first speaker is Thomas Tsakeris.

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

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

23 Now, like other prescription use IVDs,
24 over-the-counter home tests can be categorized into
25 three major groups. They're, of course, diagnostic

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 tests, such as those for testing urine and pregnancy.

2 Screening tests such as those for testing stool for
3 traces of blood that may be indicative of colon
4 cancer. And finally tests used to monitor an already
5 diagnosed disease or condition, such as the home blood
6 glucose monitors for diabetics which of course this
7 panel is now more than intimately familiar.

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

16 Vaginal pH is considered to be a key
17 criterion of the established Amsel's criteria for
18 differential diagnosis of bacterial vaginal infection.

19 May I have the first overhead, please? In their
20 evaluation of an OTC in vitro diagnostic, FDA
21 considers, of course, the risks and benefits of the
22 test in terms of intended use, conditions for use, the
23 target user, the patient population and of course
24 product performance characteristics.

25 In particular, the FDA considers whether a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 product label and other sources of user information
2 fulfill these, fulfill the requirements for adequate
3 instructions for use. In contrast to non-home-use
4 tests, the need to ensure adequate instructions for
5 use has particularly important implications for OTC
6 tests with regard to the target user and target
7 patient population, since these are usually one in the
8 same.

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

19 This morning, I would like to focus the
20 panel's attention on the FDA document to which you've
21 already been introduced, "Assessing the Safety and
22 Effectiveness of Home-use In Vitro Diagnostic Devices:
23 Draft Points to Consider Regarding Labeling and Pre-
24 market Submissions." This document addresses issues
25 about risk benefit, performance and labeling of over-

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the-counter IVDs.

2 I would like to focus on the portion of
3 this document that addresses specifically risk benefit
4 issues in the context of a proposed over-the-counter
5 test for vaginal pH. Next overhead. The first
6 benefit question posed by FDA is, what is the clinical
7 benefit of the test to the patient or society in terms
8 of screening, diagnosis or monitoring the particular
9 disease or condition or risk factor? Next overhead.

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

20 While most women associate vaginitis with
21 yeast-based infections, a significant number of
22 infections are of bacterial origin, such as bacterial
23 vaginosis or BV, a particularly serious form of
24 vaginitis that is asymptomatic approximately 50
25 percent of the time. BV has been found in ten to 25

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 percent of women in general obstetrical and
2 gynecological clinics and in up to 64 percent of women
3 attending STD clinics.

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

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

20 The benefits of making available a vaginal
21 pH test as an OTC device is consistent with the
22 existing public health measures regarding the needs of
23 women who have vaginitis. As you are aware, the FDA
24 has approved OTC medications for antifungal vaginal
25 infections. However, since most women cannot

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 currently test for any specific cause of their
2 symptoms, for example, infections by yeast or bacteria
3 or parasites, many women inappropriately self-treat
4 with an OTC antifungal medication.

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

16 Making available an OTC vaginal pH test
17 will help reduce inappropriate use of OTC medications
18 for the treatment of non-yeast vaginal infections.
19 Women will be better able to evaluate their vaginitis
20 with regard to the source of infection and make better
21 decisions about the appropriateness of antifungal
22 self-treatment and the necessity to seek advice from
23 their physician. The serious obstetric and
24 gynecological consequences of untreated or improperly
25 treated vaginal infections reported in the literature

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 and to be discussed by the speakers to follow, further
2 support the need and benefit of OTC vaginal pH tests.

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

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

23 Probable follow-up actions and medical
24 implications would likely be based on whether the
25 woman is inclined to self-treat or not with the OTC

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 antifungal medication and whether the woman is
2 performing vaginal pH testing because she is
3 symptomatic for vaginitis or she is testing to assess
4 vaginal health.

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

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

24 A, she might not self-treat, but instead
25 consult her physician. She could self-treat and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

18 In the unlikely event of Case C, in which
19 the woman consumer would ignore the test result and
20 product labeling and self-treat anyway, a false-
21 positive test would perhaps have little impact.
22 Ironically, self-treating might actually be beneficial
23 as the vaginitis may in fact be due to a fungal
24 infection. Finally, Case D, as with Case C, should be
25 rare if it occurs at all.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Since it is unlikely that an action-
2 oriented woman consumer would invest in the cost and
3 time of an OTC test and then disregard the test
4 result, particularly if the result is positive,
5 suggesting a vaginal abnormality. Next overhead. Now
6 let's look at some of the possible outcomes in the
7 false-negative over-the-counter vaginal pH test. Once
8 again we can look at risk scenarios based on self-
9 treat behavior.

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

18 In the second situation, a consumer who is
19 not inclined to self-treat uses an over-the-counter
20 vaginal pH test and obtains a false-negative test
21 result. An expected outcome is that she would consult
22 her physician as directed in product labeling and the
23 decision to self-treat or be treated by her physician
24 would occur after consultation or follow-up
25 examination in the physician's office.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 In either case, the impact of a false
2 negative vaginal pH test, should it occur, is
3 minimized as the consumer would be under physician's
4 care and no delay in treatment would be likely. Next
5 overhead. Finally, I would like to note that the
6 benefit of making pH testing available as an OTC
7 device is consistent with past actions by the FDA,
8 such as their approval of over-the-counter versions of
9 urine tests for common urinary tract infections.

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

21 I believe there is sufficient scientific,
22 medical, public health and regulatory basis to support
23 the approval of OTC versions of vaginal pH tests as a
24 means to permit female consumers to use an objective,
25 simple and effective tool to better assess vaginitis.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 The information you were provided before the meeting,
2 in conjunction with the medical information you will
3 hear from the speakers to follow, provide a strong
4 basis on which to made recommendations concerning the
5 availability of a vaginal pH test. I look forward to
6 the panel's discussion and believe the panel will
7 concur. Thank you.

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

16 DR. CAILLOUETTE: Yes, sir.

17 CHAIRPERSON NIPPER: Thank you, welcome.

18 DR. CAILLOUETTE: Thank you. I'm Jim
19 Caillouette. I've been in a solo practice of Ob/Gyn
20 in Pasadena, California since 1959. I am founder of
21 PhemTek, which is a limited liability partnership.
22 PhemTek holds a number of patents and patent
23 applications having to do with vaginal pH screening
24 devices. I've been an inventor for more than 40
25 years. I've invented medical devices, I would say

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 more than 40 years and perhaps the best known device
2 is the instant hot/cold pack. So I have a track
3 record of doing that sort of thing. I am the majority
4 shareholder of PhemTek.

5 CHAIRPERSON NIPPER: Thank you.

6 DR. CAILLOUETTE: Is that sufficient?

7 CHAIRPERSON NIPPER: Whatever you say,
8 sir.

9 DR. CAILLOUETTE: Thank you. I thank Dr.
10 Nipper and Dr. Gutman, Ms. Calvin and the members of
11 the panel for permitting me to make this presentation.

12 I'm here today with the hope that I can persuade you
13 of the wisdom of permitting a vaginal pH paper
14 screening device to be sold over-the-counter for the
15 protection of women's health and safety.

16 My interest in vaginal pH as a screening
17 device began after attending an early morning
18 conference on the relationship of bacterial vaginitis
19 to obstetrical complications, held during the American
20 College of Obstetric and Gynecology Annual Clinical
21 Meetings in Denver in 1996. I became determined to do
22 my best to develop a vaginal pH screening device that
23 would be inexpensive, easy to use and would help
24 address the problem of vaginal infection and its
25 consequences. In addition, it would provide women

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 with a self-determined way to screen for abnormal
2 vaginal pH.

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

12 He identified a vaginal pH greater than
13 4.5 as one of his four criteria for diagnosis. You
14 have been provided documents that validate the
15 seriousness of the public health concerns associated
16 with bacterial vaginitis. Over-the-counter use of a
17 vaginal pH paper screening device may help in the
18 detection and proper treatment of vaginitis,
19 particularly non-yeast forms of bacterial infections
20 as well as infections caused by *Trichomonas vaginalis*.

21 This is important because bacterial
22 vaginitis has been associated with increased risk of
23 serious obstetric and gynecologic complications and
24 disorders. An example of the utility of vaginal pH
25 testing appeared in the November 1, 1999, issue of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Ob/Gyn:News. It was reported that in a non-randomized
2 study of 2,400 women who performed vaginal pH checks
3 twice weekly during pregnancy, there was a 90 percent
4 drop in births before 32 weeks.

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

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

24 The annual cost of cerebral palsy in the
25 United States is 2.4 billion dollars, representing

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 one-third of the cost of the 18 most common birth
2 defects. As with the risks associated with vaginitis
3 in pregnancy, the risk for the non-pregnant patient is
4 also a great concern. More than ten million office
5 visits per year are due to the signs and symptoms of
6 vaginitis in the non-pregnant patient.

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

18 He said that these are the wrong rights
19 and that we need rights to prevention, not just a
20 system of payments. He advocates the right to
21 information, the right to mother and infant care, the
22 right to childhood immunization, the right to a
23 healthy environment. And, finally, the right to
24 health screening. And I certainly could not agree
25 more. Because of the impact of vaginitis on our

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 health care system, I believe that it is imperative
2 that women be provided a safe, self-initiated, self-
3 determined, inexpensive, easy to use, vaginal pH paper
4 device.

5 In the symposium entitled, Update on the
6 Management of Vaginitis, in the November 1999 issue of
7 the medical journal, Contemporary Ob/Gyn, Dr. Jack
8 Sobel states, and I quote, "I believe that the pH test
9 is the single most important determinate of which
10 direction the clinician goes in terms of differential
11 diagnosis." And on the same page, Dr. David
12 Eschenbach stated, "the pH testing really is key."
13 510(k)s have been granted for professional pH
14 screening devices and it is my sincere hope that a
15 510(k) for an over-the-counter vaginal pH paper
16 screening device will be granted.

17 I submit to you that the benefits of
18 making available a vaginal pH paper screening device
19 for over-the-counter use by women, will far outweigh
20 any conceivable risk. It is believed that over-the-
21 counter use for vaginal pH paper screening device will
22 greatly help in the education about and screening for
23 vaginitis. Further, the over-the-counter use of such
24 a device may reduce the misuse and overuse of over-
25 the-counter antifungal or yeast medications that are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 frequently initiated solely on the basis of self-
2 diagnosis by symptomatic women.

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

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

16 MS. FRENCH: Thank you very much. My name
17 is Janice French. I would like to acknowledge that I
18 am being, my travel is being reimbursed by PhemTek for
19 presenting her today. I'd like to thank the panel for
20 allowing me the opportunity to present this
21 information. I'm a Nurse Midwife and I've spent a
22 number of years working with a group of individuals in
23 Denver, Colorado, and we've primarily been
24 investigating the role of reproductive tract
25 infections as risk factors for pre-term birth.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 What I'd like to speak with you about
2 today is an analysis of our data to look at the
3 effectiveness of vaginal fluid pH testing as a means
4 of identifying women at high risk for having
5 reproductive tract infections. Next slide. As you
6 well know, there are a variety of microorganisms that
7 have been associated with increased risk for pre-term
8 labor.

