FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

MEETING OF THE NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE (NDAC)

Oxytrol for Women
New Drug Application (NDA) 202211
for the Partial Switch from
Prescription to Over-the-Counter (OTC)

Friday, November 9, 2012

FDA White Oak Campus, Building 31
The Great Room (Room 1503)
White Oak Conference Center
10903 New Hampshire Avenue
Silver Spring, Maryland

Reported by: Erick McNair
Capital Reporting Company

1 MEETING ROSTER

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1 MEETING ROSTER (Continued)

2

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1 MEETING ROSTER (Continued)

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22

1 TABLE OF CONTENTS

PAGE

2

Call to Order and Introduction of Committee
3
Marcus Reidenberg, MD, FACP
4
Acting Chairperson, NDAC 11
5

6 Conflict of Interest Statement

7 Minh Doan, PharmD

8 Acting Designated Federal Officer, NDAC 12

9
NDAC Member Appreciation and
10

11 FDA Introductory Remarks

12 Andrea Leonard-Segal, MD, MS, Director,

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15 Evaluation IV (ODE IV), OND, CDER, FDA 16

16
Sponsor Presentations 23
17
Introduction
18
Edwin Hemwall, PhD, R&D Leader,
19
Rx-to-OTC Switch, Merck Consumer Care 23
20

21

22

1 TABLE OF CONTENTS (CONTINUED)

PAGE

2 Clinical Overview of Oxytrol
3 Rajesh Mishra, MD, PhD
4 Head, Medical Affairs
5 Merck Consumer Care 31
6
7 Label Comprehension and
8 Self-Selection Studies
9 Stephen Neumann, MA
10 Head, Consumer Research
11 Merck Consumer Care 36
12
Actual Use Study: CONTROL
13 Amy Replogle, MS
14 Program Leader, Rx-to-OTC Switch
15 Merck Consumer Care 50
16
17 Oxytrol for OAB in an OTC Setting
18 Eman Elkadry, MD
19 Harvard Medical School
20 Fellowship Director and Attending
21 Physician, Mount Auburn Hospital,
22 Cambridge, MA 63

1 TABLE OF CONTENTS (CONTINUED)

PAGE

2 Consumer Education & Support
3 Kristie Licata, MBA
4 Product Development Leader
5 Rx-to-OTC Switch
6 Merck Consumer Care 69
7
8 Summary
9 Edwin Hemwall, PhD 74
10
Clarifying Questions 78
11
12 Break 103
13
FDA Presentations 103
14 Overview of the Efficacy and Safety
15 Database for NDA 21-351
16 Donald McNellis, MD
17 Medical Officer, Division of
18 Reproductive and Urologic Products 103
19 Office of Drug Evaluation III (ODE III),
20 OND, CDER, FDA
21
22

1 TABLE OF CONTENTS (CONTINUED)

PAGE

2 Oxytrol for Women Label Comprehension
3 and Self-Selection Consumer Research
4 Barbara Cohen, MPA
5 Social Science Analyst
6 DNCE, ODE IV, OND, CDER, FDA 111
7
8 Oxytrol for Women --
9 The Clinical Perspective
10 Ryan Raffaelli, MD
11 Medical Reviewer
12 DNCE, ODE IV, OND, CDER, FDA 133
13 Clarifying Questions 160
14
15 Lunch 190
16 Open Public Hearing 190
17 Nancy Muller, PhD, MBA, Executive Director,
18 National Association for Continence 192
19
20
21
22

1 TABLE OF CONTENTS (CONTINUED)

PAGE

2 Elizabeth LaGro, MLIS, Director,
3 The Simon Foundation for Continence 196
4
5 Linda Heller, JD, Special Education Advocate 201
6 Kate Ryan, MPA, Program Coordinator,
7 National Women's Health Network 205
8
9 Anthony Visco, MD, AUGS, Division Chief,
10 Urogynecology, Duke University
11 School of Medicine 210
12 Questions to the Committee/Committee Discussion 214
13
14 Break 283
15 Questions to the Committee/Committee Discussion 283
16
17 Adjournment 310
18
19
20
21
22

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

2 Call to Order and Introduction of Committee

3 DR. REIDENBERG: For topics such as those

4 discussed at today's meeting, there are often a variety

5 of opinions, some of which are quite strongly held. Our

6 goal is that today's meeting will be a fair and open

7 forum for discussion of these issues and that

8 individuals can express their views without

9 interruption. Thus, as a gentle reminder, individuals

10 will be allowed to speak into the record only if

11 recognized by the Chairperson, me. We look forward to

12 a productive meeting.

13 In the spirit of the Federal Advisory

14 Committee Act and the Government in the Sunshine Act,

15 we ask that the advisory committee members take care

16 that their conversations about the topic at hand take

17 place in the open forum of the meeting.

18 We are aware that members of the media are

19 anxious to speak with the FDA about these proceedings;

20 however, the FDA will refrain from discussing the

21 details of this meeting with the media until its

22 conclusion.

1 Also, the committee is reminded to please
2 refrain from discussing the meeting topic during breaks
3 or lunch.
4 Now I will pass this on to Minh Doan, who
5 will read the Conflict of Interest Statement. Conflict
6 of Interest Statement
7 DR. DOAN: The Food and Drug Administration
8 is convening today's meeting of the Nonprescription
9 Drugs Advisory Committee under the authority of the
10 Federal Advisory Committee Act of 1972. With the
11 exception of the industry representative, all members
12 and temporary voting members of the committee are
13 special government employees or regular federal
14 employees from other agencies and are subject to
15 federal conflict of interest laws and regulations.
16 The following information on the status of
17 this committee's compliance with federal ethics and
18 conflict of interest laws covered by, but not limited
19 to, those found at 18 U.S.C. Section 208 is being
20 provided to participants in today's meeting and to the
21 public.
22 FDA has determined that members and temporary

1 voting members of this committee are in compliance with
2 federal ethics and conflict of interest laws. Under 18
3 U.S.C. Section 208, Congress has authorized FDA to
4 grant waivers to special government employees and
5 regular federal employees who have potential financial
6 conflicts when it is determined that the Agency's need
7 for a particular individual's services outweighs his or
8 her potential financial conflict of interest.
9 Related to the discussion of today's meeting,
10 members and temporary voting members of this committee
11 have been screened for potential financial conflicts of
12 their own as well as those imputed to them, including
13 those of their spouses or minor children and, for
14 purposes of 18 U.S.C. Section 208, their employers.
15 These interests may include investments; consulting;
16 expert witness testimony; contracts/grants/CRADAs;
17 teaching/speaking/writing; patents and royalties; and
18 primary employment.
19 Today's agenda involves a discussion of data
20 submitted by MSD Consumer Care to support new drug
21 application 202211, for the partial switch from
22 prescription to over-the-counter of the oxybutynin

1 transdermal system, proposed trade name Oxytrol for
2 Women. The proposed over-the-counter use is "treats
3 overactive bladder in women." The data to be discussed
4 will include a summary of the postmarketing experience
5 with the oxybutynin transdermal system, and the results
6 of the consumer studies, including label comprehension
7 studies, self-selection studies, and an actual use
8 study. The committee will be asked to consider whether
9 the data support the appropriate and safe use of
10 oxybutynin transdermal system by OTC consumers.
11 This is a particular matters meeting during
12 which specific matters related to MSD Consumer Care's
13 NDA will be discussed.
14 Based on the agenda and all financial
15 interests reported by the committee members and
16 temporary members, no conflict of interest waivers have
17 been issued in connection with this session.
18 To ensure transparency, we encourage all
19 standing committee members and temporary voting members
20 to disclose any public statements that they have made
21 concerning the product at issue.
22 With respect to FDA's invited industry

1 representative, we would like to disclose that Dr.
2 Lorna Totman is participating in this meeting as a non-
3 voting industry representative, acting on behalf of
4 regulated industry. Dr. Totman's role at this meeting
5 is to represent industry in general and not any
6 particular company. Dr. Totman is the principal of
7 Lorna Totman Consulting, LLC. She provides consulting
8 services to the pharmaceutical industry.
9 We would like to remind members and temporary
10 voting members that if the discussions involve any
11 other products or firms not already on the agenda for
12 which an FDA participant has a personal or imputed
13 financial interest, the participants need to exclude
14 themselves from such involvement and their exclusion
15 will be noted for the record.
16 FDA encourages all other participants to
17 advise the committee of any financial relationship that
18 they may have with the firm at issue.
19 Thank you.
20 DR. REIDENBERG: Thank you, Minh.
21 I would now like to invite Dr. Leonard-Segal
22 to start her presentation. NDAC Member Appreciation and

1 FDA Introductory Remarks

2 DR. LEONARD-SEGAL: Thank you, Dr.

3 Reidenberg.

4 Good morning, everyone. Before I start in on

5 my introductory remarks this morning, on behalf of FDA,

6 I would like to recognize four members of NDAC whose

7 terms will expire at the end of May.

8 So Dr. Reidenberg, could you come up here,

9 please?

10 Dr. Marcus Reidenberg has served on the NDAC

11 this go-round since December 2011. He is a Professor

12 of Pharmacology, Medicine, and Public Health, as well

13 as the Head of the Division of Clinical Pharmacology at

14 the Weill Cornell Medical College. For over 50 years,

15 Dr. Reidenberg has enjoyed a distinguished career in

16 academic medicine as an author, researcher, teacher,

17 and physician to his many patients.

18 Dr. Reidenberg has participated in two prior

19 NDAC meetings this past term, and we have benefited

20 from his wisdom, his broad knowledge of medicine, his

21 expertise in clinical pharmacology, and his vast amount

22 of common sense. We are additionally so pleased that

1 he agreed to serve as the Chair for today's meeting.
2 In appreciation of his service, the FDA would
3 like to recognize Dr. Reidenberg with a plaque, and I'm
4 going to read it. There are four plaques, and they all
5 say the same thing, so I'll read this one once, and
6 then you'll know what the others say.
7 So it says, "U.S. Food and Drug
8 Administration Advisory Committee Service Award
9 presented to Marcus M. Reidenberg, M.D., in recognition
10 of distinguished service to the people of the United
11 States of America, Nonprescription Drugs Advisory
12 Committee, Center for Drug Evaluation and Research,
13 from December '11 to May 2013. Thank you, Dr.
14 Reidenberg.
15 DR. REIDENBERG: Thank you very, very much.
16 (Applause.)
17 DR. LEONARD-SEGAL: Dr. Norma Rogers. Hi.
18 DR. ROGERS: Hi.
19 DR. LEONARD-SEGAL: Dr. Norma Rogers has
20 served on the NDAC since January 2010. She is a
21 Clinical Professor in the Department of Family and
22 Community Health Systems with the University of Texas

1 Health Science Center School of Nursing at San Antonio.
2 Dr. Rogers has spent her life in service to her
3 community as a nurse, educator, and as an advocate for
4 the underserved population. Dr. Rogers participated in
5 the May 17th to 18th, 2011, Advisory Committee Meeting
6 on Pediatric Dosing of Acetaminophen and in the April
7 2nd, 2012 meeting on the types of consumer studies
8 needed to assess proper use of a med kit containing
9 doxycycline to be taken in the event of anthrax
10 exposure. She has discussed difficult OTC issues in a
11 clear and cogent manner, and that has been very helpful
12 to FDA.
13 In appreciation of her service, we would like
14 to recognize her with this plaque.
15 DR. ROGERS: Thank you.
16 DR. LEONARD-SEGAL: Thank you.
17 (Applause.)
18 DR. LEONARD-SEGAL: Dr. Gellad. Hi.
19 Dr. Walid Gellad has served on the NDAC since
20 December 2011. He is an Assistant Professor of
21 Medicine with the University of Pittsburgh School of
22 Medicine, and is a Staff Physician for the VA

1 Pittsburgh Health System. His research interests focus
2 on the quality, safety, and efficiency of prescribing
3 medication. We value his participation on NDAC and his
4 service at the April 2nd, 2012, meeting convened to
5 discuss the doxycycline med kit. We have benefited
6 from his comments and advice and look forward to
7 hearing from him again today.
8 In appreciation of his service, the FDA would
9 like to recognize him with a plaque.
10 (Applause.)
11 DR. LEONARD-SEGAL: And Dr. Farber, last but
12 not least.
13 Dr. Farber has served on the NDAC since March
14 2009. He is Clinical Medical Director and Professor of
15 Medicine at the University of California in San Diego.
16 His career in academic medicine spans decades, and he
17 has authored a myriad of articles on a vast array of
18 topics among which are medical ethics, patient-doctor
19 communication, patient compliance, and preventative
20 health care.
21 Because of his areas of expertise, Dr. Farber
22 has been able to provide unique insights to NDAC

1 deliberations. He participated in the June 29th to
2 30th, 2009, Acetaminophen and Liver Injury Advisory
3 Committee as well as the May 17th to 18th, 2011,
4 Advisory Committee Meeting on Pediatric Dosing of
5 Acetaminophen. We are so pleased that he is able to be
6 with us today to enrich the discussion as NDAC
7 considers a new drug for prescription to over-the-
8 counter switch.
9 In appreciation of his service, the FDA would
10 like to recognize Dr. Farber with this plaque.
11 Thank you, Dr. Farber.
12 (Applause.)
13 DR. LEONARD-SEGAL: And now to my
14 introductory remarks.
15 Well, today we're going to have, I think, a
16 very interesting day. We're going to talk about a new
17 prescription to over-the-counter switch product,
18 Oxytrol for Women, the oxybutynin transdermal system,
19 3.9 milligrams.
20 So Merck Consumer Care submitted this NDA to
21 partially switch Oxytrol from prescription to over-the-
22 counter. Oxytrol has been approved since 2003 to treat

1 overactive bladder. The proposed OTC use, as you heard
2 Minh mention a few minutes ago, treats overactive
3 bladder in women, and we mean females at least 18 years
4 of age. The product would remain a prescription
5 product for men, which is why we call this a partial
6 Rx-to-OTC switch.
7 Do you have a different one? Oh, this one.
8 Okay. Thank you. Okay. Good. We're having a little
9 technical discussion over which remote to use. Which
10 one should I use? Use this one with the FDA label.
11 Okay.
12 So among other information, the presentations
13 today will include a review of postmarketing data,
14 results of consumer studies including label
15 comprehension studies, self-selection studies, and an
16 actual use study called the CONTROL study, and these
17 were conducted to support the switch application.
18 We're asking the committee members to
19 consider whether the data support the appropriate and
20 safe use of the oxybutynin transdermal system, or the
21 Oxytrol patch, by over-the-counter consumers.
22 So this is how we will spend our day. First

1 we will hear from the team, from Merck, and we welcome
2 you. We have FDA presentations that will follow that.
3 We have lunch, the Open Public Hearing, and then the
4 committee deliberations, and then we'll adjourn.
5 We at FDA are all looking forward to very
6 interesting discussion, and we want to thank the
7 committee for the hard work that you are going to do
8 today.
9 So I guess we can proceed, Dr. Reidenberg.
10 Thank you.
11 DR. REIDENBERG: Thank you, Dr. Leonard-
12 Segal.
13 Dr. Totman, we've kind of introduced
14 ourselves a bit earlier. Now it's your turn.
15 DR. TOTMAN: I'm Lorna Totman, the Industry
16 Rep.
17 DR. REIDENBERG: Thank you.
18 One more formal statement. Both the Food and
19 Drug Administration and the public believe in a
20 transparent process for information gathering and
21 decision-making. To ensure such transparency at the
22 advisory committee meeting, the FDA believes that it is

1 important to understand the context of an individual's
2 presentation. For this reason, FDA encourages all
3 participants, including the sponsor's non-employee
4 presenters, to advise the committee of any financial
5 relationships that they may have with the firm at
6 issue, such as consulting fees, travel expenses,
7 honoraria, and interests in the sponsor, including
8 equity interests and those based upon the outcome of
9 this meeting.
10 Likewise, FDA encourages you, at the
11 beginning of your presentation, to advise the committee
12 if you do not have any such financial relationships. If
13 you choose not to address this issue of financial
14 relationships at the beginning of your presentation, it
15 will not preclude you from speaking.
16 I now would like to call on Dr. Hemwall to
17 begin the Merck presentations. Sponsor Presentations
18 Introduction
19 DR. HEMWALL: Thank you, Dr. Reidenberg.
20 And good morning. I'm Ed Hemwall,
21 representing Merck Consumer Care and our partners at
22 Watson Pharmaceuticals, who developed the prescription

1 form of the Oxytrol transdermal system for the
2 treatment of overactive bladder, or OAB.
3 As you know, overactive bladder is a chronic
4 condition with a substantial impact on quality of life.
5 It's characterized as urinary urgency with or without
6 urge incontinence and is often associated with urinary
7 frequency and nocturia. It is one of the most common
8 chronic conditions affecting American women.
9 The prevalence of OAB in women increases with
10 every decade of life with a substantial increase after
11 menopause. It is estimated that 20 million American
12 women are currently living with OAB. OAB can have an
13 impact on every aspect of a woman's life, including
14 physical and social limitations, personal
15 relationships, emotional well-being, even the ability
16 to get a full night's sleep, and these disturbances can
17 affect energy levels and can lead to anxiety and
18 depression. The effects can even spill over into
19 women's work lives and affect their productivity.
20 Despite the availability of prescription
21 medication and behavioral therapies, self-management is
22 the norm. Many women struggle with OAB for years

1 coping with and concealing their problem before seeking
2 treatment. Many use tactics like toilet mapping and
3 know where every clean public restroom is located in
4 their community. Many women practice preemptive
5 voiding before they leave the house, when they get to
6 their destination, and any other opportunity they can
7 to keep their bladder empty and reduce leaking. Often
8 they restrict fluids, which can be harmful, especially
9 in older women, who can be prone to dehydration.
10 When women go to the store for solutions,
11 this is what they find: absorbent products with little
12 education on information or other options. But they
13 need something just to give them the confidence to
14 leave home. Unfortunately, many women choose to stay
15 home.
16 And for all these women, we need to reduce
17 currently existing barriers to treatment.
18 Anticholinergic drugs have long been a mainstay in
19 helping to relieve symptoms of OAB. Oxytrol, or
20 oxybutynin, the active ingredient in the Oxytrol patch,
21 has been used to treat OAB for more than 30 years.
22 Oxytrol was approved for prescription treatment of OAB

1 symptoms in 2003 and has been a safe and effective
2 option for nearly a decade.
3 There are unique advantages with the
4 transdermal delivery that make the patch a good
5 candidate for OTC use. The Oxytrol OTC indication
6 we're proposing is for the treatment of OAB in adult
7 women who have had two or more OAB symptoms --
8 frequency, urgency, or urge incontinence -- lasting for
9 at least 3 months, and this 3-month timeframe is to
10 discourage use for treating other conditions that may
11 have similar symptoms but are more acute in onset.
12 The patch is slightly smaller than a credit
13 card, and a new patch is applied to the abdomen, hip,
14 or buttocks every 4 days.
15 As you consider this switch proposal, it is
16 important to understand how OAB is viewed and managed
17 today both by women who have had it and their health
18 care professionals. As I mentioned earlier, most
19 women, up to 80 percent of those affected, choose to
20 manage this condition on their own largely because
21 they're embarrassed and want to conceal their
22 condition. Some simply accept this condition as a

1 normal part of aging.
2 Women readily recognize their symptoms and
3 often struggle for years before ever mentioning it at a
4 doctor visit. Likewise, physicians do not routinely
5 screen for OAB or proactively ask patients if they have
6 bladder problems. Ultimately, the woman brings it up
7 with her doctor usually when she begins to have too
8 many accidents.
9 Due to the suboptimal self-management
10 situation, many women adapt their lives in an effort to
11 conceal or cope with the symptoms almost always to the
12 detriment of their quality of life. Additionally, many
13 women may be placing themselves at risk of delayed
14 diagnosis of other conditions which may have some of
15 the same symptoms of urinary frequency or urgency.
16 So it seems clear that women dealing with OAB
17 on their own could truly benefit from an OTC treatment
18 option. OTC availability of Oxytrol would provide a
19 much needed, safe, and effective pharmacologic self-
20 management tool. The combination of informative
21 labeling and a targeted education program will help to
22 guide appropriate behavior. It will increase urinary

1 health awareness and direct women when to seek
2 professional guidance, and the result will be that more
3 women will have reduced OAB symptoms and an improved
4 quality of life. And Oxytrol safety profile is well
5 understood with the product well tolerated by patients.
6 Any incremental risk over what women are already doing
7 with their ongoing approaches to self-management is
8 minimal.
9 So with these goals in mind, we set out to
10 design an OTC label with the following objectives.
11 First, to identify the right target
12 population, adult women with overactive bladder, this
13 is clearly communicated on the front panel of the
14 packaging.
15 Next, to inform these women who are often
16 self-managing their OAB about other conditions which
17 may have similar symptoms and require a doctor's care.
18 As you can see, this warning is bolded and highlighted
19 in yellow on the package. And we provide clear
20 directions to stop use and see a doctor if conditions
21 worsen, if new symptoms appear, or if the condition
22 does not improve after 2 weeks of use.