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

20 And there are over 20 prospective cohort
21 studies from around the world that show increased risk
22 for pre-term birth among women who have bacterial
23 vaginosis. Next slide. What we'd like to do is to
24 develop clinical schemes that are easy and cost-
25 effective ways of identifying individuals at low risk

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 for having reproductive tract infections and then
2 prevent unnecessary diagnostic testing. And further
3 to identify women who are at increased risk for having
4 reproductive tract infections and identify the women
5 most likely to benefit from screening for infections
6 and treatment during pregnancy. Next slide.

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

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

24 Microbiological testing was done in the
25 first or second trimester of pregnancy, as was vaginal

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 fluid pH testing which was conducted using ColorpHast
2 indicator strips. You can see a description of the
3 population and the women are approximately 40 percent
4 white and non-hispanic, 38 percent hispanic, 17
5 percent African-American, with fewer percentages of
6 women of Asian and Native American descent. Next
7 slide.

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

18 Less than one percent of women who were
19 positive for gonorrhea and certainly the genital
20 mycoplasmas, *Mycoplasma hominis* and *Ureaplasma*
21 *urealyticum*, were very common and Group B Strep
22 bacteria was present among three percent of these
23 women. Next slide. Now the vaginal fluid pH was
24 elevated or greater than 4.5 among 42 percent of the
25 women in this cohort. Shown here in the red bars,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 reflect the percent of women who had an elevated
2 vaginal pH for each one of these conditions. You'll
3 see that bacterial vaginosis, trichomonas, chlamydia,
4 gonorrhoea, each of those conditions women were
5 significantly more unlikely to have high vaginal pH.

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

15 She was 26 times more likely to have an
16 infection, a single infection with bacterial
17 vaginosis. Seven times more likely to have
18 trichomonas, and three times more likely to have
19 chlamydia. Next slide. In considering the
20 sensitivity and specificity of these vaginal fluid pH
21 and, again, I'd like to stress that 80 percent of the
22 women with bacterial vaginosis were asymptomatic. You
23 can see that a high vaginal fluid pH detected nearly
24 93 percent of the women with bacterial vaginosis and
25 71 percent of women with trichomonas.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 The specificities are somewhat reduced and
2 this is consistent with other data from the study.
3 And positive predictive value is 74 percent for a high
4 vaginal pH for bacterial vaginosis. The next slide.
5 What is key and this is the same information just
6 highlighting the negative predictive value, you will
7 see that having a normal pH or a negative test for
8 high pH, 95 percent of the women were -- excuse me,
9 accurately predicted 95 percent of the women not to
10 have BV.

11 The probability of not having trichomonas
12 was 96 percent. The probability of not having
13 chlamydia, 94. And the probability of not having
14 gonorrhoea is more than 99 percent. Next slide. So in
15 summary, having a normal vaginal fluid pH predicts the
16 absence of the studied conditions in this population.

17 It enhanced the identification of women less likely
18 to be infected and it allowed the elimination of
19 routine diagnostic testing for these selected
20 conditions. And of course, this would be a function
21 of the prevalence of these conditions within the
22 population.

23 A high vaginal fluid pH predicted women
24 that were at increased risk for having these selected
25 infections and would identify them. And most likely

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to benefit from a routine diagnostic testing, the high
2 pH prompts focus testing of individuals at the highest
3 risk and allowed focused use of more accurate and
4 expensive diagnostic tests. Next slide.

5 And finally, a normal vaginal pH is
6 reassuring for individual asymptomatic women and their
7 care providers and would reduce unnecessary testing.

8 And with education, pH testing could prompt
9 symptomatic individuals to appropriately seek
10 effective, diagnostic testing and treatment from their
11 care providers. Thank you.

12 CHAIRPERSON NIPPER: Thank you very much.

13 We'll hold questions until the last person has spoken
14 and then we'll ask questions. Dr. Roy.

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 reinforce some aspects.

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

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

20 This was the slide from Dr. Caillouette's
21 paper indicating that for normal flora or for yeast
22 you have essentially normal vaginal pH, while for Beta
23 strep, *Gardnerella vaginalis* and other mixed organisms
24 you have materially elevated pH. Next slide. This is
25 a simple predictive value table. Next slide. It

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 indicates one of the three reports that Dr. Cooper
2 showed you before showing non-specific vaginitis. The
3 sensitivity and specificity being 81 and 67 percent,
4 with the break point being a pH of 4.5. Next slide.

5 This is Dr. Caillouette's paper, wherein
6 he studied asymptomatic individuals and had
7 extraordinary sensitivity of 100 percent, specificity
8 of 92 percent. Next slide. This is a report from
9 Seattle by Dave Eschenbach using slightly elevated pH
10 as a cutoff, sensitivity being 96 percent, specificity
11 53 percent. And, this didn't turn out, that's what
12 happens with these sorts of presentations. I'm sorry,
13 but if you go back to what Dr. Cooper said, and it's
14 probably good that she showed those slides because
15 this is her summary of the pivotal studies. And next
16 slide, let's see if it's the same.

17 No, the same thing happened here as well.

18 That's okay. I think that this --

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

21 DR. ROY: It will be okay. These are just
22 copies or the same information as what Dr. Cooper
23 showed you in terms of her tabulation of the summary.

24 And this is the -- next slide. This is the tabulated
25 positive and negative predictive values. Next slide.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: That's the one I
2 needed.

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

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

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

24 If you look at BV, why is it that we're
25 interested in it. As you can see, the non-pregnancy

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 conditions with which it is associated include pelvic
2 inflammatory disease or upper genital tract
3 infections, post-abortal PID or post-hysterectomy
4 infections. These studies are done all over the
5 country and world and there's a consistency of finding
6 in this realm. Next slide.

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

17 Those case control studies are supported
18 by Gravett's report as a prospective cohort study and
19 you see the link with BV with premature ruptured
20 membranes, pre-term labor and with amniotic fluid
21 infections. Next slide. I was on the FDA Advisory
22 Panel back in '90, when we approved OTC vaginal
23 Candidal therapy because we were persuaded it would in
24 essence be beneficial to patients. Since then it's
25 been somewhat disturbing to note, as this slide

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 indicates, the numbers of individuals who use these
2 preparations inappropriately.

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

11 We have increased likelihood of STDs or
12 salpingitis. You, therefore, may increase pelvic
13 pain, injury to the fallopian tube can lead to
14 increased ectopic pregnancies, or indeed even to
15 infertility as Westrom has shown and others as well.
16 Another aspect to this issue that we don't generally
17 talk about is it may alter the risk of genital tract
18 cancers; namely, HPV is more apt to occur with
19 individuals who have vaginitis, as is HIV. As a
20 matter of fact there are four new studies that
21 indicate a link with that.

22 Delayed first full-term pregnancy is
23 linked with breast cancer and there's controversy
24 about whether it's just that reproductive technology
25 is associated with ovarian cancer. We don't really

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 believe so, but at least it's in the literature. And
2 adverse pregnancy outcomes, habitual abortion with
3 *Ureaplasma urealyticum*, and then prematurity post-
4 partum endomyoperimetritis with BV, Group B Strep, GC
5 and *Chlamydia trachomatis*, all with conditions that
6 Ms. French just showed you. Next slide.

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

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

24 CHAIRPERSON NIPPER: Thank you, Dr. Roy.
25 At this time, we can entertain a couple of questions

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 if we have some for the previous speakers and my
2 colleague on the right, Dr. Harrington-Falls had a
3 question, I believe, for Ms. French, if you'd be
4 willing to answer a question. You can just sit right
5 there. There's a microphone right there for you.

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

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

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Thank you.

2 CHAIRPERSON NIPPER: Dr. Habig had his
3 hand up.

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

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

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

20 DR. HABIG: And vaginalis is associated
21 with --

22 CHAIRPERSON NIPPER: Go to the microphone,
23 Bob.

24 DR. HABIG: I'm sorry. This is Bob Habig
25 again. There was a term with vaginalis --

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. ROY: Yes. *Trichomonas vaginalis* is
2 the term used for indicating infection with
3 trichomoniasis or trichomonads, which is the parasitic
4 organism. And of course others would argue that the
5 term bacterial vaginosis implies that bacteria have
6 gender and it's the female bacteria that have a
7 problem. And so the correct term should be bacterial
8 vaginosis, I mean vaginal bacteriosis. But we don't
9 need to redefine it beyond the difficulties which I
10 think you've correctly indicated exist in the field,
11 just trying to talk about this condition.

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

14 CHAIRPERSON NIPPER: Yeah.

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

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

23 DR. SEDLACEK: That's my understanding as
24 well that that's the genus and species of the
25 infecting protozoan. I have a question for Ms. French

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 and then for Tom Tsakeris. For Ms. French, how did
2 you collect your pH specimen? And, I'm not familiar
3 with the device you used to measure it. How is it
4 similar or dissimilar to the device in question today?

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

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

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

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

22 MS. FRENCH: Probably not very different
23 at all.

24 DR. SEDLACEK: Okay. Thank you. And,
25 Tom, one of the possible outcomes of a false positive,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 was the patient might self-treat without consulting or
2 self-treat and consult the physician. Now a false-
3 positive means an elevated pH would suggest that she
4 has a BV or one of the other infectious problems.
5 With what drug could she self-treat?

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

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

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

21 MR. TSAKERIS: Yeast, yes.

22 DR. SEDLACEK: In spite of a positive
23 test?

24 MR. TSAKERIS: In spite of a positive --
25 and you can't rule out the possibility that could

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 occur. We didn't want to make -- we want to make sure
2 we get all possible scenarios addressed.

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

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

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

20 DR. TUAZON: Right. Because that may be a
21 possibility to explain the false negatives in patients
22 who have symptoms but yet have negative pH. Do we
23 know exactly what causes the elevation in the pH? Are
24 the Gardnerella organisms producing a certain chemical
25 that causes the elevated pH?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. KOUMANS: From my understanding of
2 bacterial vaginosis, it's an abundant overgrowth of
3 *Gardnerella vaginalis* plus other microorganisms and an
4 absence of lactobacilli. And the lactobacilli are the
5 bacteria that produce acids and hydrogen peroxide in
6 the vagina. So they are usually considered the
7 bacteria that maintain a low vaginal pH. And their
8 absence is typical in bacterial vaginosis.

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

13 DR. TUAZON: And the other question I
14 have is what's the standard procedure in terms of use
15 of this vaginal pH in pregnant and non-pregnant women?

16 Do you do routinely, do this in women who come for
17 routine pelvic exam or routine Gyn visits? Or how
18 often do you do this in pregnant women?

19 DR. ROY: Well, in my practice I do use it
20 routinely because it's so simple to do and it's such a
21 useful adjunct to the algorithm leading to diagnosis
22 and/or treatment. And Dr. Caillouette can speak to it
23 as well. He's been in practice a great deal longer
24 than probably anyone in this room. And why don't you
25 describe how you --

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: Dr. Caillouette, you
2 can go to the podium or stay at the table, whichever
3 is more convenient.

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

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

21 DR. TUAZON: Thank you.

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

25 MS. FRENCH: Similar to Dr. Roy, we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 basically test all women coming for annual exams with
2 a vaginal pH, as well as a wet prep. And certainly
3 during pregnancy, all of our women are being examined
4 with pH as part of that.

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

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

20 I was just given this morning. I don't
21 know if you've had access to them or not. But they're
22 basically about diagnosis of vaginitis. Virtually all
23 of them talk about using pH in combination with either
24 a wet prep or with a gram stain. And so the question
25 is, what do we know or what studies do we have that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 look at sensitivity or specificity of, or positive and
2 negative predictive value of pH independent of these
3 other markers as opposed to in combination with them?

4 Do we have data on that?

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

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 are epithelial cells that are covered with bacteria.

2 DR. DIAMOND: Right.

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

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

12 CHAIRPERSON NIPPER: Dr. Roy.

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

23 CHAIRPERSON NIPPER: Dr. Koumans.

24 DR. KOUMANS: Yeah, thanks, Janice, for a
25 very nice presentation. I was wondering whether you

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 or any of the presenters could address other possible
2 reasons that you found in your research for an
3 elevated pH?

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

12 CHAIRPERSON NIPPER: Okay. If there are
13 no further questions or comments from the panel for
14 these speakers, I will declare the open public hearing
15 closed. And in the interest of panel comfort and
16 maybe that of the audience, I hope that our next
17 speaker won't mind if we take a brief break before we
18 come back to hear her speak. Let's reconvene at 20 of
19 11:00. Will that be all right with you, Dr. Schwebke?

20 DR. SCHWEBKE: Yeah, that's fine.

21 CHAIRPERSON NIPPER: Okay.

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

25 CHAIRPERSON NIPPER: Okay. The moment

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 we've been waiting for. Dr. Schwebke. I was worried,
2 I didn't see you.

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

4 CHAIRPERSON NIPPER: Great.

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

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

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

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

16 DR. SCHWEBKE: -- happy to hear that. And
17 as I go along I'll try to, also, put a little bit of,
18 sort or reality into what's going on as well, I think.

19 So, let's see if we can do this. I was asked to give
20 an overview of vaginal infections as part of my
21 presentation. We're going to start with some slides
22 and then move to some crude overheads. But I think,
23 they were helpful to me in trying to think through
24 some of these issues.

25 As you've already heard, there are three

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 major causes of vaginal infections. And that is
2 candida or yeast infections, trichomonas --
3 *Trichomonas vaginalis* is the full name and this is a
4 parasitic infection -- and bacterial vaginosis. And
5 of these three, bacterial vaginosis is definitely the
6 most prevalent. A few words about the normal vaginal
7 ecosystem and Emily already alluded to some of this.

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

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

24 They also produced anti-bacterial factors
25 such as hydrogen peroxide. They have other affects on

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the local immune system of the vagina, so they are
2 thought to be key. This is just some data that looks
3 at whether or not lactobacilli are there all the time
4 in large numbers and in healthy women. This is a
5 slide where you see these little boxes represent the
6 lactobacilli. The little triangles represent
7 Gardnerella and *Bacteroides*, which are organisms that
8 often are increased in bacterial vaginosis.

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

19 But in reality, even though this is what
20 we might expect would occur in all healthy women
21 without vaginal pathology, this pattern occurred in
22 only about 20 to 25 percent of women that we looked
23 at. And the other women, the majority of women had a
24 fair amount of variability, day-to-day variability in
25 their vaginal bacteria.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 So they had some days where they had four
2 plus lactobacilli, but interspersed were days where
3 the lactobacillus population fell. And the
4 Gardnerella population rose. And I show this just to
5 sort of re-emphasize that even though the lactobacilli
6 are important and we feel that they are there to
7 maintain a healthy vagina, they don't seem to be there
8 in large numbers in all women at all times.

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

21 They cause symptoms such as itching,
22 irritation, some discharge. Treatments are, as you
23 see here, and I think the key point is that
24 availability, as you all know, of over-the-counter
25 medications for yeast infections. This is the only

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 vaginal infection for which we have OTC products. And
2 just some pictures for you. Here's a typical
3 discharge of candida. Now as I go through these, in
4 terms of the clinician's perspective, there was a
5 question earlier about standard of practice in terms
6 of utilizing diagnostic tests for vaginitis.

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

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

23 The next infection is *Trichomonas*
24 *vaginalis*. This is a protozoal infection.
25 Interestingly, it was originally regarded as a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 commensal, but indeed it is a pathogen.

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

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

20 Okay, in terms of treatment, this is not
21 OTC. There is only one medication in the U.S., and
22 that's metronidazole. It's usually given at a single
23 dose and because it is a sexually-transmitted disease,
24 it is recommended that the partners be treated as
25 well. I don't think I included a slide, but I should

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 mention that trichomonas has been associated in one
2 cross-sectional study with pre-term birth. There are
3 no prospective studies, these would be very difficult
4 to do to confirm that association. Trichomonas has
5 also been associated with apposition of HIV.

6 And then finally bacterial vaginosis or
7 BV. This is again just to reiterate. It's called
8 vaginosis instead of it is because there is not an
9 obvious inflammatory component to this condition. The
10 prevalence of BV varies by the population that you
11 look at. In the general population, I would say 20 to
12 25 percent. In our STD clinic where I practice, it's
13 about 50 to 60 percent.

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 *Mobiluncus* and others.

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

11 However, 50 percent of women who meet the
12 clinical criteria for BV are asymptomatic. And here's
13 a picture of the, what they describe as a homogenous
14 discharge. Again, a physician might look at this and
15 say, oh, BV. This is a clue cell. This is one of the
16 criteria that Amsel described. And this is, we look
17 under the microscope again at the vaginal fluid and we
18 see this epithelial cell that's covered with bacteria.

19 And particularly the edges are obscured. And so this
20 is one of the diagnostic criteria that we use for
21 making the clinical diagnosis of BV.

22 Treatment of BV. I wanted to just spend a
23 minute on this, not to really get into specifics but
24 to make a comment about the efficacy of treatment.
25 The two drugs that we rely on the most, and these are,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 by the way, this is taken right from the CDC STD
2 Treatment Guidelines. And so this is what is in the
3 current guidelines. But the two drugs that we rely on
4 are metronidazole and clindamycin. And these are
5 actually, rather empirically chosen because they are
6 very effective against anaerobes, and we see a lot of
7 anaerobic organisms in bacterial vaginosis.

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

16 Okay, just to go back a little bit and
17 then talk about the diagnostic work up of vaginitis.
18 These are the things that we encourage clinicians to
19 do. Obviously, they want to take a history, they want
20 to look at the patient, describe the discharge. The
21 vaginal pH, we've certainly heard about. The whiff
22 test is another ancillary test that's part of the
23 Amsel criteria, where the clinician actually takes
24 some of the vaginal secretions and mixes it with
25 potassium hydroxide and smells it.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 And they are trying to detect a fishy odor
2 which would be indicative of increased amine
3 production by anaerobic organisms. And then looking
4 under the microscope, and I've already showed you
5 examples from the specific infections. I do think
6 it's important. It's important for the clinician and
7 maybe for you to understand as well, that it's vital
8 in terms of where the specimen is collected. Here's a
9 diagram that shows the speculum in the vagina and you
10 see the swabs there.

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

20 It's not hard to do, but it's just a
21 caveat that we need to remember. Oops, upside down pH
22 paper. But this is the pH paper that we generally use
23 in the clinic and these are individual, I mean there
24 are different things out there, but I think this is
25 probably the most widely used, individual strips with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the pH paper on the end. And you apply the vaginal
2 fluid and then match it up to your color chart. There
3 are other things besides cervical mucous that
4 interfere with pH.

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

16 For example, they can have mixed
17 infections with candida and bacterial vaginosis, which
18 is not, it's not common but it's not all that
19 uncommon. And in any event, this, you know, the use
20 of these diagnostic tests does lead to a more specific
21 diagnosis and hopefully specific therapy. Okay. Just
22 to say a few more words about the diagnosis of BV, to
23 remind you this is the clinical criteria of Amsel, et
24 al. He reminds us there's no single marker for BV
25 because we don't know what causes it.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 And so if you have three of these four
2 criteria, an elevated vaginal pH, presence of clue
3 cells, a homogenous of milky discharge and a positive
4 whiff test, any of those three, then you can make the
5 clinical diagnosis of BV. This is probably the most
6 common, next to empiric diagnoses, this would be the
7 most commonly used criteria for diagnosing BV.
8 Because it can all be done at the bedside very rapidly
9 and cheaply.

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

20 So there is pretty good agreement between
21 the two methods, although not perfect agreement.
22 These are examples of women with normal bacteria.
23 Scores of zero to three are normal. Then there is a
24 class of women that are intermediate. And if you'll
25 think back to those first couple black and white

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 slides I showed you where that one woman had a lot of
2 variation in her vaginal bacteria. If you'd done a
3 gram stain of her, on those days when she had quite a
4 bit of variability, this is what you would see. It's
5 this intermediate flora, where you see some decrease
6 in the lactobacilli and some increases in the other
7 organisms, but not enough to be --

8 CHAIRPERSON NIPPER: Dr. Schwebke?

9 DR. SCHWEBKE: Yes.

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

13 DR. SCHWEBKE: Okay.

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

18 DR. SCHWEBKE: There we go.

19 CHAIRPERSON NIPPER: Yeah.

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

25 CHAIRPERSON NIPPER: Okay.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

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

21 In terms of the Amsel criteria or the
22 clinical diagnosis of BV, what do we know about
23 sensitivity and specificity and I'm not going to dwell
24 on this because we've already heard quite a bit about
25 sensitivity and specificity of pH which is our

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 interest today. The pH test though does have a fairly
2 high sensitivity for diagnosing BV, but it's
3 specificity is certainly not all that good.

4 Other, as you've heard, other conditions,
5 particularly trichomoniasis can cause an elevated pH.

6 And I should mention that trichomoniasis and BV very
7 frequently travel together. So you very frequently
8 see these as co-infections and that may be why we see
9 some problems with the pH here. Discharge, looking at
10 the discharge really has very low sensitivity and
11 specificity. The wet mount is a good test. If you
12 see a motile trichomonad, obviously you've made your
13 diagnosis.

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

23 This now is looking at sensitivity and
24 specificity of predicted values of Amsel. So the
25 Amsel criteria and other individual diagnostic

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 criteria, this time compared to vaginal gram stain for
2 the diagnosis of bacterial vaginosis. So that gram
3 stain diagnosis that I showed you. And if we look at a
4 pH greater than 4.5, which is the third one down, you
5 can see in this particular study, this was a multi-
6 center study, sensitivity of 89 percent, specificity
7 of 73 percent.

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 collecting a vaginal specimen.