1 Our OTC development program for Oxytrol was
2 designed to create layers of self-management labeling
3 safeguards. First, the Oxytrol transdermal system is a
4 safe and effective medication appropriate for OTC use.
5 Second, the OTC drug facts label is well understood and
6 directs a large majority of consumers to make a correct
7 self-selection decision that the product is right for
8 them. They must be women with symptoms consistent with
9 OAB and none of the medical conditions the label warns
10 against. Next, the label guides appropriate use and
11 deselection, which means to stop use based on new
12 symptoms or a lack of response. Finally, the label
13 also directs women to seek medical attention for non-
14 OAB symptoms, and the clinical course of these other
15 conditions does not represent unacceptable risk for
16 women who might try Oxytrol for a short period.
17 The rest of our presentation today will
18 examine this layered approach to safe use in greater
19 depth. The totality of the resulting data strongly
20 support the conclusion that Oxytrol can be used
21 appropriately by women with OAB.
22 Our presentation begins with Dr. Raj Mishra

1 reviewing the clinical profile of the Oxytrol patch and
2 why it is especially suited for OTC use.
3 Steve Neumann will review key findings from
4 the label comprehension and self-selection studies
5 which helped us create the optimal labeling.
6 Amy Replogle will review the results of
7 control, our actual use study, demonstrating how women
8 use the product according to that labeling.
9 And Dr. Eman Elkadry will provide a
10 clinician's perspective and explain how availability of
11 Oxytrol in an OTC setting is expected to provide
12 benefit with low likelihood of unintended consequences.
13 Then Kristie Licata will review our plans for a
14 comprehensive education and support program both for
15 consumers and health care professionals.
16 And I'll conclude with a brief recap before
17 we address any questions you may have.
18 We have also invited several additional
19 subject matter experts who are available today to
20 answer your questions and provide perspective. All of
21 these outside experts are being compensated for their
22 time and travel.

1 I would now like to invite Dr. Mishra to the
2 podium. Clinical Overview of Oxytrol
3 DR. MISHRA: Thank you, Dr. Hemwall.
4 Good morning. My name is Raj Mishra. I am
5 the Head of Medical Affairs at Merck Consumer Care.
6 As Dr. Hemwall mentioned in his introduction,
7 the safe use of Oxytrol in an OTC setting is based on
8 appropriate self-management safeguards. The first and
9 foremost consideration is that Oxytrol is a safe and
10 effective medication for overactive bladder. Oxytrol
11 has been used as prescription medication for OAB since
12 2003.
13 I will briefly review the clinical benefits
14 and safety of Oxytrol. The FDA will present these data
15 in more detail later this morning.
16 The clinical efficacy of Oxytrol was
17 demonstrated in two Phase 3 trials in OAB patients
18 which were part of the new drug application for
19 prescription approval. In these two double-blind,
20 placebo-controlled studies, Study 9 and Study 11, all
21 patients, including the placebo treatment groups,
22 received behavior modification instructions. The

1 primary efficacy endpoint in both trials was the change
2 from baseline to end of treatment at 12 weeks in the
3 number of weekly and daily incontinence episodes
4 comparing Oxytrol and placebo groups in Study 9 and 11
5 respectively.
6 In both studies, a statistically significant
7 reduction in weekly or daily incontinence episode
8 frequency was observed in the Oxytrol groups compared
9 to placebo. In both studies, the secondary endpoint,
10 increase urinary void volume from baseline to the end
11 of study, was also significantly increased in the
12 Oxytrol group compared to placebo. The secondary
13 endpoint, decrease in daily urinary frequency, was also
14 significantly improved compared to placebo in Study 9
15 with a similar non-significant trend observed in Study
16 11.
17 As you heard in the introduction by Dr.
18 Hemwall, OAB symptoms have a significant impact on the
19 quality of life of the sufferer. Therefore, clinically
20 meaningful benefit of symptom treatment for an OAB
21 sufferer is improvement in the quality of life.
22 As detailed in your briefing book, both the

1 Phase 3 and Phase 4 trials used validated and
2 condition-specific instruments to measure quality of
3 life changes associated with Oxytrol treatment. For
4 example, the Incontinence Impact Questionnaire and the
5 total IIQ score in the Phase 3 trials looked at the
6 psychosocial impact of incontinence.
7 In the Phase 4 study, the King's Health
8 Questionnaire examined the health-related quality of
9 life. Overall, the quality of life data suggests
10 clinical benefits of symptom improvement.
11 Now let's look at the pharmacology of
12 transdermal oxybutynin delivery and the safety of
13 Oxytrol. As you know, anticholinergics are associated
14 with certain classic side effects such as dry mouth and
15 constipation. There is an important difference,
16 however, between oral and transdermal oxybutynin.
17 Oxybutynin is extensively metabolized in the gut wall
18 and liver. There is evidence that one of the active
19 metabolites of oxybutynin, namely, desethyloxybutynin,
20 or DEO, contributes to these classic anticholinergic
21 side effects. Transdermal administration avoids first-
22 pass metabolism of oxybutynin resulting in markedly

1 reduced levels of DEO.
2 To better understand the pharmacology of
3 transdermal formulation, let's look at the comparative
4 plasma levels of oxybutynin and DEO from three
5 formulations -- oral immediate release, oral extended
6 release, and transdermal. This display shows time and
7 hours on the X axis with plasma concentration in
8 nanogram per mL on the Y axis. Here in brown is shown
9 the plasma profile for immediate-release oxybutynin 5
10 milligram based on simulation from single-dose data.
11 You can also see very distinct peaks and troughs with
12 peak DEO concentrations approaching 45 nanograms per
13 mL. In blue, you see the profile for oral extended
14 release oxybutynin product at therapeutic doses with
15 the dark blue showing the DEO levels. This reduces the
16 daily extreme peaks and troughs of immediate release.
17 In contrast to the oral forms, the plasma
18 profile of the Oxytrol transdermal system, shown in
19 green, is smooth, without the peaks and troughs, has
20 low DEO levels, and a much lower DEO-to-oxybutynin
21 ratio relative to oral delivery. This is one reason
22 that there appears to be a better systemic tolerability

1 profile for Oxytrol compared to the oral formulations.
2 Let's now take a look at the safety data from
3 Phase 3 trials, postmarketing data, and from a review
4 of the literature. Here are the pooled adverse event
5 data as presented in the prescription labeling from the
6 two Phase 3 trials and reported by at least 1 percent
7 of the study patients. Most of the events seen with
8 Oxytrol are local application site reactions such as
9 pruritus and erythema. The adverse events commonly
10 associated with anticholinergics, such as dry mouth,
11 constipation, and abnormal vision are reported at lower
12 rates.
13 Over the last decade, worldwide postmarketing
14 safety data has been collected based on nearly 270,000
15 patient-treatment years. There has been a consistent
16 safety profile with no new safety signals. The most
17 frequently reported events were skin related and were
18 mild to moderate in severity.
19 We also performed a comprehensive review of
20 the scientific literature dating back to 2003, and no
21 new safety trends were observed. Overall, the
22 postmarketing safety profile of Oxytrol is consistent

1 with the safety profile observed during the placebo-
2 controlled Phase 3 trials.
3 In summary, there is demonstrated evidence of
4 clinical benefit from Phase 3 approval studies. The
5 clinical efficacy benefit is underscored by positive
6 quality of life data. The transdermal delivery of
7 oxybutynin allows for consistent plasma levels over 4
8 days and a low incidence of classic anticholinergic
9 side effects. Oxytrol's safety profile has been
10 consistent in postmarketing surveillance with no
11 unusual or new safety trends.
12 Together, these attributes and the supporting
13 data make Oxytrol an appropriate candidate for OTC
14 switch consideration for the treatment of symptoms of
15 OAB.
16 Now I would like to invite Mr. Steve Neumann
17 to review the label comprehension and self-selection
18 studies in the OTC development program. Label
19 Comprehension and Self-Selection Studies
20 MR. NEUMANN: Thank you, Dr. Mishra.
21 Good morning. My name is Steve Neumann, and
22 I'm responsible for consumer studies at Merck.

1 We developed the Oxytrol label to provide
2 safeguards for the proper self-management of OAB. The
3 studies that we conducted demonstrate that consumers
4 understand the label and can self-select appropriately.
5 Our development program was carefully
6 designed to understand consumer behavior as it relates
7 to
8 Oxytrol in the OTC setting. We conducted
9 three types of consumer behavior studies: first, label
10 comprehension studies to measure how well consumers
11 understand the key label messages; then self-selection
12 studies to evaluate if consumers can correctly judge if
13 the product is right for them; and an actual use study
14 to observe how consumers use the product on their own
15 and if they can stop use according to the label.
16 A common practice in OTC label development is
17 to use a multistage iterative process that incorporates
18 feedback from the FDA and from consumers. That's
19 exactly the approach we took in our development
20 program. The main label stages will be highlighted in
21 yellow. The first represents the drug facts prototype
22 that was sent to the FDA in 2007. After incorporating

1 FDA feedback, the label was studied with consumers in
2 Stage I label comprehension and self-selection studies.
3 These will be referred to as the initial studies
4 throughout my presentation today.
5 The package and the label were then updated
6 for Stage II label studies and an actual use study we
7 call CONTROL. While the front panel was redesigned
8 from Stage I, the drug facts portion of the package
9 remained consistent for nearly all of the key messages.
10 A few minor additional modifications were made to
11 enhance clarity and readability, leading to the final
12 version that's submitted in the FDA that's being
13 discussed today.
14 Specifically, we conducted six label
15 comprehension studies, three self-selection studies,
16 and one actual use study. Of the 10 studies, some were
17 among the general populations of OAB sufferers and
18 others were targeted toward specific populations. The
19 focus of my review today will be on the label
20 comprehension and self-selection studies. Ms. Replogle
21 will then review the actual use study.
22 Before I discuss specific details in our

1 development program, I would like to provide some
2 perspective on consumer behavior studies. The purpose
3 of these studies was to determine whether consumers can
4 understand the label messages and appropriately use the
5 product in an OTC setting. In these studies, we want
6 to know not only what a consumer does but why they do
7 it in order to assess whether a user's behavior is
8 correct or incorrect.
9 Different types of questions are necessary to
10 really fully understand consumer behavior. Closed-
11 ended data have pre-specified responses to questions
12 and are easy to analyze. For example, the investigator
13 asks a woman if she has urinary frequency and she
14 responds yes or no. In contrast, open-ended questions
15 have no pre-defined responses and can be difficult to
16 categorize. For example, in the use study, subjects
17 were asked why they continued to use Oxytrol if their
18 OAB symptoms stayed the same or worsened. These types
19 of responses are free-flowing and can be quite varied.
20 These varied responses make consumer behavior
21 data challenging to capture in a way that can be
22 tabulated and analyzed. Individual subject data needs

1 to be reviewed really on a case-by-case basis in order
2 to fully understand each subject's behavior and
3 determine whether it's correct. This process is
4 referred to as "mitigation" and was used in our
5 program.
6 Mitigation is an objective process that's
7 similar to adjudication in clinical trials. Often the
8 rules for classifying correct and incorrect responses
9 are prespecified. As far of the process, panels of
10 either internal or external experts can sometimes be
11 used in setting the rules.
12 The variability also makes the setting of
13 specified targets for success very difficult. We
14 usually look at the absolute percentages of subjects
15 responding a certain way, which we refer to as scores
16 or point estimates, and the corresponding error range.
17 In order to minimize risk, analysis sometimes focuses
18 on the lower bound of the confidence interval, but it's
19 important to remember that the true value is as likely
20 to be in the upper range as in the lower. The approach
21 I took in most of the data tables I'm going to show
22 today include both the point estimate and the lower

1 bound.
2 Finally, the variability also has us look at
3 the data in a more holistic way versus a binary
4 approach, where hitting a target means success or
5 failure. A point estimate of 90 percent of subjects
6 making a correct response is considered a very good
7 score in studies of these types.
8 So let's start with label comprehension. In
9 these open-label, uncontrolled studies participants are
10 presented a series of scenarios describing possible
11 real-life situations for which they evaluate
12 appropriate use of the product based on their
13 understanding of the product label, not their own
14 health status.
15 Initially, these studies test the entire
16 label, which can result in 25 to 30 scenario questions
17 and corresponding endpoints. As a result, a frequent
18 practice is to attend most to those messages that may
19 carry higher risk if not well understood. It may also
20 not be necessary to repeat testing of certain label
21 elements if the comprehension levels are strong in
22 early testing and the label does not change

1 significantly in order to manage the potential for
2 subject fatigue studies.
3 So here is an example of a label
4 comprehension scenario. "Harriet has symptoms of
5 overactive bladder that she has not started treating
6 yet. When she went to the bathroom today, she noticed
7 that there was blood in her urine. According to the
8 label, is it okay or not okay for Harriet to use this
9 product?" Then the participant is asked why they said
10 that. Both parts of the question are considered in the
11 scoring of the correctness.
12 As I mentioned earlier, we conducted initial
13 label comprehension and self-selection studies. We
14 then made some label modifications and conducted
15 subsequent studies which included several targeted
16 studies and a pivotal label study. Overall, the
17 results were very good for our initial study with the
18 strongest comprehension of what the product is for, the
19 directions for use, and some of the warnings of
20 greatest medical consequence. Please refer to our
21 briefing book for the detailed results.
22 Some of the lower results were on scenarios

1 that related to stress incontinence, glaucoma, kidney
2 stones, and developing skin irritation or itchy skin
3 while using the product.
4 The initial label comprehension demonstrated
5 strong understanding of symptoms related to possible
6 undiagnosed UTI. All scores for both the normal and
7 low-literate cohorts exceeded 90 percent.
8 Because of these strong scores and the fact
9 that the text of the UTI symptom messages remained
10 consistent from the initial drug facts label to the
11 modified label, it was not necessary to retest these
12 messages in the pivotal Label Comprehension Study. For
13 the same reason, strong scores and consistent text, the
14 messages about directions for use did not need to be
15 retested either.
16 Turning now to self-selection studies, they
17 help us evaluate the second element of the self-
18 management paradigm, if consumers can appropriately
19 decide if Oxytrol is right for them based on their own
20 health information.
21 Self-selection questions have several parts.
22 A closed-ended question, "Is this product right for

1 you?" is asked first, which is followed then by several
2 open-ended questions such as, "Why do you say that?"
3 and, "What led you to that decision?"
4 Data for all the questions was evaluated for
5 each subject. If a participant responded yes to the
6 self-selection question but was not eligible per the
7 label, they were initially classified as incorrect. The
8 follow-up question responses were carefully reviewed to
9 see if mitigating factors existed and to determine the
10 final classification as correct or incorrect.
11 For example, a pregnant woman who stated that
12 the product was right for her but in response to the
13 follow-up question added that she could use it only if
14 she were not pregnant is an example of response that
15 would qualify as correct post-mitigation.
16 In the initial self-selection study, which
17 used the same package and drug facts label as the
18 initial Label Comprehension Study, two general cohorts
19 were included, normal and low-literate subjects. The
20 subjects were recruited via advertising that focused
21 only the symptoms of frequent urination and urgency and
22 did not mention OAB.