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

14 And I think we can move to the overheads.
15 I just have a few overheads and I apologize, they are
16 just handwritten. I was trying to think about some of
17 the issues that Veronica asked me to think about,
18 considering this. And I hope you all can read my
19 scribbles. But I think it is true that the vaginal
20 pH, at least for me, is also a decision point. When I
21 approach a woman and in the STD clinic because we're
22 dealing with such a high, high prevalence population
23 for many things, we do full screening. And if the pH
24 is less than or equal to 4.5, I'm somewhat reassured,
25 from an STD point of view.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 I start thinking, well either there's
2 nothing going on here or perhaps she has a yeast
3 infection. Whereas if the pH is greater than 4.5, my
4 antennae go up and I start thinking about BV and
5 trichomonas. Now a couple of caveats. Mixed
6 infections can occur, we've already mentioned that.
7 Trichomonas can have a normal pH and actually I was
8 struck by Janice's data of 29 percent. So that would
9 have even been higher than I would have thought.

10 But we certainly do see cases where women
11 with trichomonas have a normal pH. And then again,
12 let's not forget interfering factors of blood, semen,
13 cervical secretions. I think douching is a question.

14 It's mentioned out there in the literature, but
15 frankly I've never seen a study that showed resulting
16 changes in pH or interference with pH measurement as a
17 result of douching. Next overhead.

18 You know, I should have put these slides
19 in and as I was listening to people talk, I thought it
20 might be helpful just to, I hope I'm not using up all
21 my time here. But I thought it might be helpful to
22 say a few words about some of the complications of BV,
23 just to bring everybody up to speed here. Obstetrical
24 complications, certainly the major one is pre-term
25 birth and there is no doubt that this association has

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 been shown in study, after study, after study, from
2 the U.S., from Scandinavia, from wherever.

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

15 So I put this out on the table that even
16 though there is an association, a very strong
17 association, what we're lacking is the prospective
18 data about what to do with this in some cases. In
19 terms of gynecological complications, this is what
20 made it to my short list. There are certainly others
21 that you will see floating around out there. But I
22 think it is true, from some recent studies,
23 particularly some of the recent African studies, that
24 STD and in particularly HIV apposition is linked to
25 bacterial vaginosis.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 And that BV may actually be a biological
2 risk factor for apposition of HIV. And I think this
3 is important. Again, though, we don't have
4 prospective treatment studies, of course, and we're
5 left with the dilemma that our treatments are sub-
6 optimal, if you will, and that recurrence rates are
7 high. Pelvic inflammatory disease. Again, some very
8 good associations but prospective data on this is
9 lacking. And I don't think is coming anytime soon.

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

19 So what are the risks and benefits of OTC
20 pH? This is just me thinking about this. The benefit
21 is it's simple. It should be inexpensive. It
22 certainly may increase the correct diagnosis and
23 treatment of vaginal infections. And I have this
24 scenario of the patient coming armed with this
25 information which I've already suggested that the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 doctors often don't bother to collect.

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

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

20 And also, and I think this is important to
21 think about also. I think that this could lead to,
22 and depending on the indication for the test, whether
23 it's screening or diagnostic for the OTC use, this
24 could lead to an increased number of office visits for
25 asymptomatic BV. And currently, although there will

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 be some in the crowd who disagree, currently the
2 treatment of this condition, asymptomatic BV, is
3 controversial and it is currently not recommended by
4 the CDC. Next.

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

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

19 DR. SCHWEBKE: No, I'm fine.

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

24 (Laughter.)

25 CHAIRPERSON NIPPER: I don't mind clinics,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 I just don't want to cross up the two things. Dr.
2 Habig.

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

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 simple instructions that that wouldn't be a problem.

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

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 want -- think the panel should be careful about --

2 DR. SCHWEBKE: I agree.

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

4 DR. SCHWEBKE: Umm hmm, I agree.

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

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

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

20 So that if she does have symptoms and if
21 this is a normal pH, then somewhere in the text it's
22 saying this is highly suggestive that you're problems
23 are from a yeast infection or are not due to bacterial
24 vaginosis. Some language around that point. I'm
25 really not extremely enthusiastic, personally, about

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 it being used as a screening test, for the reasons
2 that I mentioned before. Is that getting at what, is
3 that your question?

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

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

17 And she ends up going to the doctor and
18 maybe has asymptomatic BV. That may put some health
19 care professionals in an awkward position because the
20 formal guidelines are not to treat asymptomatic BV..
21 So there is some dilemma there. There is some tension
22 there about our current state of knowledge about some
23 of these conditions and the information that we would
24 be empowering the asymptomatic woman with in that
25 case. So I have some concerns about that.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: Do you mind if I open
2 the floor to some of our presenters from the public
3 hearing, if you'd like to comment on that particular
4 question, because the question went to what would the
5 intended use be.

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

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

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

25 DR. ROY: I think it comes down to the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

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

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

19 DR. KOUMANS: I'd just like reaffirm that
20 asymptomatic women may have other conditions in
21 addition to BV, which Dr. Schwebke, Jane, presented.
22 It might not only be BV, it might also be trichomonas.

23 There might be other conditions that have led to an
24 elevated pH which need to be evaluated.

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 with that.

2 MR. TSAKERIS: I'd like to --

3 CHAIRPERSON NIPPER: Yes.

4 MR. TSAKERIS: -- add something here. I
5 sometimes think that when you talk about screening,
6 you have to also define what you mean by screening,
7 because there's different flavors of screening.
8 There's, you can talk about screening the general
9 population of women who are apparently healthy for the
10 purpose of trying to determine whether or not there's
11 a vaginal abnormality, that's one thing. Another
12 context would be to look at selective screening.

13 Women, in women perhaps who have had a
14 history of vaginitis who are concerned about that or
15 looking for some way to, now we're getting in, we're
16 mixing terms, monitoring for their condition or
17 monitoring their health status. That sort of mixes
18 screening with monitoring and you're still dealing
19 with an asymptomatic issue. It's my understanding, I
20 haven't read the labeling lately for the over-the-
21 counter antifungal medication anti-use medications,
22 but it's my understanding, please correct me if I'm
23 wrong, but I think initially the labeling for those
24 products advised that these medications were not
25 intended for first time episode vaginitis.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 That they were intended only for recurrent
2 infections. And so if you look at it, if you look at
3 a so-called screening test for OTC vaginal pH in the
4 same context that you would use the medication. In
5 other words, it would be for screening/monitoring for
6 recurrent infections. I think it would be consistent
7 with how the medication is being used.

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

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

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

25 I think they would probably end up doing

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 it as a result of whatever, you know, if there were
2 commercials for the product or this sort of thing.

3 That would be my guess.

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

6 DR. SEDLACEK: No, not really, thanks.

7 CHAIRPERSON NIPPER: Okay.

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

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

12 DR. DIAMOND: No.

13 CHAIRPERSON NIPPER: Dr. Tuazon.

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

21 DR. SCHWEBKE: Yeah. I envision it, if,
22 you know, I can envision a symptomatic woman using the
23 product and then either, particularly if she's had a
24 history of prior yeast infections and now has a normal
25 pH with the product, feeling assured that, oops, this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 is my yeast infection again and I need to do OTC. But
2 if it's not a normal pH, if it's an elevated pH
3 saying, or you know, that woman or another woman
4 saying, I need to consult my physician.

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

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

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

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

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

24 DR. SCHWEBKE: Except the --

25 DR. HARRINGTON-FALLS: And some people,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 even with a diagnostic test will not see health care
2 providers.

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

7 DR. SCHWEBKE: Right.

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

10 DR. DIAMOND: No, I did not.

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

16 DR. SCHWEBKE: Sure, thanks.

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

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

22 CHAIRPERSON NIPPER: Yeah, I think we
23 ought to, we ought to seriously think hard about that.

24 For those of you who don't know, Vulcan is the statue
25 in Birmingham of the person made of steel or iron and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 honoring the ironworks in Birmingham that are now
2 rusty in the rust belt category.

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

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

16 And what I was trying to do was to get an
17 idea about what, what, how many false positives we're
18 going to see if we, if we use this product in broad
19 screening, screening of everybody that came in the
20 general population. We'll get there in a second.
21 Yeah, it's coming out. You just need to turn that
22 overhead thing off. It, the overhead really affects
23 that, what we can see on the screen. Yeah, that's
24 better, Bob, thanks. I think you've got a second
25 career ahead of you.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. COOPER: What you're looking at is
2 analysis of the three pivotal studies that were
3 provided to us. The, what the table you're looking at
4 is the recalculated positive prevalence values and
5 negative prevalence values.

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

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

9 DR. KOUMANS: Those aren't prevalence
10 values.

11 CHAIRPERSON NIPPER: Those are positive
12 predictive values.

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

22 And in the symptomatic population for non-
23 pregnant and pregnant, it's 30 percent for both of
24 those, symptomatic. And the asymptomatic population,
25 for non-pregnant, is six percent, and pregnant

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 population is 12 percent. So the, to sum it up, the
2 prevalence is 12 percent for all, 30 percent for
3 symptomatic. The only one that's really different is
4 the asymptomatic population where non-pregnant is six
5 percent and pregnant population 12 percent.

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

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

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

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

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

23 CHAIRPERSON NIPPER: Yeah, they're in
24 the -- this is a -- there's a group of literature,
25 this is not this group of N 311.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. KOUMANS: Oh, I'm sorry.

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

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

15 CHAIRPERSON NIPPER: Yeah. And I'll be
16 glad to share that with the panel at an appropriate
17 time when we get a xerox machine going. Do I have to
18 get permission? Okay. Well, anyway, I'm just trying
19 to shed a little light here. Thank you. At this
20 point we are open, the meeting is open for committee
21 discussion. And we can proceed in the way that the
22 panel feels we should, whether we have further
23 questions or comments, we can take those ad lib, we
24 don't necessarily need to go around the room formally
25 to do that. We have a little time to develop the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 issue.

2 If you have questions for other people
3 who, people who have given this data, now is the time
4 to do that. We have about 45 minutes before the
5 schedule calls for lunch, and we can proceed however
6 you see fit. I think that our assignment, between now
7 and the time we leave, correct me if I'm wrong, Ms.
8 Calvin, is to answer the questions. And of course
9 we're going to have another open public hearing later
10 this afternoon. Does anyone on the panel have
11 comments or questions at this point? Yes, Dr. Falls.

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

22 I do have some concerns about it being
23 used as a diagnostic tool, particularly in pregnant
24 women. I feel that there are a lot of issues that the
25 women need to discuss with their doctor and it ends up

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 putting them in an adversarial position with their
2 obstetric provider.

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

6 DR. HABIG: I think this question would be
7 for Dr. Schwebke. In the presentation of the probably
8 month long study that showed high levels of
9 lactobacillus and low levels, except for the general
10 population, there were excursions where the
11 lactobacillus went way down and other things came up.

12 In those studies, I think that slide you showed was a
13 summary slide that had a lot of different women
14 examinations, it was not a single person.

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

18 DR. HABIG: Okay.

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 because of?

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

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 increased episodes of intercourse, these sort of
2 things.

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

13 CHAIRPERSON NIPPER: Yes.

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

24 And then there was a group, approximately
25 19 percent of women who had the variable pattern. And

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 what Frances was able to show was the pattern most
2 often changed in the first phase of the menstrual
3 cycle, approximately Day 7 to 9 was when you noticed
4 the shift in vaginal flora towards the abnormal. And
5 she also found that an elevated pH was present among
6 these women prior to the shift in flora. And I can
7 get, leave copies of this for the panel if they like.