1 After coming to the site and reading the
2 label, the subjects were asked if the product was right
3 for them to use. Their responses were compared to
4 those of a physician who also read the label and then
5 conducted a medical exam. The medical workup included
6 urinalysis, a pregnancy test, and a pelvic exam of the
7 subject in order to judge if the subject had OAB, no
8 contraindicated conditions, and that the product would
9 be acceptable for them to use.
10 In order to be counted as acceptable, a
11 subject's decision needed to either be consistent with
12 that of the physician or be a response associated with
13 minimal or no harm. Minimal or no harm responses were
14 defined as those where either the subjects said they
15 could not use the product but the physician said they
16 could, or cases where the physician judged the subject
17 had stress incontinence. Using these criteria, both
18 cohorts attained strong scores for self-selection and
19 self-recognition.
20 This initial self-selection study also gave
21 us an opportunity to explore self-selection among men.
22 The results were unacceptable, which caused us to

1 redesign the front package graphics in an effort to
2 discourage men from interest in the product. So that
3 men could better understand that Oxytrol is not for
4 them, the color of the box changed from blue to pink, a
5 figure of a woman was added to the front panel, and the
6 name was modified to Oxytrol for Women. With regard to
7 the rest of the label, most of the messages stayed the
8 same. There were some minor refinements such as
9 bolding and highlighting of key messages, and several
10 modifications made for clarification. Diabetes
11 messages changed in order to better distinguish the
12 signs and symptoms of undiagnosed diabetes.
13 So let me summarize the Stage I label
14 development. The label obtained strong scores in many
15 important areas including comprehension of undiagnosed
16 UTI symptoms. General population self-selection was
17 also strong at 92 percent, and, as noted, we addressed
18 the self-selection score among men with the front panel
19 redesign and developed a targeted study to retest it.
20 The modified package and label were then
21 retested in Stage II consumer studies, including a
22 pivotal Label Comprehension Study, as well as targeted

1 label comprehension and self-selection studies. We
2 tested key label safety messages among women age 65 and
3 older in a Stage II Label Comprehension Study targeted
4 to this age group. A substantial majority of the women
5 in this study comprehended the key label messages. For
6 example, we tested many of the symptoms indicative of a
7 possible UTI among this age group with strong results.
8 The pivotal Label Comprehension Study
9 demonstrated that most key messages are well
10 understood. They either met or nearly missed their
11 targets. In this study, we categorized a priori
12 messages of higher medical consequence versus those of
13 lower medical consequence. The messages of higher
14 consequence, seen here, garnered scores among the
15 general population approaching or above 90 percent. The
16 messages of lower medical consequence are seen here.
17 Several of the scores approached 90 percent among the
18 general population. Stress incontinence was not well
19 understood because a number of the subjects focused on
20 the symptoms and the belief that the product helped the
21 symptoms that were present in the scenario.
22 So now let's look at targeted self-selection

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1 studies conducted in Stage II. The first was among
2 men. The percentage of men choosing not to select
3 Oxytrol improved from 71 percent in Stage I to 90
4 percent in Stage II, due largely to the changes made in
5 the front panel graphics. Men who said they would use
6 the product did so because they believed that the
7 product might help their symptoms.
8 The second study was among pregnant women. In
9 the cohort drawn from the general population, 92
10 percent of the women made a correct self-selection
11 decision.
12 Health literacy is an important issue, and we
13 strive to design labels that can be understood by low-
14 literate individuals. In our pivotal Label
15 Comprehension Study, the low-literate population
16 performed as expected, with scores ranging between 74
17 and 92 percent. On average, the low-literate
18 population scored 7.5 points below the general
19 population on the messages of greatest medical
20 consequence.
21 In self-selection, the low-literate subjects
22 performed as well as the general population in the

1 initial self-selection study and the follow-up study
2 among men. However, in the self-selection study that
3 was conducted among pregnant women, the low-literate
4 cohort performed below expectations. There were a wide
5 range of reasons, many of which centered on frequent
6 urination. A few of the comments indicated that the
7 female icon looked as if she might be pregnant, as a
8 result, we modified the icon on the proposed OTC
9 package.
10 So in summary, Stage 2 nondrug consumer
11 studies demonstrated strong results. In addition to
12 the information that I've already presented, a targeted
13 Label Comprehension Study of the enhanced pregnancy
14 warning among women of childbearing age achieved a
15 score of 93 percent. In addition, label messages
16 related to undiagnosed diabetes in two studies achieved
17 scores in the 88 to 94 percent range. Finally, a Label
18 Comprehension Study among women age 65 and over
19 achieved scores at the 85 percent level or above for
20 key safety messages.
21 In conclusion, based on our label
22 comprehension and self-selection results, we have

1 demonstrated that the Oxytrol label is well understood
2 and can guide appropriate self-selection.
3 Now, Ms. Replogle will show you how the label
4 guides appropriate deselection, our third self-
5 management labeling safeguard element.
6 Actual Use Study: CONTROL
7 MS. REPLOGLE: Good morning. I'm Amy
8 Replogle. The focus of my presentation will be
9 CONTROL, the pivotal actual use study and consumer
10 behavior data as it relates to non-OAB conditions.
11 CONTROL demonstrates that the label guides appropriate
12 use and deselection, the third self-management labeling
13 safeguard.
14 CONTROL is designed to test that the Oxytrol
15 drug facts label will allow consumers to self-manage
16 any potential safety risks over time, recognize other
17 conditions that may occur, and not delay the diagnosis
18 of a different condition, and appropriately stop use or
19 deselect if there is a change in medical status or a
20 lack of effect.
21 CONTROL was an open-label, 15-week study in
22 women 18 years and older conducted in 10 metropolitan

1 areas with sites in 26 retail pharmacies.
2 CONTROL was not designed as a self-selection
3 study, and women who did not meet all of the
4 eligibility criteria from the label were permitted to
5 use Oxytrol. This design feature allowed us to observe
6 ongoing use behaviors of women who may have had
7 symptoms or conditions which may have made them
8 ineligible per the label. Some subjects were excluded
9 at the pharmacy sites for potentially higher medical
10 risks.
11 Recruitment involved mass media advertising
12 targeted to women with OAB symptoms for initial
13 screening by telephone. Prospective subjects were
14 directed to the nearest participating pharmacy for the
15 enrollment visit. They were given the Oxytrol OTC
16 package and asked if they wanted to purchase the
17 product for their own use.
18 After making their purchase decision,
19 subjects were interviewed about their medical history.
20 Subjects were dispensed Oxytrol in the packaging with a
21 drug facts label that is intended for OTC use. Subjects
22 had only the product's label to guide their use.

1 The use phase ran for 12 weeks. Subjects
2 maintained diary cards and were interviewed by phone on
3 their use of Oxytrol as it pertained to prespecified
4 endpoints at weeks 3, 7, and 12. All subjects were
5 asked to return to the pharmacy at the end of the study
6 to provide a urine sample. Subjects had a final
7 interview by phone.
8 Two thousand seven hundred thirty-one people
9 called in response to advertising. Of those, 1,218
10 arrived at a pharmacy site as evaluators; just over
11 1,000 women decided to purchase the product; and of
12 these, 727 were verified users, which means that they
13 returned diary cards and participated in interviews.
14 CONTROL's primary endpoint was the proportion
15 of subjects who did not stop Oxytrol use either when
16 they developed a new symptom where the label directed
17 them to stop use or talk with a doctor or when their
18 OAB condition worsened. A successful study outcome was
19 defined as a misuse rate of 5 percent or less.
20 For the primary endpoint, all potential
21 misusers were identified. A potential misuser was any
22 subject who reported a symptom, or the label directs

1 them to stop use or talk with a doctor, or a worsening
2 of their OAB, and applied another patch after the onset
3 of the new symptom or worsening. No additional
4 information was considered in this initial screen.
5 As specified in the statistical analysis
6 plan, both open-ended and closed-ended data were
7 carefully examined in an adjudication process called
8 mitigation, which determined if a potential misuser
9 displayed medically acceptable behavior. Preexisting
10 conditions, progression of symptom severity, and
11 talking with a doctor or other health care professional
12 were considered.
13 Here is an example of how mitigation was
14 applied. In this example, women with OAB developed a
15 urinary tract infection while using Oxytrol and
16 continued using Oxytrol. We saw this with 15 women.
17 Because these women developed a new symptom, which
18 indicates they should stop use or talk with a doctor,
19 the program algorithm initially identified them as
20 potential misusers. However, when the full information
21 for these 15 women was reviewed, it was obvious they
22 were not in fact misusers.

1 In this example, the women recognized their
2 UTI symptoms, saw their doctors, were treated for their
3 UTIs and were told by their doctors to continue using
4 the patch to treat OAB. This is the exact behavior we
5 want to see in the OTC setting and demonstrated that
6 the drug facts label worked.
7 One hundred five users were initially
8 identified as potential misusers for the primary
9 endpoint. The mitigation panel determined that 80 of
10 these users exhibited appropriate behavior. For
11 example, 19 subjects talked to a physician about their
12 condition and were told to continue using Oxytrol, and
13 11 had symptoms of potential concern that were self-
14 limiting and resolved. As you can see, these factors
15 for mitigation were according to the label but were not
16 able to be captured programmatically.
17 These are the results of the primary
18 endpoint. The left bar represents the subjects that
19 were identified in the initial screen for the primary
20 endpoint, the subjects who did not develop a new
21 symptom or did not have a worsening of their OAB, or
22 those who did not apply another patch after worsening

1 or the onset of a new symptom. Eighty-five point six
2 percent displayed correct behavior through the first
3 screen. After mitigation, 96.6 percent of users were
4 determined to have exhibited informed and, importantly,
5 correct behaviors. Only 3.4 percent of users displayed
6 misuse, which was below the predefined rate of 5
7 percent, demonstrating that the primary endpoint was
8 met. The upper bound of the confidence interval was 5
9 percent.
10 CONTROL also had multiple secondary
11 endpoints. Two used the mitigation process. First, we
12 studied if women stopped use if their OAB symptoms did
13 not improve. Eight-nine percent of users were correct
14 for this endpoint. We also measured the time it took
15 for subjects to stop use if they did not improve. It
16 took a median of 35 days for subjects with no
17 improvement to stop use, and 8.5 days if their OAB
18 symptoms worsened. We studied if subjects used the
19 patch correctly, if they left it on for too long, or
20 wore more than one at a time. Seventy-eight point four
21 percent did not report wearing a patch longer than 4
22 days. The majority of subjects had few misuses of

1 patches over their duration of use. Ninety-six point
2 nine percent reported no simultaneous patch use.
3 We looked at potential medical risk
4 associated with new symptoms for subjects who continued
5 Oxytrol treatment. Ninety-four point five percent had
6 minimal or no medical risk. This endpoint did not use
7 the mitigation process used for the primary endpoint
8 and many of these symptoms of potential risk were
9 mitigated for the primary endpoint.
10 One of the topics the FDA asks you to
11 consider today is consumers using Oxytrol longer than 2
12 weeks if their symptoms did not improve. This
13 information is contained within the secondary
14 endpoints. Eighty-nine percent of users displayed
15 appropriate behavior concerning the 2-week timeframe.
16 Looking at these data in more detail, we see that 71
17 percent of users improved in their OAB symptoms within
18 2 weeks, and 18 percent correctly stopped using the
19 product when they did not improve.
20 As I just showed you, we looked at the time
21 it took users who did not improve to stop using
22 Oxytrol. Of the users who did not improve in 2 weeks,

1 the median time to stop was 35 days. However, for
2 subjects who reported a worsening of their OAB
3 symptoms, the median time to stop use of Oxytrol was
4 8.5 days.
5 In order to understand behaviors for this
6 endpoint more fully, we looked at the 433 women in the
7 trial who had been previously diagnosed with OAB
8 compared with the 265 users who were not. For all
9 endpoints relating to stopping use, the subjects who
10 had not been previously diagnosed with OAB behaved more
11 cautiously. Women who had been previously diagnosed
12 continued to try Oxytrol for a median of 45 days
13 compared with 23 days for those who had not been
14 previously diagnosed. For subjects who worsened, those
15 who had been previously diagnosed continued Oxytrol use
16 for a median of 17 days versus zero days for those who
17 had not been previously diagnosed.
18 Another one of the topics the FDA asked you
19 to consider today was self-selection considering study
20 participants who had ineligibilities. The medical
21 history questions were designed to identify anyone who
22 could have possibly had a contraindication or a

1 condition of possible concern. For example, subjects
2 were asked if they had a family history of diabetes. If
3 they responded yes, they may have known whether or not
4 they had diabetes and if this label criterion applied
5 to them. For urinary retention, women were asked if
6 they had a feeling they could not empty their bladder
7 completely, not if they had diagnosed urinary
8 retention.
9 Since this was not a self-selection study, we
10 did not ask follow-up questions because we did not want
11 to bias their use of Oxytrol. As I will review in a
12 second, if we had, we would have seen that many of
13 these women were eligible to use Oxytrol. This
14 provided an important opportunity to observe what
15 happened when women who may have had these
16 ineligibilities used the product.
17 Here you see ineligibilities classified by
18 categories of interest as shown in the FDA briefing
19 book on page 54. The left column is the possible
20 ineligibility category and the number of users who
21 responded to questions indicating that they may have
22 been ineligible in that category. The middle column

1 displays the number of subjects who developed a related
2 non-OAB condition. And the last column were those who,
3 after review, exhibited incorrect behavior.
4 For example, 154 women had possible symptoms
5 of UTI. After reviewing the available data for all of
6 these women, eight developed UTIs. Seven of the eight
7 recognized their UTI symptoms or were diagnosed through
8 routine care and displayed appropriate behavior. One
9 did not recognize her UTI. In all other cases, the
10 women acted appropriately. Further, the majority of
11 these women's OAB symptoms improved.
12 In order to determine whether OTC
13 availability of Oxytrol might increase the risk above
14 what already exists among those currently self-managing
15 OAB of delaying the diagnosis of other conditions which
16 share some of the same symptoms as OAB -- the
17 conditions include pregnancy, urinary tract infection,
18 bladder cancer, and diabetes -- the Oxytrol drug facts
19 label addresses these situations and guides women to
20 seek medical advice as necessary.
21 Let's look at how the label achieves this.
22 The Oxytrol label clearly warns women that urinary

1 frequency could be a symptom of other conditions. As
2 you can see, this warning is bolded and highlighted in
3 yellow on the package. The label also states that
4 women should have the symptoms of OAB for at 3 months
5 before trying Oxytrol. This criterion was added to
6 help consumers discriminate between OAB and pregnancy
7 or UTI. Along with the yellow highlighted warning, the
8 label warns women not to use the product if they have
9 pain or burning while urinating, lower back or side
10 pain, or blood in their urine, as these could be
11 symptoms of UTI or a more serious condition, like
12 bladder cancer.
13 The label informs potential consumers to talk
14 to their doctor before using if they have a history of
15 diabetes in their immediate family or if they have
16 excessive thirst, extreme hunger, or increased
17 tiredness, as these could be early signs of diabetes.
18 Remember, Oxytrol is not contraindicated with diabetes,
19 the concern is delay in diagnosis.
20 I am now going to present the totality of our
21 consumer behavior data as it relates to each of the
22 non-OAB conditions that share urinary symptoms with

1 OAB.

2 First pregnancy. The label comprehension

3 targeted to women of childbearing age demonstrated that

4 93 percent of the general population of 18- to 40-year-

5 old women understood the message about undiagnosed

6 pregnancy. Ninety-two percent of the general

7 population of pregnant women tested correctly,

8 indicating they should not use the product or would

9 talk to a doctor first. Further, in CONTROL, no

10 subjects tested positive for pregnancy at enrollment

11 and no users reported becoming pregnant during the

12 study.

13 Label comprehension demonstrated that more

14 than 90 percent of participants understood the label

15 messages for undiagnosed UTI symptoms. In the CONTROL

16 study, we looked carefully at all UTIs and all symptoms

17 that could be associated with UTI. With one exception,

18 women in CONTROL recognized their UTI symptoms and

19 acted appropriately.

20 Regarding more serious conditions. In the

21 consumer behavior studies, we looked at symptoms of

22 unexplained weight loss, pain and burning with

1 urination, hematuria, and flank or back pain as
2 possible symptoms of a more serious condition or
3 bladder cancer. In the Label Comprehension Study, more
4 than 90 percent of participants were correct for these
5 symptom messages except for weight loss, which was 88
6 percent.
7 There were subjects in CONTROL who had these
8 symptoms at enrollment and during use. Although
9 CONTROL was not designed for this purpose, there were
10 no diagnoses of bladder cancer.
11 The consumer behavior results for diabetes
12 were also positive. The scores in the Label
13 Comprehension Study were 93 percent or greater among
14 the general population and 88 percent or greater among
15 the at-risk population. In CONTROL, one user was
16 diagnosed with diabetes during the study after seeking
17 treatment due to foot pain. Another subject who was
18 excluded at enrollment was also diagnosed with
19 diabetes. But during the use period follow-up visits,
20 no subjects reported symptoms collected for possible
21 diabetes.
22 After we completed CONTROL and the other

1 studies reviewed today, final refinements were made to
2 further improve the label's clarity and readability.
3 All changes made to the packaging were minor, such as
4 this revised female silhouette on the front panel.
5 In conclusion, the CONTROL study demonstrated
6 that women can recognize when they develop new symptoms
7 where the label directs them to stop use and will
8 deselect appropriately. Ninety-six point six percent
9 of subjects met the primary endpoint.
10 Now, I ask Dr. Elkadry to give her clinical
11 perspective showing that Oxytrol can be safely used in
12 an OTC setting. Oxytrol for OAB in an OTC Setting
13 DR. ELKADRY: Thank you, Ms. Replogle.
14 Good morning. My name is Eman Elkadry. I'm
15 a practicing urogynecologist and Director of the
16 Fellowship Program in Female Pelvic Medicine at Mount
17 Auburn Hospital in the Beth Israel Deaconess Medical
18 Center. I am also a clinical instructor at Harvard
19 Medical School.
20 In my practice, I treat women with pelvic
21 floor disorders, and overactive bladder is among the
22 most common and most bothersome conditions I manage. In

1 fact, chances are everyone here knows someone who is
2 affected and silently dealing with this condition. As
3 a clinician, I have seen that effective treatment makes
4 a tremendous difference in the quality of women's
5 lives. Having Oxytrol available over-the-counter could
6 benefit countless women.
7 Now I would like to examine what an OTC
8 alternative might mean from a risk perspective.
9 Unlike UTI, OAB progresses over time, and as
10 we've discussed today, women initially adopt coping
11 strategies to manage their OAB and only reach for a
12 product like Oxytrol after their symptoms interfere
13 with their quality of life. Women who experience the
14 rapid onset of UTI symptoms -- such as pain, fever,
15 cloudy or foul-smelling urine, or dysuria -- have
16 information on the label instructing them to stop use.
17 In my experience, symptoms of pain or
18 discomfort often prompt women to contact a health care
19 provider within a matter of hours or days. If someone
20 were to mistakenly use Oxytrol for Women to treat their
21 UTI, it would have minimal effect and would not cause a
22 significant delay in appropriate treatment. In

1 practice, asymptomatic bacteriuria is not treated,
2 additionally mild cases are often ignored by patients
3 and many times regress on their own.
4 Further, the progression of UTI to urosepsis
5 or pyelonephritis is rare. Most cases of pyelo present
6 with fever and flank pain which do not respond to
7 anticholinergic medication. And urosepsis is rarely
8 preceded by UTI-like symptoms. In my experience,
9 symptomatic UTIs do not respond to anticholinergics
10 without resolution of the underlying infection.
11 Similarly, frequency in a new pregnancy is
12 highly unlikely to be confused with the chronic
13 symptoms of OAB. Most pregnant women experience a
14 combination of other more common signs of pregnancy
15 that prompt them to seek care. We know from the U.S.
16 Health and Human Services data that in the past 50
17 years there has been a long-term downward trend in the
18 percentage of women receiving no or late prenatal care,
19 with a large dip by as much as a third between 1990 and
20 2003. And while we have all heard anecdotes of women
21 who did not recognize that they were pregnant until
22 childbirth, that is the exception and it is unlikely