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

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

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

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

25 DR. KOUMANS: Yeah. In speaking to some

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

20 CHAIRPERSON NIPPER: Good. Dr. Janosky.

21 DR. JANOSKY: I'm trying to think through
22 the issue of what would be appropriate claims for the
23 product. And I think that either Dr. Schwebke or,
24 let's see, Ms. French, might have presented some data,
25 but I'm not sure whether I remember it correctly or

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 not. What I'm actually looking for is a two by two
2 table where you look at pH value for the cutoff and
3 then for the other outcome, either for screening or
4 diagnosis, whether a disease process is present or
5 not.

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

13 CHAIRPERSON NIPPER: Dr. Roy may have --

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 specificity?

2 CHAIRPERSON NIPPER: Is this the table
3 that you showed?

4 DR. ROY: Yes.

5 CHAIRPERSON NIPPER: Would you mind if I
6 read it?

7 DR. ROY: No, go ahead.

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

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

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

17 DR. ROY: No.

18 CHAIRPERSON NIPPER: Well, let me just
19 read it and we'll see if that does enough for the
20 panel. If the panel needs the information before. If
21 you make your two by two table with bacterial
22 vaginitis up at the top, and bacterial vaginitis
23 positive with a test positive, that's true positives
24 or 61. I don't know whether Dr. Janosky, that's the
25 one you were talking about?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. JANOSKY: No, I was actually looking
2 for any disease process, not just BV.

3 CHAIRPERSON NIPPER: Okay.

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

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

14 DR. JANOSKY: That's helpful.

15 CHAIRPERSON NIPPER: Yeah. Well, I did
16 my, I did some calculations on the six percent
17 prevalence and if you assume 100,000 population that
18 you're going to do screening of asymptomatic people
19 and you assume the sensitivity and specificity of 75
20 percent which is, I think I've seen some figures like
21 that. To find, you're in this, 1,500 patients when
22 you do that. And you're going to find 4,500 truly ill
23 people, but you're going to have to wade through
24 23,500 people who have false-positives. That's the
25 trouble with a low sensitivity test in an asymptomatic

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 population.

2 DR. KOUMANS: It's the trouble with a low
3 specificity test.

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

14 DR. ROSENBLOOM: No.

15 CHAIRPERSON NIPPER: Okay.

16 DR. SEDLACEK: I have a question.

17 CHAIRPERSON NIPPER: Yes, Dr. Sedlacek.

18 DR. SEDLACEK: I may have missed this, but
19 in the material that I read prior to today's meeting
20 and today, I couldn't satisfy myself that I understood
21 the frame of reference for the pH measurement.

22 Basically, how accurate is the device before us today?

23 When I look at the, at the, one of the studies in our
24 handout, a study by Sagawa, et al, they used a digital
25 pH meter to measure pH in the population of pregnant

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 women.

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

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

9 DR. SEDLACEK: Thank you.

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

21 Maybe questions will occur to us over
22 lunch time that we need to ask. We'll open it up for
23 further questions and then we'll look at the questions
24 the FDA has asked us to consider. There is a distinct
25 chance that we will be finished and ready for the open

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 public hearing which is scheduled at 2:00. There is a
2 chance we may open up earlier for that.

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

12 (Whereupon, the foregoing matter went off
13 the record at 11:48 a.m. and went back on the record
14 at 1:04 p.m.)

15
16
17
18
19
20
21
22
23
24
25

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

2 (1:04 p.m.)

3 CHAIRPERSON NIPPER: Okay. If we can get
4 started. If you'd look over to Steve Gutman's chair,
5 you will notice Steve is not there. And then we've
6 got Dr. Woods in the audience also backing us up,
7 hopefully keeping us straight. All right, predicting
8 that I've stirred up a hornet's nest, maybe not
9 hornets, we've just, we've generated some further
10 comment and our morning presenters would like to
11 clarify some issues regarding prevalence and how the
12 test performs. Who's going to do it? Now we haven't
13 heard from you yet.

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

17 CHAIRPERSON NIPPER: Yes.

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

22 CHAIRPERSON NIPPER: Oh, this binder.

23 DR. FADEN: Which is a generic discussion
24 of vaginitis. I also produced a nine or ten page, it
25 was originally a letter to FDA which reviewed the, the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 various studies that existed at that time, and
2 summarized them and tried to present some idea of what
3 the worst case scenario would be. And that's one
4 thing I'd like to correct. Those numbers that were in
5 there for prevalence were my review of the literature
6 and then saying what are the ranges that exist in the
7 various studies?

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

18 The presentation by Janice showed a
19 positive predictive value of asymptomatic patients in,
20 I believe, in the 60 some percent range. Also Jane's
21 presentation, when she showed her numbers, the PPV was
22 also I think around 70 percent. So I would perhaps
23 use those, mine is only merely a theoretical
24 presentation for worst case. Can I clarify a number
25 of other things too?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: Let's don't move off
2 that subject there --

3 DR. FADEN: Sure.

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

11 So if, what I like to do is look at, I'm
12 looking at this product in a couple of different ways.

13 One is that if you have a situation such as we heard
14 about from Ms. French, who had a high prevalence
15 population, but then I wanted to contrast that without
16 taking anything away from the presenters, from Dr.
17 Schwebke or Ms. French, I'd like to contrast that with
18 an asymptomatic population.

19 So that's why I was looking for the
20 prevalence in an asymptomatic populations or
21 essentially a population that might walk into a drug
22 store or wherever they pick this product up and say,
23 oh, this looks interesting, I might do this. So
24 that's why, that's why I asked for the numbers because
25 I wasn't trying to distance myself or devalue any of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the presenters' information. But I still think it's
2 valid to look at what the prevalence is, the
3 prevalence of these diseases are in asymptomatic
4 populations that may walk up and buy this test, buy
5 this device to use on themselves.

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

10 CHAIRPERSON NIPPER: Right.

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

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

24 DR. KOUMANS: Can I, can I correct that
25 again. I don't think the mic is on.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: Yeah, it is now.

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

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

14 DR. KOUMANS: Actually with a chlamydia
15 culture test, which has a sensitivity of about 50 to
16 60 percent. With a specificity of 100 percent, you
17 can reduce the prevalence by screening using that
18 test.

19 CHAIRPERSON NIPPER: Yes, you can. But I
20 would, without meaning to be argumentative, I would
21 cite to you that if you had a better chlamydia test
22 with a higher sensitivity, I bet you'd walk into that
23 and walk away from the test you have with only 50
24 percent sensitive. If you're looking for disease,
25 you've got to have high sensitivity, as high as

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 possible. It's not to say you can't take a low
2 sensitivity test and find disease, but you're going to
3 have a lot of overhead doing it.

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

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

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

16 CHAIRPERSON NIPPER: Okay, have we
17 clarified the issue?

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

20 CHAIRPERSON NIPPER: Sure.

21 DR. FADEN: First of all, this is a
22 generic discussion, so I've made all my product for
23 the panel to be generic. This not a discussion of a
24 particular product at this time. In that vein, we
25 have also in the past provided FDA labeling, proposed

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 labeling for products like this to complete the
2 product. And some of the points of that I'd just like
3 to make clear. The indication was not to tell
4 somebody to go do a test if they get low value, I mean
5 to a treatment if they got a value less, we did not
6 say that.

7 We merely said that a value greater than
8 4.5 is indicative of a bacterial infection, please
9 contact your physician. The other thing was that the
10 labeling warned against doing the test within 24 hours
11 of sex, douching, menses and a couple of other things.

12 I believe we also warned against this test being
13 interpreted in any way to be related to any sexual
14 disease, such as HIV or gonorrhea or any other
15 diseases.

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

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

24 DR. KOUMANS: Yes, I am, I'd like to
25 follow up on Dr. Janosky's question earlier on having

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 a two-by-two table showing BV -- not BV, pH above the
2 cut-off, below the cut-off and then disease, yes/no.

3 And I'm wondering whether Ms. French, Janice, would be
4 able to pull that together from the data that she has?

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

8 DR. KOUMANS: We could calculate it.

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

10 DR. KOUMANS: You have the total --

11 MS. FRENCH: I don't have the raw numbers
12 here to make a two-by-two table --

13 DR. KOUMANS: But you have the total --

14 MS. FRENCH: -- for any infection versus
15 no infection.

16 DR. KOUMANS: But you have total sample
17 size and you have prevalence of each of the
18 infections.

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

20 CHAIRPERSON NIPPER: Any other comments?
21 Okay, thank you. At this point we can spend some time
22 and I'm not sure the panel is ready yet because we're
23 still asking for data or for information. But I, we
24 have several questions that have been raised by FDA
25 staff about these devices. So I guess what I'd like

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to do, if the panel is willing to do that now, is to
2 go through the questions and see what our panel's view
3 is about this particular device that's in front of us.

4 Question 1, I'm not sure, yes.

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

7 CHAIRPERSON NIPPER: Sure.

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

14 CHAIRPERSON NIPPER: Dr. Cooper.

15 DR. COOPER: I'm speaking for Dr. Gutman.
16 What I think we're trying to obtain is not a vote.
17 We're trying to get some input so that we have help
18 with the decision-making process for these types of
19 products. Does that answer your question?

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

22 DR. COOPER: I think that's something we
23 could consider. I don't think that was something we
24 originally intended to do. But it would help give us
25 some clarifications of input from the panel. I mean

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 that's what we were hoping to obtain so that we could
2 then get clearer in our mind which direction we're
3 going and that might, down the road, lead to a
4 guidance document. But I don't think that was the
5 original intent.

6 DR. HABIG: May I continue?

7 CHAIRPERSON NIPPER: Please, do.

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

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

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

20 DR. COOPER: I think there's general
21 guidance for over-the-counter use, but I think the
22 questions we're asking are over and above what's in
23 the guidance. Issues come up periodically in the
24 review process which aren't particularly answered in
25 the guidance. Our guidances are generic as possible.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 And sometimes we run into situations, such as we
2 have. These questions represent that we would like
3 some input on so that we have some more information so
4 that when we make a decision, it's the best possible
5 one we can make.

6 DR. HABIG: Thank you.

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

16 Question 2 deals with intended use for an
17 OTC product or measurement of vaginal pH. He would
18 like that, to break it down by four groups. In other
19 words, to consider Question 2 as having four parts.
20 And what you'll do is pan to the sentence or the
21 question such that the first part would read, what
22 intended uses are appropriate for an OTC product for
23 measurement of vaginal pH in an asymptomatic, non-
24 pregnant population. And then we'll take the same
25 prefix and add, in asymptomatic pregnant population.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Third, in a symptomatic non-pregnant
2 population, in a symptomatic pregnant population. So,
3 that we'll actually ask, have four sub-parts to
4 Question 2. Then, if you think about it, Question 3
5 then changes because Question 3 deals with should the
6 device be used with pregnant women? Obviously we're
7 going to be dealing with intended uses in pregnant
8 women in Question 2, now. So let's line through the
9 first question there, the first part of Question 3.

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

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

25 DR. HABIG: I do. Is, is there reason to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 suspect a difference in performance with pregnancy
2 versus non-pregnancy?