1 that OAB was the factor confounding recognition of
2 pregnancy.
3 If there was a delay in diagnosis, Oxytrol
4 for Women is a Category B medication, which means that
5 there is no evidence of risk to the fetus. In fact,
6 most of the drugs we use during pregnancy are Category
7 B. Furthermore, the majority of women affected by OAB
8 are past the reproductive age.
9 Finally, Oxytrol would not significantly
10 improve symptoms of frequency and urgency in the
11 setting of a growing pregnancy. Therefore, Oxytrol is
12 unlikely to contribute to a delay in prenatal care.
13 Let's consider diabetes. Even if the
14 safeguards included in the OTC label were not heeded,
15 it's important to consider the clinical course of
16 diabetes. Diabetes is a slowly progressing condition
17 most typically caught through routine labs during
18 annual visits. The hallmark signs of diabetes are
19 polyuria and polydipsia in the setting of additional
20 symptoms. Neither polydipsia nor polyuria will improve
21 with anticholinergic treatment. Frequency and urinary
22 symptoms that persist despite treatment may drive women

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1 with potential diabetes into their physician's office
2 sooner, providing a greater opportunity for diabetes
3 diagnosis.
4 According to the timeframe in the latest ADA
5 guidelines with regard to the initiation of treatment
6 for diabetes, even a few-week delay in a diabetes
7 diagnosis would not have a negative impact on outcomes.
8 Additionally, there is no literature published over the
9 last 15 years linking the delay in diagnosis of
10 diabetes to presenting symptoms being confused with
11 overactive bladder.
12 Finally, I would like to examine bladder
13 cancer. It is again very unlikely that the
14 availability of Oxytrol for Women would increase the
15 delay in bladder cancer diagnosis. First, it is
16 important to remember that hematuria is the presenting
17 symptom in 85 to 90 percent of cases. This symptom
18 usually prompts women to immediately seek medical
19 attention. In the absence of gross hematuria, a delay
20 in diagnosis is not a significant concern, as the
21 majority of bladder cancers are not aggressive.
22 Furthermore, in cases of bladder cancer, the symptoms

1 of frequency and urgency are usually refractory to
2 treatment with anticholinergics, and, in fact, in my
3 practice, that is what prompts further evaluation.
4 In reality, the risks of unintended
5 consequences are minimal. However, the detrimental
6 effect of OAB on women's lives is indisputable. My
7 patients who respond to anticholinergic therapy tell me
8 that treatment has changed their lives. They tell me
9 they are more active. They even sleep better. There
10 are tangible changes in their lives physically,
11 socially, and professionally.
12 I'm here today because I am personally
13 encouraged that an OTC option will expand access to
14 treatment. Having an OTC treatment for OAB sends a
15 message to women that it is a real medical condition
16 and not a normal part of aging that should be
17 concealed. Equally important is that access to
18 treatments and information about Oxytrol will broaden
19 awareness of bladder and urinary health and improve
20 outcomes for more women who suffer from OAB. I feel it
21 would be a disservice to deny millions of women access
22 to an effective treatment option given that any risk of

1 misuse is highly unlikely to result in clinical
2 consequences of concern.
3 The educational efforts that will be
4 presented next by Ms. Licata are extensive and greatly
5 needed in the area of OAB and bladder health. They
6 have been developed in conjunction with several
7 professional and consumer organizations.
8 Thank you. Consumer Education & Support
9 MS. LICATA: Thank you, Dr. Elkadry.
10 My name is Kristie Licata, and I am going to
11 review the comprehensive evidence-based education
12 program we have developed to support Oxytrol for Women.
13 In developing this plan, we consulted key professional
14 and consumer organizations as well as our
15 multidisciplinary board of health care providers in
16 order to determine where educational gaps exist today.
17 We then supplemented this information with extensive
18 consumer research, including literature reviews,
19 quantitative research and hundreds of one-on-one
20 interviews in order to gain an in-depth understanding
21 of how women feel about their OAB condition, how they
22 currently choose to manage it, and the impact it has

1 had on their lives.
2 In order to establish a measurable baseline
3 of current consumer beliefs and behaviors, we fielded
4 an attitudes, awareness, and usage study in July among
5 812 females who self-reported they had experienced OAB
6 symptoms within the past 12 months. The insights
7 gained from this study, in combination with our prior
8 research, helped to guide the development of our
9 educational plans.
10 The results of this study validated that most
11 women choose to manage their OAB condition on their own
12 by altering their lifestyle and attempting to conceal
13 that the problem exists by using absorbent products and
14 other coping strategies. Among these women who are
15 self-managing today, 61 percent claimed they did not
16 know that effective pharmacologic options existed. When
17 asked why they chose not to discuss this condition with
18 their health care provider or why they waited so many
19 years to do so, the answers boiled down to
20 embarrassment and shame and a resignation that OAB is
21 simply a normal part of aging and that nothing could be
22 done about it.

1 Taking these prevailing attitudes and
2 behaviors into account, the goals we established for
3 our educational program include increasing awareness
4 that OAB is a treatable medical condition and not a
5 normal part of aging; providing an important public
6 health benefit by informing women about other potential
7 causes of urinary frequency; educating women about both
8 behavioral and pharmacological treatment options so
9 they will feel empowered to take control of their OAB;
10 and, finally, reducing the current barriers that are
11 preventing women from having conversations with their
12 health care providers.
13 The first and most fundamental component of
14 this educational program is the drug facts label. It
15 will inform women that their urinary symptoms could be
16 due to other conditions, an important communication
17 point that is currently not being delivered either on
18 prescription products or on the absorbent products that
19 so many of these women use to help them cope with this
20 condition.
21 In addition to the label itself, the
22 educational website will have the label text available

1 in Spanish and will also contain detailed graphics and
2 a step-by-step video on applying, changing, and
3 removing the patch to help aid the low-literate
4 consumer.
5 The next component is our collaboration with
6 the organizations featured here on this slide. With
7 these organizations, we developed and executed several
8 unbranded national programs to educate both women and
9 health care professionals alike about overactive
10 bladder. These initiatives will address our overall
11 program goals as well as the educational goals of these
12 different organizations.
13 The initiatives developed with these
14 organizations will be multifaceted and broad reaching.
15 These pre-launch unbranded programs will reach women
16 online, in the media, and in health care providers'
17 offices. These efforts will be enhanced and expanded
18 post-OTC launch with educational consumer advertising,
19 an interactive website, and an extensive public
20 relations campaign. In addition, a strong pharmacy
21 education program including both behavioral and
22 pharmacologic options will ensure that these frontline

1 health care providers have the resources they need to
2 appropriately guide their consumers.
3 These educational initiatives will form an
4 integrated support program that includes different
5 behavioral strategies women can try, pharmacologic
6 treatment options, and interactive online support
7 tools. Used either alone or in totality, these
8 different program elements will empower women to take
9 control of their OAB condition to best suit their
10 individual needs and lifestyles. These different
11 components have been designed to work synergistically
12 to improve overall outcomes, very similar to other OTC
13 lifestyle management categories such as weight loss or
14 nicotine replacement.
15 Finally, a crucial element of the education
16 and support program is that it will be measured and
17 modified as appropriate. Changes in relevant attitudes
18 and behaviors will be assessed at regular intervals
19 against our baseline research. Key measures will be
20 changes from baseline scores that directly relate to
21 the overall goals, including shifts in awareness that
22 OAB is a treatable condition, awareness of other

1 conditions that may cause frequency, awareness of
2 treatment options, and a shift in their willingness to
3 discuss with a health care provider, as appropriate.
4 The results from this research will help to
5 serve as a compass to evaluate the success of our
6 program and measure the impact it has had on women's
7 attitudes towards OAB. This will be an ongoing
8 iterative process, and efforts will be redirected and
9 refined as necessary to accomplish our educational
10 goals.
11 And now I would like to turn the presentation
12 back over to Dr. Hemwall. Summary
13 DR. HEMWALL: Thank you, Kristie. We've told
14 you about the distress OAB causes in nearly every
15 aspect of a woman's daily life, and it seems reasonable
16 that a simpler, easier access to the Oxytrol patch
17 could really help to improve their quality of life. OTC
18 status will provide a welcome option for the great
19 number of American women who are currently self-
20 managing this common condition.
21 But despite the availability of prescription
22 treatments, there are barriers. Conversations do not

1 always occur in a doctor's office, and most women
2 choose to manage OAB on their own. These self-
3 management strategies carry concerns of misdiagnosis or
4 delayed diagnosis of a potentially more serious
5 condition.
6 Further, these products provide consumers
7 little or no information about OAB or urinary health in
8 general. Twenty million women currently suffer from
9 OAB in the U.S., and the number is growing as the
10 population ages. So there is a need for a proven
11 tested OTC product for OAB, and the Oxytrol transdermal
12 system is especially suited for this need.
13 Oxybutynin has been a mainstay of OAB
14 treatment for over 30 years. The Oxytrol patch was
15 approved by FDA almost 10 years ago based on placebo-
16 controlled clinical trials. The patch has improved
17 safety and tolerability from anticholinergic side
18 effects, and it has a favorable pharmacokinetic profile
19 delivering steady lower levels of the active ingredient
20 with only a fraction converted to the active metabolite
21 thought to be responsible for much of the side effects
22 seen with oral use. And OTC availability of Oxytrol

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1 would not only provide symptom relief and quality of
2 life improvement, it would also provide important
3 education regarding other symptoms that may share some
4 of the same symptoms.
5 You've seen today how we developed and
6 examined each element of this layered approach to self-
7 management. We have a proven medication with a safety
8 profile which is appropriate for OTC use. Our label
9 comprehension and self-selection studies have shown
10 that the majority of potential users understand the
11 label and will self-select correctly. And we have
12 identified where there are some small potentials for
13 error.
14 The CONTROL study, which deliberately
15 included a large group of women who were not exactly
16 correct according to the label, showed that the large
17 majority deselected or stopped use when appropriate.
18 Over 95 percent met the primary endpoint in this target
19 in this regard.
20 We've examined, with the help of outside
21 experts, that small remaining subset that might use the
22 product longer than directed or for a potential non-OAB

1 condition. The actual and theoretical circumstances
2 that might exist for such users did not represent an
3 unacceptable risk compared to the larger benefit for so
4 many women. And, importantly, any potential risk
5 created by OTC access is not expected to be greater
6 than those risks already present among women who are
7 currently self-managing without the benefits of this
8 helpful product.
9 In conclusion, the OTC drug facts label has
10 been extensively studied and improved at each step
11 along the way. It communicates the most important
12 messages about appropriate use without the aid of a
13 health care professional but clearly directs women when
14 they do need to see a provider. In other words, OTC
15 Oxytrol for Women provides access to an effective
16 treatment option together with a much needed teaching
17 opportunity to help educate women about urinary health.
18 Thank you for your attention and
19 consideration this morning, and we look forward to
20 answering your questions.
21 DR. REIDENBERG: Thank you very much. And I
22 would like to particularly express appreciation to each

1 of the presenters for staying well within the time
2 limits so that we even have a little additional time
3 for questioning.
4 Now, at the beginning we all went around the
5 table. So, Dr. Koff, can I ask you to simply introduce
6 yourself to the group, please?
7 DR. KOFF: I'm Stacey Koff. I am a urologist
8 in the military.
9 DR. REIDENBERG: Thank you very much.
10 Clarifying Questions
11 DR. REIDENBERG: Now, we have time for
12 clarifying questions from the committee to the sponsor.
13 I would like to say one thing at the beginning, and
14 that is that we will accept efficacy as a given so that
15 we don't have any issues about efficacy in our
16 discussion.
17 Whoever has a question, please state your
18 name, and if possible, direct it to a specific
19 presenter. Then we'll record the names of those who
20 want to ask questions in the order she sees them, and I
21 will simply go down the list.
22 Okay. Dr. Hanno?

1 DR. HANNO: Thank you. I may have missed it.
2 I have two questions. One is, is there anything on the
3 label that says that women who have failed two or more
4 anticholinergics prescribed by their doctor should
5 avoid buying this or that it would be unlikely to be
6 effective?
7 Shall I give both my questions?
8 DR. HEMWALL: I'll take the first one. And,
9 of course, the answer is no. And it's certainly a
10 worthwhile suggestion, but we're expecting that the
11 vast majority of women who will use this product will
12 not have tried an anticholinergic before or will not
13 have seen a doctor, as we know they have already been
14 self-managing for a long time.
15 DR. HANNO: Okay. Well, the data suggests
16 that there is a fair amount who had been on
17 anticholinergics, who had been diagnosed at least.
18 DR. HEMWALL: That's correct.
19 DR. HANNO: My second question is one of the
20 most confused diseases with overactive bladder is
21 bladder pain syndrome, interstitial cystitis, the
22 keynote symptom of which is pain, and I really don't

1 see anything on the label telling patients who have
2 pain associated with bladder filling that they should
3 see their doctor rather than just self-treat with this.
4 DR. HEMWALL: Exactly that particular
5 statement, pain associated with bladder filling is not
6 on the label. We do have pain as a warning or pain
7 upon urinating. So if that is a concern of yours, I
8 think we would be very willing to discuss that if
9 that's a clarification to go further in that
10 discussion, but to be clear, that particular line of
11 warning is not in the label.
12 DR. HANNO: Yeah, I think up to 3 percent or
13 higher of women do have this symptom, and it's
14 different than dysuria or pain during urination, so I
15 think it would be worthwhile.
16 DR. REIDENBERG: Dr. Burnett?
17 DR. BURNETT: Thank you. I have some
18 questions about the actual use study, and I want to be
19 sure I'm clear about the generalizability of the
20 results, so could you clarify a bit more about the
21 demographics there? And I also want to understand more
22 about the population that eventually comprised the

1 group with regard to having primary physicians or not.
2 I think that may have influenced how some of them may
3 have sought care if they develop urinary tract
4 infections or other consequences. I certainly want to
5 understand how the final group was determined because
6 there seem to be some that were not included.
7 And then I know that early in the
8 presentation there was a mention that there were
9 patients who had certain exclusionary risks for medical
10 reasons. Could you clarify a bit more about that?
11 DR. HEMWALL: Okay. Thank you. There is a
12 lot of information that would come to bear to respond
13 to those questions.
14 With regard to the demographics, we can
15 provide a slide that shows you the overall makeup of
16 the population. And you can see that we looked at the
17 evaluators and then the users, and you can see the
18 median ages, the age breakouts, and the racial and low-
19 literacy percentage.
20 I'm not sure if we have data on whether or
21 not the primary care -- their medical care background,
22 so I'm not going to be able to provide that

1 information. I don't think we captured their overall
2 care.
3 And then in terms of the exclusions on
4 enrollment, I'm going to ask Ms. Replogle to talk about
5 that particular element of study keeping in mind that
6 there were administrative reasons, that is, people
7 wouldn't sign informed consent, for instance. There
8 were also some exclusions that were agreed with FDA
9 that in the initial protocol design would be people
10 that we would not enroll in the study just from a pure
11 IND IRB type study approach.
12 MS. REPLOGLE: Thank you for the question.
13 There were 214 women who were excluded from the use
14 phase of the study. The majority of these were for
15 administrative reasons. There 187 subjects excluded
16 for administrative reasons, which was really by their
17 choice, they either didn't want to sign informed
18 consent or some of them, when it came time to actually
19 pay for the product, they didn't want to actually pay
20 for it.
21 And then, as you said, there were 27 women
22 who were excluded for medical reasons. So the medical

1 reasons were hematuria, or blood in their urine,
2 breastfeeding, narrow-angle glaucoma, allergy to
3 oxybutynin, a compilation of symptoms of UTI, or being
4 pregnant. There, in fact, wasn't anyone who was
5 pregnant.
6 DR. REIDENBERG: Dr. Farber?
7 DR. FARBER: Thank you. Two questions. One
8 is I was wondering if either on the package or if you
9 could give us data about the efficacy of behavioral and
10 physiologic treatment of OAB, if you have any of those
11 data, and a comparison with the efficacy of oxybutynin.
12 And the second issue is, what percentage of
13 the people who on the actual use study would have been
14 deemed not to be appropriate users for the oxybutynin
15 at the onset?
16 DR. HEMWALL: Okay. Thank you, Dr. Farber.
17 First off, behavioral modification is a very important
18 component of treatment of overactive bladder, and, in
19 fact, most clinical studies include behavioral
20 modification in the placebo arm. And we don't have
21 information on the box itself about behavioral
22 modification, and that is intended to be more part of

1 our educational program with website access and
2 brochures at the point of sale. The reason we don't
3 put it on the box but certainly could be considered,
4 but we want to make sure the information on the box is
5 very focused on the key elements and women need to know
6 about using the product, but the reason we don't do
7 that is we want women to be able to avail themselves of
8 those opportunities first before they would actually
9 have to purchase the product. And so, yes, it's
10 important to have part of that as our program, but we
11 want it to be independent of having to purchase Oxytrol
12 in part of our education support programs.
13 As far as the actual use study, as Ms.
14 Replogle explained, we deliberately included people who
15 were not necessarily appropriate according to label
16 mainly because we had already learned from our label
17 comprehension studies that there was a high level of
18 comprehension, and from the self-selection studies,
19 that there were good scores in self-selection, but as
20 you saw, the scores were in the low 90s, high 80s, and
21 that meant that some people would possibly still use
22 the product incorrectly. So the best way to examine

1 that is to use a natural use study that allows some of
2 these same women to use the product and follow their
3 behavior and observe whether or not they actually incur
4 any negative consequence, which in the vast majority
5 was clearly not the case.
6 So that's the big feature of the CONTROL
7 study, is that it allowed some of those people not
8 according to label to be using the product. And if you
9 like, we can go through a list of what those elements
10 were. I think it may come up again in the FDA's
11 presentation later.
12 DR. FARBER: But the two essential questions
13 I don't think were answered. One is the efficacy of
14 behavioral modification and behavioral approaches
15 versus the efficacy of oxybutynin, in terms of the
16 first question.
17 And the second one was, what percent of
18 people were deemed, would have been deemed, not to be
19 appropriate users in the CONTROL study?
20 DR. HEMWALL: All right. I'm sorry. I
21 possibly misunderstood your question.
22 I'm going to ask Dr. Elkadry to comment on

1 the comparative efficacy and obviously the combined
2 efficacy of behavioral modification and the oxybutynin
3 patch because she's been using the product and can give
4 you a better feel for that.
5 DR. ELKADRY: Thank you, Dr. Hemwall.
6 And thank you for your question. The
7 literature is clear that behavioral modification and
8 bladder retraining are similarly effective to
9 anticholinergic treatment, and the combination of
10 behavior and anticholinergics together are much more
11 effective than either alone. Unfortunately, we know
12 that the women who are self-managing have no access to
13 education or information about the behavioral aspects
14 of treatment either, so having awareness about OAB and
15 a product that identifies OAB as a condition that is
16 treatable will raise awareness and improve both
17 behavioral and effective pharmacologic treatment option
18 in women.
19 DR. HEMWALL: And maybe you could rephrase or
20 restate the second question because I obviously didn't
21 get to it the way you wanted.
22 DR. FARBER: So in the CONTROL study -- and

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1 maybe the FDA will provide these data, which is fine if
2 that's the case, but what percent of women, or overall,
3 not only women, but men included -- would have used the
4 product where you allowed them to proceed?
5 DR. HEMWALL: Okay. I'm going to ask Ms.
6 Replogle to respond to that question. And just as a
7 methodology clarification, because it's not a self-
8 selection study, we couldn't interview these consumers
9 about why they made the decision. We don't know some
10 of the extra information about why they at least were
11 nominally inappropriate, but in a self-selection study,
12 we would have had that information and then could have
13 done that mitigation step. But I'll ask Ms. Replogle
14 to respond to your exact question.
15 MS. REPLOGLE: Okay. So to answer your exact
16 question, if you look at the users in the study who
17 answered one of the eligibility questions yes and made
18 a purchase decision and then went on to use the
19 product, there were 24.3 percent of our population was
20 eligible to use the product. So as Dr. Hemwall said,
21 that's just raw data. And just some important things
22 to keep in mind is that doesn't include the women who

1 went in and talked to their doctor. Twenty-five
2 percent of these people went and talked to their
3 doctors about their eligibility criteria.
4 And I also think urinary retention is a
5 really good example, that many of these women were
6 probably not actually ineligible. Forty-one point one
7 percent of our users responded yes to the question that
8 they had a feeling that they could sometimes not empty
9 their bladder completely, but, in fact, only one of
10 those women reported urinary retention during the
11 course of the study, and her doctor told her to
12 continue using it. So I think that many of these
13 women, in fact, were eligible.
14 DR. REIDENBERG: Thank you.
15 I would like to call on Dr. Gellad now.
16 DR. GELLAD: Actually, my question was the
17 same as Dr. Farber's, I think. So I just wanted to
18 reconcile what was in the FDA briefing documents
19 because it says here that 78.5 percent of the women in
20 the CONTROL study had ineligibilities according to the
21 label. So that's saying that 78 percent of women
22 should not have been using it, if we're just going by

1 the label and what they reported.
2 MS. REPLOGLE: Okay. So the 78.4 percent
3 that was in the FDA briefing book was based on all the
4 people who said yes to the purchase decision, and as we
5 talked about is one thing that's sort of related is
6 that 187 of those women were excluded for
7 administrative reasons, which was really a self-choice,
8 and then some of those women decided not to use it. So
9 the women that I was just referring to are the 785
10 users, so the women that we have use data on, so we
11 know what they did once they got the product home and
12 started using it. And of that, it was about 75 percent
13 were not eligible.
14 DR. REIDENBERG: Thank you.
15 Dr. Parker.
16 DR. PARKER: So I was curious to know, even
17 though it's not a self-selection for the CONTROL, how
18 many men attempted to use?
19 DR. HEMWALL: Yeah. Good question. And
20 again I'll ask Amy Replogle to respond to that.
21 MS. REPLOGLE: Okay. So men were screened
22 out at the site, so they never saw our label, but of

1 the 2,731 people who called into the site, 45 of them
2 were men.
3 DR. PARKER: And then the other question I
4 have is, could we see the actual label and the drug
5 facts, not just a print of it? Can you make that
6 available for us to look at?
7 MS. REPLOGLE: The actual boxes?
8 DR. PARKER: Uh-huh.
9 MS. REPLOGLE: Yes, we can.
10 DR. PARKER: That would be great.
11 DR. REIDENBERG: Thank you.
12 Dr. Howards?
13 DR. HOWARDS: I want to thank the sponsor for
14 very lucid and concise presentations. I have two
15 questions. I'm not totally clear in the actual use
16 study whether the subjects had any extra incentive to
17 read the label because obviously -- well, maybe not
18 obviously, but it seems to me that people who purchase
19 an over-the-counter product because a friend recommends
20 it or because they saw an ad on TV or on the Web will
21 probably not read the label. So that's my first
22 question.

1 My second question is a little more
2 complicated. I didn't see any information in any of
3 the presentations or in the material that was provided
4 regarding the concern about effects on mentation in
5 elderly patients with antimuscarinics.
6 DR. HEMWALL: Okay. Thank you. First,
7 you're absolutely right, that the label was very
8 cursorily read by consumers to start using the product,
9 but the test of the CONTROL study was to see what they
10 would do when they took the product home and read the
11 label in their home use. So in the situation that you
12 suggest, that a person might just buy the product in
13 the store without reading the label or be recommended
14 by a friend to use the product and assume they don't
15 need to read the label, what we did test here was what
16 they did with the product when they got it home, and
17 that's what's the importance of those results, to see
18 that they were reading the label then and they were
19 following directions and ultimately the endpoint of
20 seeing them stop using the product if their condition
21 did not improve or they developed new symptoms was met.
22 And, additionally, we do have data that show

1 that people who are buying an OTC product for the first
2 time, especially of a new indication, do read the
3 labels at high rates.
4 Your second question, if I answered your
5 first --
6 DR. HOWARDS: Well, I'm still not clear
7 whether the individuals in the practical use study were
8 somehow, because of the way they were selected, the way
9 the opportunity was presented, would be more likely to
10 read the label than the random patient after it's on
11 the market.
12 DR. HEMWALL: That's an interesting question.
13 I would like to have Amy again, Ms. Replogle, respond
14 to that because I think she has some of the insight of
15 how the consumers were recruited here.
16 MS. REPLOGLE: Actually, it's sort of
17 indicative that this was not a self-selection study
18 because when women first arrived at the pharmacy site
19 early in the study design, they were simply handed the
20 box and said, "Would you like to purchase this for your
21 own use?" Some of the investigators felt that that was
22 awkward, so partway through the study the script was

1 changed to say, "Treat this as you normally would. Look
2 at the box as you normally would if you were purchasing
3 an OTC product," and then they asked the purchase
4 decision question.
5 Just because I introduced that fact, we just
6 want to say that we did do a sensitivity analysis to
7 make sure that the women who were told the first
8 statement versus the second that there was no
9 difference in the endpoints of our studies, and the
10 subjects performed very similar for the endpoints that
11 we were measuring. But I think that the subjects in
12 the study weren't necessarily given incentive to read
13 the label more than they normally would if they were in
14 a pharmacy.
15 DR. HOWARDS: Thank you.
16 DR. REIDENBERG: Thank you. Let's go to the
17 second question, about anticholinergic effects, please.
18 DR. HEMWALL: Okay. So we thought about that
19 very carefully when we looked at this product as a
20 potential for OTC use. And as you heard in the
21 original presentation from Dr. Mishra, that the product
22 has a much lower level of circulating anticholinergic

1 moieties than an oral anticholinergic. And, in fact,
2 in a prescription label for prescription Oxytrol, it is
3 not contraindicated or warned against to be used in
4 conditions of low cognitive function or that it's
5 actually to be warned that it might cause those sorts
6 of situations.
7 So in developing the label with FDA and
8 determining what are the most important messages to put
9 on the label and to be tested, a statement of this type
10 was not included per mutual agreement. If the
11 committee, in their deliberations today, think that
12 that might be worth putting forward, that's exactly the
13 type of thing that FDA is interested in. But in
14 reality, the product itself is very safe, has low
15 levels, very low levels, of those types of side
16 effects, and that's exactly why we think it could be
17 considered for OTC use.
18 DR. REIDENBERG: Thank you.
19 Dr. Rogers?
20 DR. ROGERS: Thank you. My question is to
21 Amy. I'm wondering, on your consumer organizations
22 that you all used, to someone, I don't know, maybe it's

1 not Amy -- of the consumer organizations that you used,
2 which ones did you use and how were they selected?
3 DR. HEMWALL: Your question may be for
4 Kristie Licata.
5 MS. LICATA: Just so I make sure I understand
6 your question, you wanted to know how we picked the
7 particular organizations that we did? We actually went
8 around and talked to maybe 30 or 40 different
9 professional and consumer organizations. The ones we
10 ended up actually working with in this pre-launch phase
11 was because mutually we wanted to work together. So
12 that is probably the primary reason. We kind of chose
13 each other, it wasn't us selecting.
14 DR. ROGERS: Okay. One more question, and
15 that is in regards to the labels. I know, as a Latino,
16 that the Latino population is basically 50 percent of
17 us are illiterate. How is the label -- because labels
18 can be very complex, difficult to read; when you
19 translate them into Spanish, you have to use simple
20 language. So I'm wondering if that was done when you
21 translated the labels into Spanish so they could be
22 easily understood.

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1 MS. LICATA: We have translation services
2 that we use when we do translate into Spanish, and we
3 will ensure that the language is as simple as possible,
4 but we use companies that do specialize in health care
5 translations for the Hispanic population.
6 DR. ROGERS: Do we have samples of those?
7 MS. LICATA: No, we do not yet.
8 DR. ROGERS: Okay.
9 MS. LICATA: That will be available online
10 versus on the box, the Spanish label text.
11 DR. REIDENBERG: Thank you.
12 Dr. Moffitt?
13 DR. MOFFITT: I have two questions. Being a
14 patient representative, these are important to me.
15 First of all, on your back panel I do not see any
16 information for potential purchaser of your product
17 that says you may experience dry mouth. I know it's a
18 significant complaint, it may not have a lot of
19 scientific basis to it, but it is bothersome, you have
20 a dry mouth, you drink more liquids, the more liquids
21 you drink, the more you urinate, and it's contradictory
22 to the whole process, and to me it's very important

1 that that be on your label so that patients or people
2 understand that they may have this symptom. The first
3 thing you do is you grab water. Maybe then you'll go
4 to a cough drop or a piece of hard candy or something,
5 but because it's contradictory to the use of it, I
6 think it's very important that it be on there.
7 DR. HEMWALL: Okay. That's a good
8 suggestion. And, again, that's the type of input I
9 think that the FDA and we're interested in hearing
10 today.
11 DR. MOFFITT: Okay. And the second one is
12 where to apply Oxytrol. In what you presented, it's a
13 given that the population is growing that will be using
14 these, baby-boomers, whatever, over 65, and because
15 sometimes some of the older people, the cognitive
16 understanding of all of this, I think it would be well-
17 advised that on your instructions on where to apply, if
18 it read something like after removing the old or used
19 patch and put on a new patch, use a different area of
20 skin, but only apply and wear one patch at a time.
21 If you've ever gone and gotten a flu shot,
22 they put a Band-Aid on it, by the end of the day, you

1 forget that Band-Aid is there. If your patch is as
2 comfortable as that little Band-Aid is, I can see where
3 people would apply more than one, also because we have
4 the mentality if one is good, two is better. People
5 who find that it's not working as well as what they
6 want it to would be more likely to apply a second one
7 when they shouldn't be doing it.
8 DR. REIDENBERG: Since everybody has had a
9 turn, I'll take a turn now. And I guess my question is
10 for Dr. Hemwall. We heard a lot of data on misuse rate
11 or inappropriate use under these circumstances. Is
12 there any data on what the rates are in the present
13 real world as it's being used under prescription
14 limitations? Give me a little context in which to
15 interpret your values.
16 DR. HEMWALL: Well, that's actually a really
17 important question because obviously we're here today
18 to make a determination of what is the additional
19 incremental risk, so if it's misused -- and we know
20 that medicines are misused in prescription settings of
21 some way or another. Is there going to be more misuse
22 or a similar type of misuse with OTC? I don't think

1 that that has actually been recorded for prescription
2 drugs as far as the types of misuse, and I might ask
3 Dr. Diane Newman, who is with us today, who uses this
4 product quite often in her patient population and has a
5 really good perspective on that, but it's going to be
6 more from her clinical perspective as opposed to a
7 study that's been done to determine rates of misuse.
8 DR. NEWMAN: My name is Diane Newman. I'm at
9 the University of Pennsylvania. I'm the Adjunct
10 Associate Professor of Urology and Surgery, Nurse
11 Practitioner, and I've been practicing in the field of
12 pelvic floor dysfunction for 25 years. I do
13 nonsurgical treatment, so I do behavioral treatment and
14 prescribe medications. I've been using Oxytrol since
15 it came out because of the fact that it has a low
16 anticholinergic systemic side effect, and in my
17 practice I see many, many women with overactive
18 bladder.
19 As far as use in the clinical practice, I
20 find that women know how to use patches. They use them
21 in gyne, they use them in over-the-counter products for
22 their kids to open airways, so they're used to it. I

1 do not see overuse as far multiple patches. What
2 happens after about 3 to 4 or 4 to 5 days is it falls
3 off, it starts to lift up from the skin because of the
4 oil in your skin, and basically it tends to fall off,
5 and it's actually easier than a Band-Aid, which
6 actually has more adhesive. So the only thing I may
7 see is some skin irritation, and women will come back,
8 and if they don't like the irritation, they stop using
9 it and they tell me, "I don't want to use that for that
10 reason," or they apply lotion to it.
11 So we really don't see -- and I really don't
12 see multiple patch use in patients over the past -- you
13 know, it's been out since 2003, I've been using it. I
14 have women on it for 7, 8 years now, and I don't see
15 really misuse of this.
16 DR. REIDENBERG: So then there are no
17 postmarketing studies or any sort of market research
18 that would give us data on the inappropriate or misuse
19 at the present time. Is that right?
20 DR. HEMWALL: That's right, but I think, as
21 Dr. Newman mentioned, that patches are quite commonly
22 used in a number of OTC settings and so I imagine if

1 there are concerns, that they're still within the
2 acceptable rate compared to the benefit that is
3 actually achieved with some of these products, and it's
4 an inherently safer way to deliver this particular
5 drug.
6 DR. REIDENBERG: Thank you.
7 Dr. Gellad.
8 DR. GELLAD: I wanted to take again the
9 opportunity to reconcile something that the FDA had
10 provided in its briefing document about the CONTROL
11 study and this issue of the primary endpoint. So,
12 again, it was 3 percent of the total subjects that
13 failed to stop use, but among those that had symptoms,
14 it was 17 percent who didn't stop use, so I would just
15 like to hear some clarification from you on that point,
16 if possible.
17 DR. HEMWALL: Go ahead, Amy.
18 MS. REPLOGLE: So the misuse rate that I
19 presented in my presentation were all the users in the
20 study. The endpoint -- I guess the comparator is just
21 the subjects who developed a new symptom or worsening
22 and did not stop use. And so of the 141 women who

1 developed a new symptom referred to on the label or a
2 worsening, 25 of them did not stop use. And I think
3 what's important is that of those 25 women who did not
4 stop use, they still weren't necessarily putting
5 themselves at risk. There was only one of those
6 subjects who developed a UTI and never recognized it
7 until the end of the study. There were subjects who
8 worsened but had continued to use it and didn't talk to
9 their doctor quickly enough, but I really think that
10 they weren't determined to be acceptable for
11 conservative reasons and we didn't see anything that
12 would put them at risk.
13 DR. GELLAD: Just as a follow-up, I think,
14 and maybe we'll discuss this more later, I don't
15 necessarily feel very comfortable talking about what
16 actually happened to them in a small kind of study. You
17 know, here it's looking at based on the label and based
18 on what they should be doing, and so 17 percent of
19 those who should have stopped did not. Is that correct
20 in saying?
21 MS. REPLOGLE: So we captured anyone as a
22 misuser who applied another patch after the onset of

1 the worsening, so they continued to use beyond that and
2 didn't talk to their doctor quickly enough.
3 DR. GELLAD: Okay. Thank you.
4 DR. REIDENBERG: We're a little bit ahead,
5 which is wonderful. Does anybody else on the committee
6 have any clarification questions at this time?
7 (No audible response.)
8 DR. REIDENBERG: Okay. We will now take a
9 15-minute break. We will resume at 10 minutes after
10 10:00. And I would like to remind all the committee
11 members that we don't talk about anything with respect
12 to the subject of this meeting until we resume in 15
13 minutes. Thank you very much.
14 (Break from 9:54 a.m. to 10:10 a.m.) FDA
15 Presentations
16 DR. REIDENBERG: Okay. We will now have the
17 FDA presentations, and I would like to ask Dr. McNellis
18 to start. Overview of the Efficacy and Safety Database
19 for
20 NDA21-351
21 DR. MCNELLIS: Good morning. I'm Don
22 McNellis, and I'm a Medical Officer in the Division of

1 Reproductive and Urologic Products. I would like to
2 discuss two things with the committee this morning.
3 First I would like to say a bit about overactive
4 bladder diagnosis and treatment, and then I would like
5 to very briefly present some of the information that
6 supported the approval of Oxytrol as a prescription
7 product in 2003.
8 On this slide, we see a definition of OAB
9 that was adopted by the International Continence
10 Society in 2002. Note that OAB is a symptom complex;
11 however, there is no pathognomonic symptom that defines
12 OAB nor is there any laboratory test or biomarker that
13 defines it. In order to make a diagnosis, other
14 factors should be ruled out.
15 On this slide we have some common conditions
16 that might have symptoms similar to those of OAB. We've
17 already heard a nice discussion about diabetes, bladder
18 cancer, urinary tract infection, and pregnancy.
19 Although this product is not directed at men, I would
20 point out that there would be a significant number of
21 men who could have symptoms similar to those of OAB
22 that would be caused by prostate disease.