3 DR. HARRINGTON-FALLS: This is Dr. Falls.

4 Intuitively I think there are the potential for more
5 pH changes in the pregnant woman due to different
6 secretions.

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

9 DR. KOUMANS: There is data.

10 DR. HABIG: -- based on what?

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

14 CHAIRPERSON NIPPER: Did you say PV or BV?

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

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

19 DR. KOUMANS: And I believe --

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

23 DR. ROSENBLUM: Certainly one reason for
24 decreasing pH would be the high estrogen levels
25 associated with pregnancy as a mechanism.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. KOUMANS: Right.

2 DR. HABIG: Okay, that, the performance,
3 the technical performance is what I was interested in.

4 Is there any reason to believe that the ability to,
5 of these devices to test accurately the pH, would
6 change. I want to subcategorize this, because my
7 fundamental question is, what's different about
8 pregnancy? So it's not the actual performance? If
9 you get the pH, it's going to be the pH. It's the why
10 would pH be different in pregnancy and, then I presume
11 also, the differential decision making that would
12 occur after you get the result.

13 CHAIRPERSON NIPPER: The ROC curve may
14 change.

15 DR. HABIG: Okay.

16 CHAIRPERSON NIPPER: Okay?

17 DR. HABIG: Yup.

18 CHAIRPERSON NIPPER: Did I get that right?

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the performance of it.

2 CHAIRPERSON NIPPER: The medical reason
3 for using the device?

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

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

16 DR. MITCHELL: Well, for example,
17 screening populations for pregnant versus non-pregnant
18 individuals to recommend that you -- if you're going
19 to recommend that you use the test for screening in
20 patients, just to examine them, to see whether or not
21 they have the disease, you might behave, the physician
22 might react differently to an asymptomatic woman who
23 has, who's not pregnant, who has a alkaline pH as
24 opposed to a pregnant woman who has, who's
25 asymptomatic, who has an alkaline pH.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 So it would be in terms of the labeling
2 and the way you treat the person if the tests were
3 examined and if the test comes back with an alkaline
4 pH.

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

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

15 CHAIRPERSON NIPPER: But I'm thoroughly --

16 DR. MITCHELL: I mean part of --

17 CHAIRPERSON NIPPER: I'm thoroughly
18 confused.

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

22 CHAIRPERSON NIPPER: We need to focus on
23 the, we need to really fine tune this question. And I
24 think Dr. Habig is right. I'll get to you in a
25 minute. Okay. I thought you said, when you answered

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 this question was that there may be a difference in
2 labeling because the physician may use the data
3 differently.

4 DR. MITCHELL: That, okay.

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

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

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

19 DR. MITCHELL: No, you're not.

20 CHAIRPERSON NIPPER: Okay.

21 DR. MITCHELL: I skipped the step which
22 was an assumption, which is part of what you're going
23 to talk about today. That regardless of the results
24 of the study or the test, you contact the physician.
25 So that's where the confusion lay.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: But there may not be
2 such a contact, as people have presented this morning.

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

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

7 DR. MITCHELL: Yes.

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

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

20 Would a physician recommend, is there an
21 indication to recommend using a pH on a weekly basis
22 or a monthly basis during pregnancy that might help
23 the physician decrease the risk of a negative outcome
24 to that pregnancy and hence that might affect how
25 recommendations are labeled?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. DIAMOND: Those are all the questions
2 we don't have answers to. And that's actually my
3 biggest fear of having this available over-the-counter
4 for pregnant women to use is someone will use it, will
5 get a response and then will call their obstetrician
6 and what do I do? And in the litigious environment in
7 which we live and the physicians are going to feel
8 compelled to respond in certain ways for the result of
9 a lab test, the consequences of which we do know,
10 which they may never have performed if it was
11 something they were themselves doing in their office
12 with something that was approved for physician use.

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

17 DR. DIAMOND: I don't if there is or there
18 is not. I don't know, I don't think there is data now
19 to say that we ought to be doing it on a routine,
20 regular basis such as that every month. There are
21 some data that we were given showing that it's helpful
22 in identifying certain obstetrical problems, but none
23 of them that I've read talk about using it in a
24 systematic fashion periodically, week after week or
25 month after month.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: Okay, do we have
2 other questions of concerns before we start working on
3 Question 1? Yes, Dr. Diamond.

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

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

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

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

25 CHAIRPERSON NIPPER: Yes.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 MS. FRENCH: There is information from a
2 study from Giles Monif, I think he's from Nebraska.

3 CHAIRPERSON NIPPER: He's at Creighton.

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

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

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

23 It's older information from the '70's.
24 Also after sexual intercourse the pH remains elevated
25 for a short time. Not days, but more like one to two

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 hours. Does that help? I'm sorry, I'm Jan French,
2 I'm a Nurse Midwife.

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

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

23 DR. MITCHELL: But, but, how, if we in
24 this room don't have the answer and if you as the
25 experts who have done these studies don't have the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 answer, how is the physician's office going to respond
2 when Mrs. Smith calls and says, "I've got this
3 response." We have no guidance to give the
4 physician's office on how to respond. That's what it
5 sounds like.

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

16 CHAIRPERSON NIPPER: But the question, the
17 follow-up question I would have for you is that if --
18 and I'm certainly not an expert in this area -- but
19 in general, in any medical issue, if you don't have
20 data on which you recommend that a person access the
21 health system, and you don't base that on information
22 that's well developed by studies, have you used
23 anecdotal or intuitive information? I'm sure that
24 this is not a unique situation and I certainly
25 understand why Dr. Diamond is saying this is not

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 different information to develop, for the most part of
2 it.

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

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

15 DR. DIAMOND: I think so.

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

18 DR. SEDLACEK: Yes. During the
19 discussions today I've had sort of a recurring
20 nightmare about the patients with vestibulitis or
21 vulvadynia, many of whom present to our offices with
22 the complaint of a mild discharge and burning and
23 itching of the vulva. Are you aware of any studies or
24 is anyone aware of any studies looking at pH with
25 this?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 And when you start off with such a
2 subjective issue as burning or itching vulva, isn't
3 that a little bit shaky to start a scientific study
4 on?

5 CHAIRPERSON NIPPER: It's a good question.

6 Does anybody want to comment on that, either from the
7 panel or from the presenters this morning?

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

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

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

24 CHAIRPERSON NIPPER: Is there someone who
25 would volunteer an answer to start? Dr. Diamond.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. DIAMOND: I'll say something. I think
2 the majority of the data I've seen today indicates
3 that there looks like there's a very close
4 relationship between pH and states of vaginal disease.

5 And would lead me to believe that it would probably
6 in the long run be a very good marker. I think there
7 are, though, additional things that could be done and
8 should be done and actually should be relatively easy
9 to do, as you were indicating which would provide some
10 important information for patients as well as for
11 health care providers as to what are the influence of
12 acute changes in the vaginal milieu, which may affect
13 the pH readings. And are these changes that will
14 last, over how long a period of time will they change?

15 And I can envision that being tested relatively easy
16 with initiating some of these events and then serially
17 checking pH at hour intervals, two-hour intervals for
18 six hours, 12 hours, however long it takes to get back
19 to a steady state.

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

25 CHAIRPERSON NIPPER: Dr. Falls.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

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

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

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

25 At this point, we don't have those

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 answers. And on the other hand, we do have some data
2 that shows, hopefully we'll get a little bit more
3 before the end of the afternoon, but showing how good
4 the pH is in distinguishing disease versus non-
5 disease. I think the question in my mind is how much
6 more data do we need?

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

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

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

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

23 We've had different methods described.
24 One is measuring in the distal third of the vagina.
25 One is measuring in the middle third. It seems to me

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 that there ought to be some kind of a more specific
2 way to get the test done. I'd like to see a double
3 blind study with the patient testing herself in a
4 fashion that you would expect to be consistent with
5 the labeling, in the doctor's office. And then have
6 the doctor repeat the test.

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

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

17 DR. EVERETT: Yeah, I agree that there
18 appears to be sufficient data for that association to
19 be made between pH and various states of vaginal
20 disease. My difficulty is trying to pull that
21 association closer to the pH changes. That is, as you
22 mentioned earlier about the menstrual cycle, that is
23 a few days or, she didn't state exactly how many days,
24 but there is a time period prior to the menstrual flow
25 where pH begins to change.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 But that itself didn't appear to be
2 characterized as it relates to performing this test in
3 a home environment. Nor was the incidence of having
4 sexual intercourse. And it was mentioned that within
5 a few hours it should return back to normal. But
6 there was no data presented, in essence, as to what
7 can I expect with the general population. So there
8 are a number of variables that, in some instances,
9 appear to pull that association between pH and
10 vaginitis further apart.

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

20 And I would not have, at this point, a
21 good idea as to how long she should wait or if it
22 occurred just prior to her menstrual flow, again, how
23 long should she wait or how long should I tell her to
24 repeat the test, wait and repeat the test? Or should
25 she come into my office? And in a general sense, with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 all of that, it sounds as though if one of my patients
2 called me up and said I had symptoms of vaginitis,
3 would I really have her do the test?

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

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

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

17 DR. HABIG: I do have some. I think the
18 simple answer to Question 1 is yes, there is
19 sufficient data. I think the issue here is, ought to
20 be focused on can the test be done adequately by lay
21 people with instruction and can it be interpreted
22 correctly by lay people with instruction? Some of the
23 testing referred to earlier is probably useful, but
24 shouldn't be, isn't typically the criteria that FDA
25 uses to clear over-the-counter products.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 This is a test known useful under the
2 conditions already being used by practicing health
3 care folks. And the issue is can it be used
4 successfully by lay people over-the-counter?

5 Personally, I believe a well-informed populous, a
6 well-informed set of patient are their best health
7 care advocates. And I think this would add to that.

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

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

23 DR. HABIG: I've got to go back to the
24 question I asked when we started this afternoon or the
25 fact that we clarified we're not talking about a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 product here. We're talking about how is FDA going to
2 look at some series of products and typically the
3 sponsor of a product makes claims and argues them
4 through the process of clearance to the market with
5 FDA. Intended use being the principle of them and
6 typically the resolution of that is a negotiation
7 about labeling with FDA.

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

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

24 CHAIRPERSON NIPPER: Okay, thank you. Ms.
25 Kruger do you have any comments on Question 2?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 MS. KRUGER: I would agree. The thing
2 that still confuses me is why a woman who is totally
3 asymptomatic would reach for this and pay cash for
4 this? So, I guess, and then I guess if she were that
5 symptomatic, I'm wondering why you wouldn't go in for
6 a Gyn visit? But I guess I don't see the need to
7 split it all out based on the fact that I just don't
8 understand why an asymptomatic person, pregnant or not
9 pregnant would want to be testing.

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

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

18 DR. EVERETT: Well, I tend to agree with
19 her. That I don't really see a need to break it out,
20 again, unless we're trying to pull the association
21 between the change in pH and vaginitis closer together
22 in one group. Or if it's expected to be different,
23 let's say in pregnant women versus non-pregnant women,
24 or is it expected to be different in those who are
25 asymptomatic versus those that are symptomatic.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 And I would think the test itself, in
2 reality, from what we do in the office, I know it is
3 different. That is when pregnant women come in and I
4 do this test, I generally start thinking of things
5 that might interfere with the test, just because she's
6 pregnant, so I don't make the wrong diagnosis and
7 treat her for something that she really doesn't have.