1 OAB is a common problem. It's difficult to
2 pin down the prevalence exactly. I've put on this
3 slide some statistics that were in the American
4 Urological Association guideline that came out
5 recently. It's quite a broad range, but it says that
6 there is perhaps 7 to 27 percent of men, and 9 to 43
7 percent women who experience overactive bladder. Some
8 studies report higher prevalence rates in women than in
9 men, and other studies have found similar rates in both
10 sexes. It's generally accepted, however, and
11 consistently found that urinary urgency incontinence is
12 more common in women.
13 The initial management of overactive bladder
14 should be conservative. Lifestyle interventions such
15 as limiting fluid intake and avoiding beverages with
16 caffeine and alcohol, possibly bladder retraining,
17 should be the first line of treatment. In a number of
18 cases, these may be all that are needed.
19 When drug therapy is appropriate, I've listed
20 here the currently approved pharmacotherapy for OAB. We
21 can see that the transdermal oxybutynin patch is there,
22 and oxybutynin is also available as a transdermal gel

1 and oral tablets and syrup. There are five other
2 approved antimuscarinic products, and there is one
3 beta-3 receptor agonist product. All of these products
4 are prescription products. There is no currently
5 approved over-the-counter product. I would also
6 mention that we have reviewed no data that would
7 indicate any one of these products to be more effective
8 or to be safer than the others.
9 I would like to move on to the approval of
10 Oxytrol. It was approved in 2003, as we've heard, and
11 the indication is for the treatment of overactive
12 bladder with symptoms of urge urinary incontinence,
13 urgency, and frequency. The approved dose is the 3.9
14 milligram per day patch which is the dose that is being
15 considered for over-the-counter switch. The efficacy
16 database, the application was supported by two Phase 3
17 placebo-controlled trials, both of 12-week duration and
18 both having change in urinary incontinence as the
19 primary endpoint.
20 In Trial 9, it was the change from baseline
21 and weekly incontinence episodes, whereas in Trial 11,
22 it was the change from baseline and daily incontinence

1 episodes. Both trials also had, as key secondary
2 endpoints, change in urinary frequency and change in
3 average void volume.
4 On this slide, which is somewhat busy, we
5 have the efficacy results for Trial 9. Trial 9 showed
6 that with respect to both the primary and the key
7 secondary endpoints, Oxytrol was statistically
8 significantly better than placebo. With respect to the
9 key -- correction -- with respect to the incontinence,
10 we see that there was a median improvement of 19
11 episodes per week with Oxytrol whereas there was an
12 improvement of 15 episodes per week with placebo. The
13 difference of four episodes per week was statistically
14 significant. With respect to frequency, there were two
15 less episodes per day with Oxytrol, one less with
16 placebo. Again, this difference was statistically
17 significant. And there was also a statistically
18 significant improvement in the average void volume.
19 In Trial 11, we see somewhat similar results.
20 This trial also was successful in terms of the key
21 endpoint being statistically significant. The Oxytrol
22 group had three less incontinence episodes per day

1 whereas the placebo group had two less episodes per
2 day. This difference of one episode per day was
3 statistically significant.
4 With respect to daily urinary frequency,
5 while the results of this trial are numerically similar
6 to those of Trial 9, with two episodes less per day
7 with drug and one less episode per day with placebo, in
8 this case, this was not a statistically significant
9 effect. However, it did meet its statistical goals for
10 increasing urinary volume.
11 The conclusions with respect to efficacy were
12 that the Oxytrol transdermal system achieved the
13 primary efficacy objective, namely, reduction in
14 incontinence episodes in both trials. There was a
15 reduction in urinary frequency as compared to placebo
16 in Trial 9 but not in Trial 11. The increase in void
17 volume was statistically significant as compared to
18 placebo in both trials.
19 I would like to move on to safety. Safety
20 was supported by sixteen Phase 1 trials, one Phase 2,
21 and two Phase 3 trials. Approximately 600 subjects
22 were exposed for periods that ranged from 1 to 428

1 days. The average exposure was 150 days. The
2 population was mostly female. There was approximately
3 92 percent females in the safety database, and the
4 average age was approximately 63 years of age. There
5 were no deaths on drug during the clinical trials.
6 During the clinical trials, 37 subjects experienced a
7 total of 47 serious adverse events, but none of the
8 serious adverse events were considered to be related to
9 Oxytrol.
10 On this slide we see the common adverse
11 events that were seen during the Phase 3 trials. As
12 has already been mentioned today, application site
13 reactions are the most prominent reactions seen. We
14 see pruritus, erythema, and vesicles, and the
15 anticholinergic effects of dry mouth, constipation,
16 abnormal vision are also noted.
17 So the safety conclusions were again that the
18 major safety issues were skin tolerability and the
19 expected anticholinergic side effects. No safety
20 issues were identified that precluded Oxytrol's
21 approval.
22 I would like to just mention a few additional

1 items that may be useful to the committee in their
2 deliberations today. How long does it take for Oxytrol
3 to work? When is it reasonable to expect an effect? In
4 both Phase 3 clinical trials, the primary endpoint was
5 shown to be significantly improved in the Oxytrol
6 cohort as compared to the placebo cohort at the very
7 first on-treatment visit, and this efficacy was
8 maintained through the 12-week trial. In Trial 9, this
9 first visit was at week 3, and in Trial 11, the first
10 visit was at week 2.
11 I'll just mention something that has already
12 been mentioned. Oxytrol is labeled at Pregnancy
13 Category B. This classification has not been a
14 deterrent to the switch of other prescription drugs to
15 OTC status.
16 I would like to just draw your attention to
17 the contraindications to Oxytrol use that are mentioned
18 in the label. Urinary and gastric retention,
19 uncontrolled narrow-angle glaucoma, and known
20 hypersensitivity reactions.
21 I would also draw your attention to the
22 warnings and precautions in the label. I would mention

1 that these are all drug class effects and are not based
2 on any specific safety signals that were seen during
3 the development program of Oxytrol. But it's mentioned
4 that there is a risk of urinary retention, a risk of
5 gastric retention, a risk of exacerbation of
6 esophagitis in patients with GI reflux. There are
7 potential CNS effects that include dizziness and
8 somnolence. Angioedema has been reported with oral
9 oxybutynin use. Skin hypersensitivity has been seen.
10 And it should be used with caution in patients with
11 myasthenia gravis.
12 That completes my presentation. And I'm
13 going to turn the podium over to Barbara Cohen to
14 discuss the label comprehension studies.
15 Thank you. Oxytrol for Women Label
16 Comprehension and Self-Selection Consumer Research
17 MS. COHEN: Thanks, Don.
18 And, again, I'm Barbara Cohen. I'm a social
19 science analyst for the Division of Nonprescription
20 Clinical Evaluation. And I'm going to speak to you
21 this morning about the Oxytrol's label comprehension
22 and self-selection consumer research.

1 So there is a lot to cover. Merck did a lot
2 of research on this. Just a brief outline of what I'm
3 going to go into today, an overview of some more
4 nuances about label comp and self-selection. I'm going
5 to be discussing the key medical issues, and you've
6 heard about these already this morning, addressing the
7 consumer research, other important medical issues that
8 were addressed, a summary of what I call the good news
9 from the research, a summary of the caveats that I see
10 from the research and a couple of gaps, and then I'll
11 talk about the sponsor's proposed labeling changes as a
12 result of the research as well as some considerations
13 for other labeling enhancements.
14 So, as you can see, the sponsor submitted
15 five label comp studies. I think they said six, but
16 there were two that were really in the pivotal label
17 comp study. And most of my remarks are going to be
18 focused on that study because it was the pivotal, it
19 was the most recent research, but where appropriate and
20 relevant, I'm going to be bringing in other research
21 results as well from these other studies that you see.
22 Self-selection, again, that's been discussed

1 already this morning, and there were three studies and
2 I will again bring those in as appropriate.
3 So in label comp and self-selection, the
4 objective of label comp is to get at: Do consumers
5 understand what the label says when they're asked to
6 focus on it? And with self-selection it's: How might
7 consumers apply what they take away from the label to
8 their own personal situation?
9 Again, these are all studies, and the actual
10 use kind of is where things happen in the more
11 naturalistic basis, and we can observe there as well,
12 but these are kind of foundational studies.
13 So the typical design in label comp is to
14 establish primary communications objectives based on
15 the unique elements of the label, ask scenario
16 questions that address these communications objectives,
17 and set, a priori, target thresholds that reflect the
18 medical consequences and risk considerations.
19 And I just want to make two points about the
20 target thresholds. These are a clinical judgment call.
21 Now, the sponsor did not discuss the methodology of
22 this study before they did it, the pivotal study, with

1 us, but we may have agreed and we might not have agreed
2 with the exact thresholds, but, by nature, they're
3 subjective. I mean, reasonable people can disagree.
4 There is an underlying clinical rationale for them.
5 And the other point I want to make is that
6 they're not the same as what we think of as traditional
7 success thresholds in a clinical trial. These are
8 guide points, but they're not the same as sort of drop-
9 dead metrics for success.
10 And, again, as Merck mentioned this morning,
11 the lower bound of the 95-percent confidence interval
12 is how we typically discuss the target thresholds and
13 the scores on them. And so, therefore, that is a
14 conservative estimate. And I'll be presenting to you
15 this morning for the most part that lower bound
16 information. I will also be presenting point
17 estimates, and that more applies to the normal
18 literacy, when I talk about normal literacy versus low
19 literacy scores since those weren't measured against a
20 threshold, we're just trying to get an idea of the
21 gaps.
22 So for the pivotal study, the sponsor

1 established target thresholds somewhere -- were 90
2 percent based on higher medical consequences, some were
3 at 85 percent based on what the sponsor determined to
4 be lower medical consequences.
5 And, again, just to review the terms I'm
6 going to speak about or show you the abbreviations:
7 lower bound; NL and LL refer to normal and
8 low literacy; LCS, label comp study; and OAB,
9 overactive bladder.
10 So I came to FDA about a year and a half ago,
11 but in reviewing the major medical concerns, all of the
12 meetings that took place in the 4 years that we
13 discussed this drug, I was sort of taken by these
14 issues came up kind of over and over in the
15 discussions. So I'm going to be focusing my
16 presentation around these issues and then discuss some
17 of the medical concerns later.
18 The first is consumer identification of OAB.
19 Do consumers really understand what the condition is?
20 This is as the label says it.
21 Secondly -- I've just grouped them together
22 here, but obviously they are separate conditions --

1 urinary retention and gastric retention.
2 Next is diabetes risk. Next is UTI. Next is
3 pregnant women, and that is both women who know that
4 they're pregnant and women who don't know that they're
5 pregnant. And men and the elderly.
6 So I'll go through these one-by-one beginning
7 with consumer identification of OAB.
8 Now, we've talked about the pivotal study,
9 but
10 I just want to provide you a little bit more
11 insights into the questions asked since the way you ask
12 the question can gear the results. The communication
13 objective tested was: "You may be suffering from
14 overactive bladder if you have had two or more of the
15 following symptoms for at least 3 months: urinary
16 frequency, the need to urinate more often than usual,
17 typically more than 8 times in 24 hours; urinary
18 urgency, a strong need to urinate right away; and urge
19 incontinence, leaking or wetting yourself if you can't
20 control the urge to urinate." And this is straight
21 from the label.
22 And as you can see, there is a lot to chew --

1 I mean, there is a lot for a consumer to look at and to
2 really kind of take in. And, I mean, that's fine, I'm
3 not critiquing that, but the question is how to best
4 test it. And you can see here that there is a lot of
5 numbers. We have two or more of the following
6 conditions for at least 3 months, 8 times in 24 hours,
7 et cetera.
8 So the communication was split into two
9 questions, and I get that, that was fine. Only one
10 question pertaining to symptom duration was measured
11 against the target threshold, which was set at 85
12 percent. And the other question pertaining to more,
13 "What are the exact symptoms here?" was not measured
14 against a target threshold.
15 So the first question was: "According to the
16 label, for how long should you have symptoms of
17 overactive bladder before trying the product?" And
18 this came very close. A conservative estimate to the
19 85 percent target threshold knowing that you had to
20 have it for at least 3 months. Just one point about
21 that, by far the largest percentage of don't knows in
22 the survey responses came in for this question. For

1 all the other questions they were typically 1 or 2
2 percent, but even when people were sort of directed,
3 "Look at the label and what does it say?" I mean, it's
4 not a huge amount of don't knows, but it's still much
5 more than any other communication objectives tested.
6 Here you can see the literacy spread. And
7 I'm just pointing out these literacy spreads when they
8 were -- as the sponsor has indicated, there was about
9 maybe on average an 8-percent spread between the
10 literacy groups, so I'm just going to point out here
11 where there was a bigger than usual spread in the point
12 estimates.
13 And this question was also tested in the
14 earlier age 65-plus label comp study, and there the
15 score was lower. Again, that meant knowing that it had
16 to be 3 months or more to suffer the condition. That
17 was lower, at 74-percent lower bound.
18 And the next question was -- and this again
19 was not measured against the success threshold, but
20 there was a question, for the -- we described label
21 comp studies as often involving a scenario, so this is
22 where kind of the scenario was presented that people

1 have to really sort of understand how all the elements
2 together, which ties to self-diagnosis and self-
3 identification of the condition.
4 So the question was: "For the past 4 months,
5 Betsy has had to urinate more often than usual, about 9
6 times every 24 hours. She has also had several leaking
7 accidents. She has no other medical conditions. Betsy
8 would like to use this product. Is it okay or not okay
9 for her to use this product?"
10 And I just want to point out that everything
11 in this scenario was sort of more than above what the
12 label indicated. So I would just say that the question
13 did not really measure the ability of consumers to
14 comprehend when one specific element of the scenario
15 was incorrect. And, in fact, in two previous label
16 comp studies where they did use a similar question --
17 not identical, but similar -- and a 2-week scenario,
18 consumers had much lower levels of comprehension. So
19 all I'm saying is that the results of the lower bound
20 here really might be the best case.
21 Next is urinary and gastric retention. The
22 communication objectives tested were, "Do not use if

1 you have urinary retention or are unable to empty your
2 bladder," and, "Do not use if you have been told by a
3 doctor that you have gastric retention, your stomach
4 empties slowly after a meal."
5 So they came pretty close on both. They were
6 assigned both a higher level of medical risk, and they
7 came within 3 points. Here you can see the point
8 estimate spread between normal and low literacy. This
9 is not -- again, we see this kind of spread typically
10 in our studies, so it's not particularly unusual, but
11 I'm just highlighting it because it was more than
12 average for this. And in the previous age 65-plus
13 label comp study, the lower bound on this question was
14 81 percent.
15 So the only thought here to bring up is that
16 gastric retention may have more resonance with people
17 who have actually been told that they have it and they
18 may be more sort of attuned to that on the label. So
19 this could be a little bit conservative here, I don't
20 know.
21 The same with urinary retention. It came
22 pretty close, just 2 points below the threshold. Again

1 for the age 65-plus population, the lower bound was
2 lower. There was less understanding among that
3 population, but it was above 80 percent. And the label
4 was subsequently revised, as I think we've mentioned
5 here already today, to reflect that actually one should
6 be diagnosed by a doctor for urinary retention.
7 The next issue is diabetes risk, and here the
8 sponsor stated that the communication objective -- and
9 when I say "stated," I mean that was in the submission,
10 the NDA submission -- "Ask a doctor before use if you
11 have a family history or frequent urination with
12 excessive thirst, extreme hunger, or increased
13 tiredness." And this was also split up into two
14 questions. The target threshold of each was set at 85
15 percent, but it still wasn't completely addressed,
16 which I'll get to in a minute.
17 So the first question was: "For the past 5
18 months Megan has had to urinate frequently and urinate
19 right away. Her mother has diabetes. Megan would like
20 to use the product. According to the label, what, if
21 anything, should she do?"
22 And the comprehension here was at 83 percent,

1 which was close to the 85-percent threshold. You can
2 see the literacy spread on the point estimates. The
3 elderly study, the age 65-plus, also was at 88 percent
4 lower bound. And there was an earlier LCS of diabetic
5 warnings among the general population, and that was 90
6 percent. I should point out that this cohort was --
7 this was a part of the pivotal that was a cohort that
8 was really recruited for those at diabetes risk.
9 The next question was: "Rachel has been
10 experiencing excessive thirst. She also has noted that
11 she has been needing to urinate more often than usual.
12 Rachel would like to use this product. According to
13 the label, what, if anything, should she do?"
14 And here the comprehension was a little bit
15 lower, at 82 percent. You can see the point estimate
16 spread for normal literacy and low literacy. This
17 question was not asked in the age 65-plus label comp
18 study, but it was asked in the earlier LCS among the
19 general population diabetic warnings, and very similar
20 point spread there and very similar scores between
21 normal and low literates.
22 But my point here is just that neither of

1 these questions incorporated extreme tiredness or
2 hunger, although they were stated communications
3 objectives, and they are, of course, also on the label,
4 extreme tiredness and hunger is on the labeling. And
5 they also were not asked in other studies.
6 UTI is the next issue, and the sponsor
7 determined that this was not a communications objective
8 for the pivotal, and there weren't any questions in the
9 pivotal about common symptoms such as pain, burning, or
10 cloudy urine. There was a question about foul-smelling
11 urine, and that did okay, it was above 80 percent.
12 Age 65-plus, there was a study. They asked a
13 lot of questions in that LCS about UTI, and you can see
14 that population did well on that, ranging from the
15 lower bound of 88 percent to the lower bound of 94
16 percent for a comprehension of not okay to use if blood
17 in the urine.
18 And the first, the initial, Label
19 Comprehension Study that was done did address UTI and
20 some of these symptoms, and you can see here the
21 numbers on there, and that also did very well. I just
22 want to point out that this study was a little bit

1 different than -- at least the label comp studies that
2 I've seen since I've been here, which is that
3 it was split into two cohorts: OAB sufferers and non-
4 OAB sufferers, and the OAB sufferers were not the
5 general population, it was just normal literacy people.
6 So there is a gap still with who was looked at in UTI
7 symptoms. We've looked at the normal literacy
8 population of OAB sufferers, but we haven't necessarily
9 looked at the low literacy population of OAB sufferers.
10 We have looked at them both for non-OAB sufferers.
11 Pregnant women, as I said, there were two
12 aspects of that: people who know that they're pregnant
13 and people who do not know they're pregnancy. And
14 pregnancy was not asked about in the pivotal, but it
15 was addressed in an earlier LCS on enhanced pregnancy
16 warning, and the communication objective tested was:
17 "If you need to urinate frequently, it could be a sign
18 of pregnancy, diabetes, UTI, or more serious condition.
19 If you think you have one of these conditions, it is
20 important to see a doctor before using the product."
21 And the question was: "Melissa has noticed
22 that she has had to urinate more frequently. She also

1 has noticed that she has missed two periods. Melissa
2 thinks this product may help her with her more frequent
3 urination. According to the label, what, if anything,
4 should she do?" And 90 percent said she should talk to
5 the doctor, and, of course, that's good. I would just
6 point out that the question has two missed periods, and
7 I think that if somebody missed two periods, even
8 regardless of any other symptoms or not, they might
9 think that they were pregnant, and so perhaps it would
10 have been better to just ask about one, but anyway, it
11 did well.
12 On known pregnancy, that, as we've discussed,
13 was a large scale self-selection study of pregnant
14 women with OAB symptoms. Study participants were given
15 a copy of the label to read, and they were asked, "Do
16 you believe this product is appropriate to use right
17 now or not? Why do you say that? And what led you to
18 that decision?"
19 So that didn't meet the primary endpoint, and
20 I think we've discussed already here today the
21 mitigations on that, but I just want to point out an
22 additional issue, which is that those mitigations

1 involved not only a second probe of, "Why do you say
2 that?" which are in a lot of the studies that I see,
3 but they also involved a third probe, which the sponsor
4 themselves has described as a challenge -- called a
5 challenge question. And essentially they challenged
6 the people as to why they said what they said if they
7 were wrong. And so I think in those circumstances some
8 people might get defensive and then say, "Well, right,
9 I missed it, I really meant to say this," or, "I didn't
10 see it." And so the mitigations involved that, and
11 that's the point I wanted to make there.
12 But in the end, and perhaps most importantly,
13 I just wanted to make the point that the labeling
14 drawing was revised, as was indicated, to emphasize a
15 woman with a slender silhouette. So there was that
16 first, when the pregnancy self-selection study was
17 conducted. There is that tent-like dress that we
18 talked about, and a picture can be worth 1,000 words,
19 particularly perhaps in the case of lower literacy
20 populations, but here you can see that there is a
21 narrow-waisted woman and doesn't look like the product
22 is supposed to be for pregnant women.

1 Next, for men, and I'm not going to spend any
2 time on this since I basically concur there. I mean,
3 the men did pretty well on this, and, yes, the low
4 literacy cohort scored approximately the same as normal
5 literacy, so that was good.
6 And, finally, elderly. Now, again, I looked
7 at two elderly populations in this. First the age 65-
8 plus from the pivotal LCS, and then, of course, the age
9 65-plus LCS. And generally in the pivotal, there were
10 no statistically significant differences between age
11 60-plus and under 60, so that's a good thing. I think
12 the liver disease warning -- or mention, not warning,
13 was the only thing that really scored lower among the
14 over 60 population. And as we've mentioned in the age
15 65-plus LCS study, the comprehension was from the lower
16 bound of 85 percent and up.
17 And just briefly I'm going to touch on some
18 of the other communications objectives because these
19 are still important, and these are the ones that were
20 assigned at a higher medical risk by the sponsor, and
21 these all did pretty well, not okay to use if allergic
22 to oxybutynin, 93 percent; stop use and ask a doctor if

1 allergic reaction, 91 percent; stop use and ask a
2 doctor if developed blisters and red/itchy rash, 85
3 percent. Glaucoma was one of the ones that came in
4 lowest, but I just want to point out there that first-
5 generation OTC antihistamines have a glaucoma warning
6 already on the label, and we haven't really seen safety
7 signals on that, and we think that this may fall kind
8 of into an analogous category, if you will, as the
9 gastric retention, where if you know that you have it,
10 you're more kind of attuned to looking for it on the
11 label.
12 The communications objectives with lower
13 medical risk, you can see how those went, and this "Not
14 okay," you can see that "Ask a doctor if you have liver
15 disease" overall scored pretty low, I mean, relatively
16 lower than the other ones. And the "Not okay to use if
17 you have stress incontinence" was the lowest, but again
18 that's not really a medical concern per se.
19 So to summarize the good news, in the general
20 population findings, most communications objectives
21 scored within a few points of the thresholds, if not
22 above, and on an absolute level, most were at 80

1 percent or above. And the age 65-plus did not have
2 significantly lower comprehension on most labeling
3 elements than the younger people did, so that's also
4 good. And again, as was mentioned previously, with
5 normal literacy versus low literacy, the low literacy
6 findings, although they were lower than normal
7 literacy, as we've anticipated, were not unusually low.
8 That self-selection on pregnant women was the lowest,
9 but again the picture has been changed.
10 But just a couple of caveats. Again with the
11 general population findings, there is a potential that
12 these findings had upward bias in them as well. And
13 one, as I mentioned, the question wording on the
14 pregnancy and the mitigation challenge question there.
15 And the second point is that in all of these
16 studies, the low literacy representation in the general
17 population cohort was really suboptimal, and it ranged
18 from the pivotal study only had 6 percent low literacy
19 respondents. The self-selection in men was actually
20 the best proportion at 16 percent.
21 Gaps, again as I said before, the
22 comprehension testing on consumer OAB identification

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1 had limitations. That whole putting together
2 everything that's in that section of the label was not
3 really, I would say, rigorously tested. The
4 comprehension of extreme tiredness and hunger as
5 diabetes symptoms was not assessed. And there was no
6 assessment of UTI comprehension in the female OAB
7 general population, it was the normal literacy
8 population and the elderly of 65-plus.
9 So now to some labeling changes that were
10 made by the sponsor, and I think these were all good as
11 a result of the research that was conducted. The
12 underlying conditions listed in the warning section
13 have been bulleted to further emphasize, so I'm not
14 going to go with the laser because it's a little bit of
15 a hard angle to do this at.
16 But the label that was used in the pivotal
17 LCS and the actual use study was if you need to urinate
18 frequently, you can see it was just a sentence listing
19 these different underlying conditions, but in the
20 proposed label that was in the NDA submission, it's
21 bulleted. So it's a lot easier if someone is just
22 looking at the label and not scouring it to kind of see

1 these underlying conditions.
2 They further emphasize the UTI symptoms
3 through placement, bulleting, and wording. Here was
4 the label used in the pivotal and again it said do not
5 use if you have any of the following symptoms. And
6 they listed them, but they didn't really say that it
7 could be UTI, and here in the proposed label they
8 actually state, "Do not use if you have any of these
9 symptoms, which could be the sign of a UTI or other
10 serious conditions." So it's clear, I think,
11 especially if you're looking at it quickly.
12 They added symptoms of urinary retention to
13 the "Stop Use and Ask a Doctor" section, so -- oh, in
14 the "Do Not Use" section there was, "Do not use if you
15 have urinary retention," but then in the current
16 proposed label it was, "Do not use you have been told
17 by a doctor that you have urinary retention," which
18 could clarify that confusion. And also the "Stop Use
19 and Ask a Doctor," as I just mentioned, in the original
20 label it wasn't there, and in the label that was in our
21 NDA submission, it says, "Stop use and ask a doctor if
22 you are not able to empty your bladder, urinary

1 retention."
2 Finally, there were diabetes symptoms that
3 were bulleted in the "Ask a Doctor Before Use" section.
4 Here is how it was originally, and you can see that
5 second bullet has the symptoms in it, but they are just
6 separated by commas, and here in the proposed label,
7 it's been bulleted out more, and I think this is good,
8 I think it's easier to see.
9 But I just have a few other labeling
10 recommendations for consideration. The first is that I
11 think based on all the research that I talked about,
12 this 3 months minimum symptom duration was not as well
13 understood as some of the other items, and so I think
14 in some way to enhance the "at least" in that phrase
15 may make it stand out more in a section that does
16 really cite various numbers.
17 So here is the section again. And perhaps if
18 that "at least" is somehow highlighted, that would be
19 good.
20 The next is separate out diabetes risk
21 factors from diabetes symptoms to make each stand out
22 more. And here is the current proposed label as we have

1 it. But again I just think it could be a little bit
2 confusing because that first sentence sort of lumps
3 together risk factors and symptoms of diabetes, and
4 somebody who is really not knowledgeable about that
5 might sort of gloss over it. So I think it would help
6 to clarify if there was one section on risk factors and
7 then somehow one on diabetes symptoms.
8 And, finally, I would recommend to add back
9 into the label the importance of seeing a doctor, back
10 into the UTI section. This was in an earlier pivotal,
11 "It is important to see a doctor before using the
12 product," but again in what we have in the NDA
13 submission, it's not there. So it might be helpful to
14 put that back in.
15 And again I will now turn it over to Dr.
16 Raffaelli to discuss the actual use study. Oxytrol for
17 Women -- The Clinical Perspective
18 DR. RAFFAELLI: Good morning. I'm Ryan
19 Raffaelli. I'm a medical officer with the Division of
20 Nonprescription Clinical Evaluation, and I'll be
21 discussing the application before us today from the
22 clinical perspective.

1 So as far as the outline, first I would like
2 to discuss the actual use study design a bit, and then
3 as part of that I'll discuss the purchase decisions and
4 then label ineligibilities. I may run over that a
5 couple of times, so forgive me.
6 Then I would also like to discuss the primary
7 and secondary endpoints, the major ones. I'll get into
8 the primary safety topics and the label ineligibilities
9 as they're applied to that. And just as a form of a
10 definition or context, the label ineligibilities were
11 those medical conditions, symptoms, concomitant
12 medication uses that should have either instructed
13 subjects or users to not use the drug at all or should
14 have instructed them to seek medical advice prior to
15 use.
16 Finally, I'll end my talk with discussing
17 prescription Oxytrol postmarketing experience and
18 talking a little bit about some labeling items for
19 discussion.
20 So, again, the title of the actual use study
21 was the "Consumer Trial of Oxytrol." This was an open-
22 label, single-arm, multicentered trial across the

1 country at 26 pharmacy sites, which is very typical of
2 actual use studies, and both the study population and
3 the design of the study were adequate as far as our
4 review is concerned.
5 Actual use studies generally are meant to
6 predict in a naturalistic OTC setting how consumers
7 might use a drug. The purpose of this study was to
8 assess use and misuse in that naturalistic setting. The
9 major endpoints that we evaluated, there were three.
10 Really the sponsor wanted to look at misuse rates. And
11 again this is also very typical of actual use studies.
12 The primary endpoint looked at subjects or users who
13 had new or worsening symptoms that were on the label
14 and that were reported by any user of at least one TDS
15 over the duration of the trial. And TDS is transdermal
16 system, and that's generally how I will refer to
17 Oxytrol.
18 The other major secondary endpoints were
19 secondary endpoint 3, which looked at users who
20 reported no improvement, so be it either their OAB
21 symptoms stayed the same or they worsened after 2 weeks
22 of use. Secondary endpoint 5 was subjects who reported

1 or were determined to be incorrectly using the product
2 either by prolonged duration, be it using it for longer
3 than 4 days, or simultaneous use of more than one TDS.
4 There were some other secondary endpoints,
5 but they were relatively minor, and they didn't impact
6 our interpretation of the results or our determination,
7 conclusions, about the study. The duration of this
8 study included a 12-week use phase, and this was also
9 adequate for our concerns. And just to point out the
10 level of data that we were able to review, we had 88
11 percent of all the users completed the week 12
12 interview, so we had lots of data points to evaluate.
13 So the design of the CONTROL trial, I would
14 like to go over a little bit of the methods. So there
15 were recruitment and screening objectives. The
16 recruitment included some advertisements that were very
17 targeted towards women, so they were pink, they had
18 blue lettering saying, "Attention Women." There were
19 lots of photos and images of women again to try to
20 limit recruitment of men in the study. It seemed to be
21 pretty successful, as the sponsor was saying. Only 45
22 men inquired about being involved in the study.

1 Enrollment procedures have been described
2 previously. Basically use was assessed at home, that's
3 the point of these types of studies. And as far as
4 evaluating that at-home use, the evaluation measures
5 included three interviews at weeks 3, 7, and 12. The
6 scripts of these interviews were adequate. Diaries
7 were kept by users and submitted to the investigators
8 to confirm use over the use period. And then there
9 were end-of-study testing including urinalysis and an
10 interview.
11 And again just also to point out the data
12 points we had available to evaluate, almost 60 percent
13 of users completed the end-of-study urinalysis, and 82
14 percent of all those who were dispensed the drug
15 completed the end-of-study interview.
16 As to the exclusion criteria, I just wanted
17 to point out in the box to the right that males and
18 those under 18 were excluded at screening. Again, it
19 was a really very small percentage, about 1.8 percent
20 of all those who were screened. And then additionally,
21 as per the proposed label, subjects who were pregnant
22 or breastfeeding, reported narrow-angle glaucoma,

1 reported hematuria, had symptoms that might be
2 consistent with pyelonephritis or more severe urinary
3 tract infection, be it fever or chills with OAB
4 symptoms and either dysuria, hematuria, cloudy urine,
5 or foul-smelling urine, and in addition, allergy to
6 oxybutynin or other ingredients in the product, all
7 these subjects were excluded.
8 So as to the subject disposition, as the
9 sponsor indicated as well, there were about 2,700
10 callers. Of those, 1,230 were enrolled. Only 1,218
11 actually evaluated the label. Some of these subjects
12 were excluded because they didn't complete all of the
13 enrollment proceedings. And where I indicate here at
14 plus one, this was a subject who was excluded at the 3-
15 week interview because she hadn't reported that she was
16 a nurse, which would have qualified her for exclusion
17 from the trial. But as you can see, she was given the
18 drug after she made a purchase decision, but she did
19 not use the drug, so none of those subjects will be
20 further discussed.
21 So the subjects who made a purchase decision
22 was 1,069. Of them, 855 were actually dispensed the

1 drug, and then as has been stated, there were 785 total
2 users, so the 727 who were verified and 58 who were
3 nonverifiable users. And then there were 70 subjects
4 who for whatever reason purchased and brought home the
5 drug but decided not to use it.
6 So here I just want to point out the 214
7 subjects who had made a purchase decision but were
8 subsequently excluded from the use phase. And as has
9 been stated previously, 187 of them were
10 administratively excluded, be it they didn't complete
11 the informed consent or decided not to purchase at the
12 last minute, that sort of thing. There were 27 who
13 were excluded for medical reasons, and I'll talk about
14 some of those in a moment.
15 I would also like to point out that of the
16 subjects who decided not to purchase the drug, only
17 four would have been excluded for medical reasons. So
18 two had hematuria, one had symptoms of possible UTI,
19 and another reported allergy. It's not clear
20 necessarily why. We can surmise some things as far as
21 the severity that subjects considered their OAB
22 symptoms over what might be these label ineligibilities

1 that we considered or other exclusionary reasons, but
2 that could be up for discussion. And then, finally,
3 703 subjects or users and nonusers completed the end-
4 of-study interview.
5 So as to the purchase decisions and the label
6 ineligibilities, here I would like to just list some of
7 the ineligibilities that interested us the most and
8 that were most frequently reported. So you can see
9 that incomplete bladder emptying was the most
10 frequently reported, quote/unquote, label
11 ineligibility, and it was meant to equate to urinary
12 retention. Almost 43 percent of subjects who made a
13 decision to purchase the drug reported these symptoms.
14 Additionally, as it goes down the list,
15 subjects reported diabetes risk factors, possible
16 symptoms of UTI, potential bladder cancer risk factors,
17 which included weight loss in association with dysuria
18 or hematuria or flank pain or abdominal pain. And then
19 subjects who did not meet the OAB symptom conditions,
20 be it that they either had less than two OAB symptoms
21 or that they had symptoms for less than 3 months.
22 So in total, we determined that 21.5 percent

1 of subjects who made a decision to purchase the drug
2 were eligible as per the label. And again this spanned
3 the gamut of all these label ineligibilities, be it
4 subjects who had kidney disease or subjects who
5 reported only stress incontinence compared to subjects
6 who might have a possible UTI or something more
7 serious. So obviously that means that 78.5 percent of
8 subjects who made a decision to purchase the drug were
9 ineligible as per the label. Again, you have to keep
10 this in context.
11 So as to the findings for the indication, you
12 can see I circled 13 percent of the subjects making a
13 purchase decision did not meet the OAB symptom
14 conditions, it was 138 who said yes. Only 11 percent
15 of all the users did not meet the conditions. And I
16 would like to point out that 12 percent, or 22, of the
17 label evaluators who were ineligible by the indication
18 reported being told by their doctors that they had OAB,
19 and half of them, or 11 of them, decided to use the
20 drug.
21 I would like to move now into discussing the
22 endpoints. So the major endpoints related to misuse of

1 Oxytrol for Women at home, misuse by the primary
2 endpoint and the major secondary endpoints, which were
3 3 and 5, were mitigated. The sponsor went over a lot
4 of the mitigation criteria and how these strategies
5 were processed.
6 I reviewed all of the mitigation strategies,
7 all of the a priori established criteria. I felt that
8 overall they were very reasonable. The sponsor's
9 misuse proportions, again, for the primary endpoint
10 were based on the total users of at least one patch.
11 For the secondary endpoint 3, they were based on all
12 those users who used the drug for 2 weeks and completed
13 the week 3 interview. And for secondary endpoint 5,
14 the misuse is based on the total users of at least one
15 patch. Again, like I've said, FDA found these
16 endpoints acceptable, so it was after negotiations with
17 the sponsor, and we agreed that these were appropriate
18 to monitor. In addition, as you'll see on the next
19 slide, we considered some additional proportions.
20 So here is a table of all the misuse rates
21 for the major endpoints we considered. So the middle
22 column is pre-mitigation, the last column, the post

1 mitigation. So for the primary endpoint, of those
2 users who reported new or worsening symptoms and failed
3 to stop use out of all the users of at least one patch,
4 as the sponsor noted, 3.4 percent was the misuse rate.
5 Again, just to point out, the a priori threshold
6 established by the sponsor was less than or equal to 5
7 percent.
8 The sponsor and FDA looked at another
9 proportion, and we felt like there was some clinical
10 heft to this one, and that was looking at the same
11 users who reported new or worsening symptoms but who
12 failed to stop use out of only those users who also
13 reported pertinent symptoms. So here we're looking at
14 the ones who had pertinent symptoms, did they correctly
15 or incorrectly continue or stop using the drug? And as
16 was pointed out in the discussion after the sponsor's
17 presentations, that 17.7 percent of the subjects post-
18 mitigation continued to misuse if you look at this
19 proportion.
20 I would like to point out, however, that the
21 design of this trial was not powered to fully evaluate
22 this misuse rate to sort of try to guess during the

1 design phase. How many subjects might have pertinent
2 symptoms that would indicate that they should stop use
3 is something that would be fairly difficult to
4 determine a priori.
5 The secondary endpoint 3 was looking at the
6 users who had no improvement of their OAB symptoms and
7 failed to stop use, and this was out of all the
8 subjects who used the drug for 2 weeks and completed
9 the week 3 interview. And as the sponsor pointed out,
10 11 percent of the subjects post-mitigation had misused
11 the product here. If we sort of go along FDA's same
12 line of thinking and again keep in mind that these were
13 exploratory post-hoc subgroup analyses, we looked just
14 at all the users who used the drug for 2 weeks and
15 reported no improvement. Here the misuse rate is
16 higher, but again you have to keep this in context with
17 what I was just stating. So 38 percent of these users
18 misused post-mitigation.
19 And, finally, just to give the numbers for
20 the secondary endpoint 5, the incorrect users, so these
21 were the people who used the drug for either too long,
22 more than 4 days, or used too many of the TDSs at one