8 But in the -- go ahead.

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

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

16 CHAIRPERSON NIPPER: I apologize for
17 getting ahead of you.

18 DR. EVERETT: That's okay. But in the
19 home situation I wouldn't expect the lay customer to
20 do what I would do in the office. So I really
21 wouldn't expect them to be, to be separated into those
22 categories. So I would leave it simply the way it is,
23 without breaking it down into pregnant, non-pregnant,
24 symptomatic and non-symptomatic. I just don't think
25 that's necessary.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: Okay. How about you,
2 Dr. Manno, do you have a comment?

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

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

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

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

19 CHAIRPERSON NIPPER: Thank you. Dr. Falls.

20 DR. HARRINGTON-FALLS: Since pH is only
21 one element of what's involved, we talked about the
22 Amsel criteria which are four. The exam provides so
23 much more of an opportunity to put it into
24 perspective, that I don't think the lay person at home
25 is going to have. In specific answer to Question 2,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 one of the examples is if the result is non-alkaline,
2 will that be used to direct use of antifungal cream?

3 And I would say no in an asymptomatic person.

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

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

18 DR. DIAMOND: I think we do. I can tell
19 you the question, the question was asked as we were
20 going around the table, why would people pay money for
21 a test if they are asymptomatic, they don't know what
22 it's going to do? I can tell you my patient
23 population, which is infertility patients, many of
24 them would probably utilize these and other sorts of
25 tests. And for sure, once they got pregnant, I think

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 there would be a high chance that they would try to do
2 it after all they've gone through trying to conceive.
3 They are going to probably try to do anything they can
4 to try to avoid the potential of losing a pregnancy.
5 So I can definitely see my patients reaching for this
6 off the shelf, even if they are asymptomatic.

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

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

25 CHAIRPERSON NIPPER: Thank you. Dr.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Tuazon.

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

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

19 CHAIRPERSON NIPPER: Thank you. Dr.
20 Koumans.

21 DR. KOUMANS: I have a couple of comments.
22 In our blue folder that the panelists got is a copy
23 of the most recent STD treatment guidelines from the
24 CDC. And they do distinguish between symptomatic and
25 asymptomatic women who, both pregnant and non-pregnant

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 women. So I think it's an important distinction to
2 make. In terms of, just to review that, for
3 symptomatic pregnant women we recommend that all women
4 are tested and treated to evaluate the cause of their
5 symptoms. For asymptomatic pregnant women, our
6 recommendation is that for women who have had a prior
7 pre-term birth, physicians may consider screening and
8 treating bacterial vaginosis. For example, to prevent
9 pre-term birth. Now this is only for BV. But it
10 certainly raises a distinction between asymptomatic
11 and symptomatic pregnant women.

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 practitioners when, even when they do this test in
2 their own office.

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

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

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

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

25 DR. KOUMANS: Correct.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: So they don't refer
2 to over-the-counter diagnoses or treatment in any way?

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

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

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

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

25 DR. RIFAI: No, I don't really have a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 direct answer to your question. This is, as was
2 indicated earlier, is a quite unusual case. We
3 usually, we are asked about the indication of a device
4 after having the opportunity to review the performance
5 of the particular device and the specific questions
6 and then you'll determine whether it works in a
7 particular situation and doesn't work in another.

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

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

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

24 DR. JANOSKY: I actually would concur with
25 what Dr. Diamond had said earlier.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: Thank you. Dr.
2 Rosenbloom?

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

13 And the asymptomatic, we have no idea
14 whether that's of value as a routine. And we have
15 concerns about it being promoted much like the example
16 of douches that are more harmful than they are
17 helpful. So it seems to me that the, certainly in the
18 high risk groups that are described in the New England
19 Journal paper, that this is an additional risk factor
20 that bears consideration, prima gravida. Just this,
21 prima gravida as an independent risk factor is
22 equivalent, is the same relative risk as bacterial
23 vaginosis for being associated with pre-term delivery,
24 1.4.

25 And the greatest, most important risk

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

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

21 CHAIRPERSON NIPPER: Thank you.

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

25 CHAIRPERSON NIPPER: Yes.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. MITCHELL: However, if the panel feels
2 that there also are additional non-clinical
3 investigations that would be warranted, we certainly
4 would like to hear that.

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

10 DR. MITCHELL: That's correct.

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

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

20 CHAIRPERSON NIPPER: Well, come on.

21 MR. TSAKERIS: It seems to me that you're
22 struggling with, you know, the various use scenarios
23 of a vaginal pH test. I'd like to reflect back on my
24 comments I made this morning and probably, or most of
25 you maybe didn't think about it too much, but I think

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 it's quite important. And that is I think the model
2 for these questions, at least in terms of how you
3 answer these questions, may have already, the FDA may
4 have already looked at some of these issues and
5 perhaps we could hear from them in the context of the
6 home-use test, you know, the dipsticks for UTI.

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

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

25 But I'd like to hear from the FDA. What

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 have they, what were there concerns or what were their
2 considerations that led to the clearance of the UTI
3 strips?

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

13 MR. TSAKERIS: No --

14 CHAIRPERSON NIPPER: I'd like to, at this
15 point I would like to ask you to step back and let us
16 go through the questions and do the best we can with
17 what we've been given and then maybe you can work out
18 those other issues with the FDA outside of the panel.

19 I hope that I'm not stepping on too many toes here
20 and I apologize if I'm cutting you off. But I do
21 think that issue is not directly germane to the
22 question we have in front of us.

23 I think Dr. Habig has raised the issues
24 about approvability, about guidance documents, about
25 precedents for other over-the-counter devices. It

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 seems to me that he's eloquently stated those issues
2 and this is information that will be taken back to the
3 FDA. I don't think anybody on the panel chose to
4 argue with him about his particular, in his particular
5 viewpoint about this particular issue. I'm not saying
6 that we all automatically agree with him, but this was
7 not a controversial statement.

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

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

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

22 DR. DIAMOND: My comment is more from the
23 point of view of logistics and while I would think it
24 would be probably very unusual that someone would do
25 something to disrupt the cervix or disrupt the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 cervical mucus plug, or if someone had prematurely
2 dilated and was not aware of it, potentially could
3 even rupture membranes. So I think there may need to
4 be greater clarifications of the mechanism, how far
5 into the vagina it would be placed and depending on
6 how much is known about and what is defined by what
7 would be done in a non-pregnant patient.

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

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

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

17 CHAIRPERSON NIPPER: What's your question?

18 DR. KOUMANS: Should I --

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

21 DR. KOUMANS: Yeah.

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

24 DR. KOUMANS: It's not my personal
25 information, it's done by other people.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. COOPER: I think you would need
2 permission from those people before you provide that
3 information.

4 DR. KOUMANS: Okay.

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

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

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

19 DR. KOUMANS: Okay. I've been recently
20 reviewing a lot of the evidence specifically around
21 bacterial vaginosis and pregnancy. And while it's
22 clear that some women benefit from screening and
23 treatment in certain circumstances, there may be other
24 circumstances where treatment may be harmful. And
25 it's, we don't, I don't think we completely understand

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 what those situations are and it's certainly not
2 something that I think all practitioners, certainly
3 not the general public, is aware of.

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

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

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

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

23 DR. HABIG: Dr. Nipper.

24 CHAIRPERSON NIPPER: Yes.

25 DR. HABIG: I think that you jumped from,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 is this a good test to the treatment paradigm. And I
2 think you should be careful about what the panel is
3 trying to consider, which is could this test be an
4 over-the-counter test? And then go back to my, the
5 informed patient is his own best health care advocate.

6 The patient isn't going to treat, the patient would
7 take information to their health care provider and
8 then your guidelines and that thought process would
9 come into play.

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

13 CHAIRPERSON NIPPER: Dr. Falls.

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

21 DR. KOUMANS: Right, right.

22 CHAIRPERSON NIPPER: Others who have
23 something to offer on Question 3? Okay, well let's
24 move to Question 4 and again remember that Dr. Gutman
25 asked us to break it down about asymptomatic or

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 symptomatic and pregnant versus non-pregnant. And now
2 he's asking us or the FDA is asking us to comment on
3 what labeling may be appropriate for these devices.
4 How should the performance be captured? What
5 limitations should be included in the labeling?
6 Should the labeling be written similar to an
7 educational brochure?

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

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

23 It doesn't tell them anything that they
24 may need to be cultured for. So the importance of
25 seeing a health care provider is so important. So I'm

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 not sure if an educational component to the label,
2 like an educational brochure describing different
3 causes of vaginitis, if it would be more helpful or
4 more confusing.

5 CHAIRPERSON NIPPER: Dr. Habig.

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

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

22 So, you know, that seems to be the right
23 way to go with that particular circumstance. But
24 typical labeling in this case would probably say if
25 symptoms persist. I mean there's over-the-counter

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 labeling for a lot of medications that say take this
2 for three days, but if symptoms exist, if your
3 temperature doesn't go down, see your health care
4 provider, would be appropriate.

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

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

22 Having confused that issue sufficiently,
23 the performance captured in the labeling should be, I
24 believe, part of the educational brochure kind of
25 approach. It ought to say what pH measures. It ought

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to say what pH is normally and what acidic versus
2 alkaline pH typically means.

3 CHAIRPERSON NIPPER: Okay. I'm being
4 advised by my Executive Secretary not to postpone the
5 open public comments too much longer. We're sort of
6 in the middle of the panel's deliberations on Question
7 4. We are, we still have a Question 5 to do. It's
8 2:15 and we have several items in the open public
9 hearing to deal with. So I'd like to suspend open
10 committee discussion at this point and let's deal with
11 the items in the open public hearing.

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

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

23 I went into my Ob's on three separate
24 visits complaining of external vaginal burning. I was
25 never cultured but prescribed medication for a yeast

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 infection. On the last visit, the afternoon prior to
2 my daughter's death, I was given a forceful cervical
3 exam that caused Group B strep to cross my intact
4 placenta and cause her to be still-born. I was so
5 particular and careful about all aspects of my
6 pregnancy but, unfortunately, trusted my Ob's
7 judgement call about treating my symptoms as a yeast
8 infection without culturing me.

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

19 I don't know if doctors don't culture
20 because of the expense or the time it takes to do a
21 pelvic exam or what. I was very irritated, not only
22 because of my symptoms, which were not treated
23 properly, but because I wasted my time waiting forever
24 in the doctor's office to be seen at multiple offices
25 and then wasted my money on my insurance co-pays and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 useless prescriptions. This was even after telling my
2 primary care provider of the reason why my daughter
3 was still-born.

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

14 Many women have lost their babies and will
15 continue to lose babies, some without even knowing why
16 because both symptomatic and asymptomatic bacterial
17 vaginosis can cross placentas and cause miscarriages
18 and still-births. Women should have the right to
19 monitor their own health care, especially with
20 frequency during pregnancy and before cervical exams.

21 Because, unfortunately, no one has as much concern
22 for their babies or unborn children as they do.

23 Most sincerely, Marti Perhach."

24 I hope I pronounced that correctly,

25 "11 El Dorado Court, Pomona, California.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Enclosed, "Our Baby, Julia Rose", with copyright
2 credit from "Time Stand Still", Lee/Lifeson, Peart,
3 copyright 1987, Core Music, SOCAN, all rights
4 reserved. Performed by RUSH.

5 (Whereupon, the video is shown.)

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

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

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 refilled, again with culturing.

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

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

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

23 Then at 5:50 a.m. contractions went to one
24 to three minutes apart and I had the chills and shakes
25 until 6:10 a.m. At this point I started to wretch for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 a few minutes. Due to morning rush-hour traffic, we
2 arrived at the hospital at 7:05 a.m. While waiting
3 for a room I distinctly felt my baby kicking at about
4 7:20 a.m. I handed the desk nurse my IV antibiotic
5 request while waiting. Once a monitor was put around
6 me at 7:28 a.m. in the labor and delivery room, the
7 nurse told my husband and me that there was a weak
8 fetal heartbeat, probably because the baby was already
9 down so far in my pelvis. That seemed logical to me
10 because I had just felt her kick me.

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

20 As none of my Obs were there, the nurse
21 delivered our baby girl after I pushed once, but the
22 neonatal team could not revive our baby daughter. I
23 was not encouraged to have an autopsy done on my baby
24 and no one thought to have a bacterial culture done
25 from the placenta. We decided to have our baby's

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 heart and lungs examined by the pathologist and have a
2 tissue sample taken for examination.

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

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

21 Never was pneumonia or meningitis or death
22 mentioned to me. I was told that the IV killed the
23 bacteria instantly, whereas it actually needs a
24 minimum of four hours to be effective. I was not
25 cultured for my vaginal burning, even after my third

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 office visit complaining of my symptoms. There was no
2 literature available in the office regarding GBS and I
3 was not told that a fever was a symptom of GBS
4 infection.

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

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

21 (Whereupon, the video is shown.)

22 VIDEO: Hi, my name is Verna Arnold and
23 this my husband, Steven Arnold. And we are here today
24 to talk to you about Group B strep and what it has
25 done to change our lives. I became pregnant earlier

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 this year of 1999, with twins, I had identical twin
2 girls and I had, because I was going to have twin
3 girls I had my regular Ob/Gyn visit every two weeks
4 and I was also seeing a perinatologist every two weeks
5 to monitor my high risk pregnancy.

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

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

25 I went to five and a half months of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

9 Tuesday morning I woke up feeling a little
10 bit achy, I wasn't, I just wasn't feeling great. I
11 thought maybe it was pregnancy achiness which was
12 bound to occur at some point because I was having a
13 perfect pregnancy with no morning sickness, no nausea,
14 no body aches to really speak of other than just being
15 35 years of age and pregnant. So I woke up on that
16 Tuesday morning feeling a little bit achy.

17 I went and did my daily routine of things
18 that I do. At noon time I wasn't feeling any better.

19 I thought, gee, this is really a bummer of a day.
20 I'll go home and lay down, which I did. By 4:00 I
21 decided to call my doctor's office because I still
22 wasn't feeling well. My doctor's office said for me
23 to get into the office immediately. I had my next-
24 door neighbor take me to the doctor's office and
25 subsequently I found out that the twins had died.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 It's not a pleasant thing to have to hear,
2 I actually did not believe the doctor, even though I
3 could see on the ultrasound nothing moving or anything
4 going on. But I was convinced I felt movement because
5 of the fact that the twins were, had already been
6 deceased, deceased since noon when I wasn't feeling
7 well, at the worst point, which was noon time, and
8 they were just bouncing around in the amniotic fluid
9 which I thought was movement.

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

24 I couldn't have this happen. By 9:00 that
25 night I had delivered the twins and I became deathly

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

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

23 But more importantly, I'm also here to
24 testify and to ask that the FDA approve the test for
25 women to test at home and to also, and to test at home

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 for Group B strep and any other sort of vaginal or
2 bacterial infections. But also to test more
3 frequently and to make it a mandatory test that women
4 are tested before they deliver and to test earlier.
5 And also to have more routine testing, so that the
6 labs, when doctors submit tests, the labs don't use
7 chicken broth or lamb broth and another culture
8 differently in different labs.

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 50,000.

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

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

21 They never swabbed the babies to check.
22 They never swabbed the babies. Our babies were
23 swabbed so that way we definitely know it was GBS. We
24 didn't have an autopsy because we were positive it was
25 Group B strep that took the babies.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 But they didn't send it to the CDC. We
2 went to, we've been to two functions in the last eight
3 weeks to try to educate the women out there. And
4 there was a lady that came up and said her sister had
5 a baby that was infected by GBS and it was at the
6 hospital for an extra eight weeks. So that means we
7 know of four babies that have been infected, and
8 that's just us. So when we hear that there's 20 to 30
9 percent of the women that have it or are carriers and
10 there's three million births a year.

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

21 CHAIRPERSON NIPPER: At the FDA's
22 suggestion, we've stopped the tape because as
23 compelling as their case is and as tragic as it is, it
24 is off the topic for the day. If anyone on the panel,
25 I assume that if anyone on the panel wishes to see the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 rest of the tape, we can do it afterwards? Yes. I do
2 have three other letters to read and I hope we can do
3 this quickly, but to get them in the record and to
4 make them available for the panel.

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

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

21 Recently I've had some symptoms of which I
22 was unsure if they were related to pregnancy or a
23 bacterial vaginal infection. Since I work during
24 normal business hours in a non-private setting, it is
25 very awkward to call my ob's office during their

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 business hours and describe my symptoms. A product I
2 could use at home would certainly give me some peace
3 of mind.

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

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

13 CHAIRPERSON NIPPER: The second letter is
14 to Veronica Calvin.

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

23 If only I had this test before I
24 delivered, I would of known that something was wrong
25 and the doctor would of been able to test me further

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 because the bacteria would of shown up in my home
2 test. I believe this test could of saved our family
3 from all the horror we had to go through. Please
4 support home vaginal pH screening.

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

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

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

16 "I respectfully submit this written
17 testimony for consideration by the Clinical Chemistry
18 and Clinical Toxicology Devices Panel at its December
19 7th, 1999, meeting regarding consumer-use devices for
20 measuring vaginal fluid pH. Litmus Concepts, Inc.,
21 LCI, is dedicated to improving women's health by
22 providing simply, easy to use, accurate, on-site tests
23 for common vaginal infections.

24 We have developed and commercialized two
25 professional use products for infectious vaginitis,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the FemExam, registered, pH and Amines TestCard,
2 trademark, and the FemExam, registered, Gardnerella
3 vaginalis PIP Activity Test Card, trademark. As a
4 result of our development efforts in clinical studies,
5 we have extensive experience in evaluating the
6 clinical significance of elevated vaginal fluid pH.

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 costs.

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

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

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

21 Thank you.

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

24 That brings us to the end of the
25 statements from the open public hearing. The open

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 public hearing is now closed and we will continue open
2 committee discussion.

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

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 it doesn't, then that should be there as well.

2 CHAIRPERSON NIPPER: Thank you. Dr.
3 Manno.

4 DR. MANNO: I have no additional comments.

5 CHAIRPERSON NIPPER: Thank you. Dr.
6 Sedlacek.

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

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

25 CHAIRPERSON NIPPER: Thank you. Dr.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Falls.

2 DR. HARRINGTON-FALLS: I answered before.

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

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

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

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

15 CHAIRPERSON NIPPER: No.

16 DR. DIAMOND: Okay.

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

20 DR. DIAMOND: Okay.

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

23 DR. DIAMOND: Okay. Things that I think
24 ought to be included in the label? We sort of skipped
25 over Number 2-A, up above, there ought to be some

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 indication of whether it's for recurring, b is for
2 recurring, or monitor or recurrence in women with a
3 history of vaginal infection. I think that would
4 probably be a reasonable use. We've discussed who
5 it's indicated for, whoever that ends up trying to be,
6 ought to be very clearly identified.

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

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

22 If the results of the test are that it's
23 acidic, less acidic, more basic, than the individual
24 should, sorry, the other way around. If it's more
25 acidic, on the testing and the individual is going to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 use an antifungal agent, it ought to be very clearly
2 specified at what point they should, if it's not
3 working, see a physician. I think it would be very
4 helpful to have actual diagrams of the testing
5 methods, where in the vagina the device is to be
6 placed and step-by-step diagrams of how the analysis
7 is to be done.

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

13 CHAIRPERSON NIPPER: Thank you. Dr.
14 Tuazon.

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

22 CHAIRPERSON NIPPER: Dr. Koumans.

23 DR. KOUMANS: Thanks. I'd like to support
24 the previous comments about post-menopausal women and
25 the differences that might be seen in the results. I

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 think the key issues for labeling that I've heard and
2 would also like to add is to, that it should include
3 what a pH is, what does it mean, what is normal and
4 what is not. That it is not a test for sexually-
5 transmitted diseases. How it differs. How the
6 results may differ and in different kinds of women,
7 pre-menarcheal, pre-menopausal and post-menopausal.

8 What might change the results of the test.

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

14 CHAIRPERSON NIPPER: Thank you. Dr.
15 Rifai.

16 DR. RIFAI: Nothing to add.

17 CHAIRPERSON NIPPER: Dr. Janosky.

18 DR. JANOSKY: Nothing to add.

19 CHAIRPERSON NIPPER: Dr. Rosenbloom.

20 DR. ROSENBLOOM: I think that the labeling
21 for menopause, if I'm not mistaken, there is not, this
22 is not something that's routinely used in the
23 physician's office to monitor estrogen status so that
24 it would be premature to consider it in an over-the-
25 counter preparation.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON NIPPER: Okay. How about
2 Question 5? Risks versus benefits. What risks are
3 associated with having this test available over-the-
4 counter. Anybody want to start? Dr. Falls is willing
5 to start.

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

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

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

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

19 DR. SEDLACEK: I had trouble, if that one
20 slide that was shown of the pH strip was an example of
21 a positive, I had trouble interpreting it because it
22 seemed to me like it should have been moved about
23 three strips to the left. So I don't know if that was
24 just an example of the strip or if that was the
25 correct answer. If it was the correct answer, I got

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 it wrong. And I'm afraid patients might as well.

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

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

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

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

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

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

23 DR. ROSENBLOOM: Well, I was actually
24 going to address the same thing. One of the benefits
25 might be it would address the issues that were brought

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 up in the testimonials. A broader education about
2 infectious risk during pregnancy that may have alerted
3 such well-read or highly motivated individuals to be
4 even more insistent with their health care providers.

5 CHAIRPERSON NIPPER: Any other comments?

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

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

25 CHAIRPERSON NIPPER: Well, at this point

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 we've reached the end of the numbers of questions.
2 Unless someone has other things to add. I hope we've
3 done some good for the FDA and for the public today.
4 Are there any closing comments that any of the panel
5 would have before I close off the meeting? Yes, Dr.
6 Habig.

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

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

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 another Husker fan.

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

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

9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25