1 time, out of all the subjects who used at least one
2 patch, 21 percent of them misused the product post-
3 mitigation. I would like to point out that between 85
4 and 96 percent of all the patches that were used by
5 products over the duration of the trial were used
6 appropriately, so there weren't any significant issues
7 as far as patterns of misuse. And most subjects
8 appeared to understand that only one patch should be
9 used and that it should be used for 4 days, 4 days or
10 less.
11 I just wanted to show the numbers here
12 quickly as we move along, but for the primary endpoint,
13 the total number of verified users who had symptoms
14 indicating that they should have stopped use was 141,
15 so that was 20 percent of the total users. And, again,
16 you can see the upper and lower bounds of the misuse
17 rate where the sponsor met the a priori threshold. So
18 the upper limit was 5 percent, which was equivalent
19 with the threshold.
20 Again, same sort of thing. So we had 187
21 users who reported no improvement of their OAB
22 symptoms, either the symptoms stayed the same or

1 worsened after 2 weeks of use. So we had 187 subjects,
2 or 30 percent of the total, who completed the week 3
3 interview, which was 643 subjects or users.
4 Finally, the secondary endpoint 5, this is
5 broken down by the type of incorrect use, so in total,
6 the total users who incorrectly used either by more
7 than 4 days or by simultaneous use again was 21 percent
8 post-mitigation, or a total of 152 users. But if you
9 break it down, 155 users incorrectly used by duration
10 only and 22 users by simultaneous use only.
11 The bullet underneath the table indicates
12 that this was really the only implicator when I looked
13 at the subgroup analysis by age, race, or literacy. So
14 I evaluated all of the misuse rates by those subgroups
15 for the primary and the secondary endpoint 3 and the
16 secondary endpoint 5. Really only this one showed any
17 significance to me, and that was just that misuse by
18 either method increased with age, so 18 percent of
19 subjects misused who were under 65, up to 29 percent
20 over 75. And that's how the data laid out.
21 So as far as safety for the CONTROL trial, 66
22 percent of all users reported at least one adverse

1 event. By age, there were no significant differences
2 in the reporting overall, however, I will point out
3 that subjects who were under 65 more frequently
4 reported application site reactions and constipation,
5 whereas subjects who were over 65 more frequently
6 reported UTI or cystitis.
7 The next bullet shows the adverse events that
8 were reported by more than 2 percent of all the users
9 who reported an AE, and the most frequently reported
10 was application site irritation, at 18 percent; UTI and
11 cystitis, dry mouth, urge incontinence, constipation,
12 and back pain followed. Four point five percent of all
13 users had a serious adverse event. There was one death
14 reported. This was a subject who was HIV-positive and
15 succumbed to viral pneumonia.
16 Of the serious adverse events, the only ones
17 that were listed two or more times were UTI, which was
18 included in five serious adverse event reports, stroke,
19 back or chest pain, and cholecystitis. Overall, 141
20 users, or 27 percent of those, reporting adverse events
21 discontinued due to their adverse event. Thirteen of
22 these discontinuations were due to serious adverse

1 events, but only UTI, fractures, and stroke were
2 reported more than once.
3 I would like to point out that the most
4 common reason for discontinuation from the trial was
5 application site reactions. And I would also like to
6 point out that of the serious urinary tract infections,
7 there were no clear reports of urosepsis. And I
8 reviewed all of the case report forms for all subjects
9 reporting UTI.
10 I would like to get into a little bit more
11 detail on the primary safety topics that we considered
12 and as they pertained to the label ineligibilities. So
13 there were subjects who reported possible symptoms of
14 UTI. These were fever or chills and dysuria,
15 hematuria, flank pain, cloudy or foul-smelling urine.
16 Subjects needed to meet all these criteria in order to
17 be excluded from the trial, or mixes of them, so fever
18 and chills with dysuria or hematuria. If subjects
19 reported isolated symptoms, if they only reported
20 dysuria or only reported cloudy urine, they were not
21 excluded from the trial, again just to get an idea of
22 this naturalistic setting and how subjects might use

1 and follow the instructions and warnings on the label.
2 Diabetes risk factors included the family
3 history of diabetes and excessive thirst, hunger, or
4 tiredness. Incomplete bladder emptying was meant to
5 define urinary retention. And bladder cancer risk
6 factors, as I've explained previously, included weight
7 loss with some other urinary symptoms.
8 So for subjects who reported possible
9 symptoms of UTI, the table at the bottom indicates that
10 260 of the label evaluators and 154, or 20 percent, of
11 the users reported possible symptoms of UTI. Only
12 three who made the purchase decision were excluded for
13 the stricter UTI criteria that I talked about, having
14 fever and chills plus any of the other symptoms. In
15 total, only eight users were diagnosed with UTI during
16 the trial, eight of the users who reported these
17 enrollment symptoms. In addition, 26 users reported
18 new possible symptoms of UTI during the trial, 15 of
19 them correctly stopped using the drug, and only 4 were
20 diagnosed with
21 UTI.
22 I would also like to point out that five

1 users were diagnosed with UTI who had not met the OAB
2 symptom conditions, be it that they either reported
3 less than two OAB symptoms or had symptoms for less
4 than 3 months. None of these users who were diagnosed
5 with UTI had reported possible symptoms of UTI at
6 enrollment. All of them recognized their UTI symptoms
7 and sought prompt medical attention. And I would also
8 like to point out that 2.7 percent, or 33, of all the
9 subjects who looked at the label reported OAB symptoms
10 that lasted only for 1 month duration, so this
11 indicated to us that the likelihood of confusing
12 idiopathic OAB with acute UTI was unlikely, that most
13 of the subjects who proceeded through the trial seemed
14 to understand that 3 months was a reasonable window to
15 have had symptoms, and obviously if you had any
16 coincident symptoms that were more concerning for UTI,
17 that those subjects sought medical evaluation.
18 So overall, over the entire trial, 66 UTIs or
19 episodes of cystitis were diagnosed, and five of them
20 were serious. Almost all of the users either
21 recognized their symptoms or were diagnosed either at
22 the end of study urinalysis, may have been relatively

1 asymptomatic, or diagnosed during routine health
2 maintenance for other reasons.
3 All five users who had serious urinary tract
4 infections had reported long-term OAB symptoms, again
5 supporting that these subjects -- some subjects could
6 have a UTI and have idiopathic OAB, that's not out of
7 the realm of possibility. So it seems like most
8 subjects were able to recognize what distinguished UTI
9 from idiopathic OAB. We didn't feel that there were
10 any apparent delays in diagnosis of UTI, but again this
11 could be up for discussion with the panel.
12 Moving on to the diabetes mellitus risk
13 factors, again you can see -- and from my previous
14 slide -- there were a fair number of subjects who
15 reported diabetes risk factors, but again that's part
16 of our society. A lot of these subjects made a
17 decision to purchase, several were dispensed the drug,
18 many of them were users, not as many spoke with their
19 doctor. It seemed like most people gave reasons such
20 as they didn't feel it was necessary to speak to their
21 doctor.
22 As the sponsor pointed out, only two subjects

1 were diagnosed with diabetes over the course of the
2 trial: one was a user and one subject had been
3 excluded for hematuria. Neither diagnosis appeared
4 delayed due to their considered use of oxybutynin.
5 For subjects who reported feeling that they
6 had incomplete ability to empty their bladder, this was
7 meant to define urinary retention. Again, as Ms. Cohen
8 and the sponsors pointed out, the label has sort of
9 gone through an iteration to ask subjects if they have
10 -- the current label asks subjects if they have a
11 diagnosis of urinary retention rather than sort of this
12 more vague trying to equate urinary retention to
13 incomplete bladder emptying.
14 I would like to point out that again this was
15 the most commonly reported label ineligibility, but as
16 you can see, a fairly significant number of users
17 reported these symptoms and may even have felt like
18 this explained their OAB symptoms. This is also
19 supported by the fact that so few actually spoke with
20 their doctor. It seems like most of the users felt
21 like this was the reason for their symptoms, that they
22 couldn't empty their bladder, and that's why they had

1 urinary frequency and urgency.
2 I will point out that there were no cases of
3 acute urinary retention. There were seven reports of
4 subjects describing worsening of their incomplete
5 bladder emptying, that sort of thing, but, again, I
6 looked at all the case report forms, and nothing was of
7 concern.
8 None were serious, all were mild and self-
9 resolved, and only one user discontinued on the advice
10 of her doctor.
11 Finally, I would like to point out that
12 bladder cancer risk factors were reported, however,
13 there were no cases of bladder cancer, but again the
14 design of this trial was not meant to try to capture
15 cases of bladder cancer. And I will point out that in
16 my review there have been no reports of delayed
17 diagnosis in the literature or other studies due to use
18 of drugs for OAB.
19 There were some other important safety topics
20 that we considered in this trial and in postmarketing,
21 allergy in particular. There were 185 adverse events
22 reporting some form of allergy or hypersensitivity.

1 Seventy-eight subjects discontinued, but most of these
2 were due to skin-related adverse events. There was one
3 serious adverse event, but this was believed to be due
4 to the use of a concomitant muscle relaxant.
5 There were 186 adverse events that matched up
6 with some skin reactions. Seventy-three discontinued
7 use. There was one serious adverse event, which was
8 skin blistering, but the blistering occurred in the
9 subject 3 months after she had completed the use phase,
10 so it was unlikely related to the patch or the TDS.
11 Sorry for the busyness of this slide, but I
12 wanted to just combine some of these effects that may
13 be related to anticholinergics. So sort of grouping
14 together anticholinergic effects, there were 105
15 adverse events reported by 89 users. The most
16 frequently reported were dry mouth, constipation,
17 dizziness, or somnolence. There were no serious
18 adverse events, and 25 of these subjects discontinued
19 use, however, and most frequently due to dizziness or
20 dry mouth. Ninety percent of the adverse events
21 resolved or improved on follow-up interviews. And none
22 of the events worsened.

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1 We consider that disorientation and confusion
2 and even falls and accidents could be associated with
3 CNS-related anticholinergic effects, as has been
4 pointed out in the discussion after the sponsor's
5 presentations as well. This is a possibility, and we
6 did notice that there were 79 adverse events related to
7 disorientation or confusion by 78 users. One of these
8 subjects discontinued use. There were two serious
9 adverse events.
10 Keep in mind the sponsor captured these
11 categories with many, many preferred terms, which are
12 the adverse events that we monitor in a lot of our
13 postmarketing databases in particular, and in clinical
14 trials. So it's a wide variety of adverse events that
15 could have made up the grouping of disorientation and
16 confusion.
17 So the two serious adverse events here were
18 reports of schizoaffective disorder and convulsive
19 syncope, which we felt were unrelated. Additionally,
20 some falls and accidents were reported. Some of these
21 may overlap with the anticholinergic effects. There
22 were 19 adverse events by 17 users with 3

1 discontinuations. There were seven serious adverse
2 events. Only three were in the use phase, and none
3 appeared related to CNS anticholinergic effects.
4 So I would like to move on now into the
5 postmarketing safety data. We evaluate postmarketing
6 safety from a variety of sources, including the NDA
7 holders database, the FDA-AERS system, the WHO
8 database, and the American Association of Poison
9 Control Centers. Overall -- and most of these adverse
10 events are included in the NDA holder's database --
11 over 13,700 adverse events reported worldwide since
12 2004 when market launch occurred. As part of keeping
13 this in context, over that same time period, about 40
14 million TDSs have been distributed.
15 In addition to the postmarketing safety
16 databases, we also looked at some data from a
17 postmarketing trial that was conducted by the NDA
18 holder on their own to evaluate quality of life
19 measures. This was the MATRIX trial.
20 So the postmarketing data in this table
21 reflects U.S. data. It's adapted from the applicant's
22 submission. The findings are representative of

1 worldwide data. I would like to just point out that
2 these were the eight most common adverse events
3 reported.
4 I would like to also point out that the most
5 common of the most common are application site
6 reactions, so you can see application site erythema,
7 pruritus, rashes and irritation. These make up about
8 40 percent of the AEs that have been reported since
9 market launch. And 96 percent of reports are
10 nonserious and really only .7 percent were serious and
11 labeled. I would also just like to take note of the
12 fact that these other more commonly reported adverse
13 events are consistent with the anticholinergic effects
14 that are well-known with oxybutynin as well as other
15 OAB drugs, particularly the dry mouth, blurry vision,
16 dizziness. These are common.
17 So for the panel's discussion and as
18 pertinent to some of the questions that will come up
19 later this afternoon, some of the labeling concepts
20 that we're asking you to consider are to consider
21 possibly strengthening the sleepiness, dizziness,
22 blurry vision warning. As Dr. McNellis pointed out,

1 there has been a recent prescription label update as
2 per the somnolence warning. We would like you just to
3 consider the drug's use in an older population and that
4 consumers may also be taking other drugs with similar
5 anticholinergic effects.
6 The second bullet is that we would like you
7 to consider some additional warnings for
8 anticholinergic effects, for example, dry mouth and
9 constipation, that are not infrequently reported but
10 can be quite bothersome to consumers.
11 So in conclusion, the CONTROL trial was
12 adequately designed and populated as far as we believe.
13 The sponsor met their primary endpoint. The upper
14 limit of the misuse rate was 5 percent. Major
15 endpoints in the mitigation strategies were acceptable.
16 In total, I would just like to point out that 276
17 users, or 38 percent of the verified users, did develop
18 new symptoms or reported that their OAB condition had
19 not improved, indicating that they may have considered
20 stopping use. Only 65, or 23.5 percent, of these
21 subjects talked to a doctor, but many of them, on the
22 advice of their doctor, continued use, over 70 percent.

1 Finally, close to 80 percent of those who
2 made a decision to purchase had any label
3 ineligibility, and we spent a lot of time talking about
4 that. I would like to point out that again some misuse
5 and incorrect use analyses showed that users may not
6 always follow the label directions and the warnings.
7 However, we didn't feel like there were any apparent
8 delayed diagnoses of more serious medical conditions
9 that also can present with OAB symptoms, be it UTI or
10 diabetes. There were also no concerning safety trends
11 in the trial or signals identified in the trial or in
12 the postmarketing data. Again, application site
13 reactions and anticholinergic effects appear to be most
14 common, but mostly these are nonserious, and we believe
15 they could probably be labeled to caution consumers
16 about use.
17 And there I would like to conclude, and I
18 believe FDA will take some questions.
19 DR. REIDENBERG: Thank you very much. And
20 again I would like to thank all of the presenters for
21 staying well within our time limit. Clarifying
22 Questions

1 DR. REIDENBERG: I will now welcome
2 clarification questions from the committee, and then
3 we'll put down your names and we'll call in order of
4 being recognized.
5 Okay. Dr. Gellad?
6 DR. GELLAD: I forgot to ask this for the
7 sponsor, but I can ask the FDA as well. Were the
8 subjects in the CONTROL trial actually purchasing the
9 drug? Did they have to pay for the drug? And how much
10 did they pay? I don't know if FDA or --
11 UNIDENTIFIED MALE SPEAKER: Right, they're
12 called a purchase.
13 MS. REPLOGLE: Initially the price was $10,
14 but we were having issues with enrollment, so the price
15 was reduced to $5.
16 DR. REIDENBERG: Dr. Farber?
17 DR. FARBER: Thanks. Two questions, and
18 whoever wants to answer them is fine with me.
19 First of all, in terms of the clinical
20 efficacy, Dr. McNellis, that you indicated on the
21 Oxytrol, was there clinical -- i.e., subjective --
22 improvement? And to what degree? For example, by an

1 SPF36 or some other quality of life indicator?
2 And the second question is: Were any
3 neurologic conditions considered in terms of warnings
4 ahead of time? Things like normal pressure
5 hydrocephalus, frontal lobe brain tumors, can all cause
6 symptoms similar to OAB.
7 DR. REIDENBERG: Let me interrupt for a
8 minute. I have been told by the FDA specifically that
9 we are to accept efficacy as a given, so that if one
10 wants to answer the question for description, why,
11 fine, but efficacy we have to accept as given for the
12 purpose of our decision-making, for the second
13 question.
14 Could you repeat the second question?
15 DR. FARBER: The second question is regarding
16 clinical conditions that would be sort of a warning or
17 an eligibility or something that patients should
18 consider similar to UTI or pregnancy, and that is,
19 neurologic conditions, such as normal pressure
20 hydrocephalus, certain degenerative conditions,
21 degenerative neurologic conditions, frontal lobe brain
22 tumors, any of those kinds of things can cause

1 prolonged urinary tract symptoms.
2 DR. MCNELLIS: Patients with those conditions
3 would have been excluded from the Phase 3 trials.
4 DR. FARBER: I didn't see anything in any of
5 the writing that was a consideration or whether those
6 patients should be warned about that.
7 DR. MCNELLIS: As far as plans for over-the-
8 counter label, I don't know if you have any plans to
9 put that type of information in the label.
10 DR. REIDENBERG: Okay, then if we want to
11 discuss this, this afternoon and make recommendations
12 to the FDA, I think that's one of our charges for our
13 committee.
14 Dr. Howards.
15 DR. HOWARDS: I have a question for the FDA
16 and/or the permanent panel members. I don't know how
17 you weigh the advantages of over-the-counter
18 accessibility for patients versus the fact that in
19 spite of all we heard today, many patients will not
20 read the label. How do you balance that?
21 DR. REIDENBERG: Okay. Would somebody from
22 the FDA care to comment on this? Do we want to think

1 about it for a couple minutes and then come back to it?
2 I'll give you the choice of the first response.
3 DR. LEONARD-SEGAL: Hi. Dr. Andrea Leonard-
4 Segal, for the purpose of the record. We have an
5 enormous number of products that are over-the-counter.
6 We cannot force people to read labels, but we do
7 provide on all of our over-the-counter products
8 labeling that we hope when read will help people use
9 products effectively and safely.
10 So your question was how we make a balance?
11 Can you please repeat for me?
12 DR. HOWARDS: Yes. For some things, reading
13 the label isn't critical. Here I think it could be
14 quite critical, and so I want to know how you balance
15 the positive aspects of over-the-counter availability
16 for these people versus the fact that many of them will
17 not read the label. How do you come to a conclusion
18 about whether this is --
19 DR. REIDENBERG: May I comment on this for a
20 minute? I think that you have quoted what the actual
21 FDA law is with respect to when a drug can be over-the-
22 counter, and I think it has to meet certain criteria,

1 but I don't believe that the degree of reading the
2 label is included within it. Would you care to comment
3 on that, Andrea?
4 DR. LEONARD-SEGAL: Sure. The laws that
5 control over-the-counter drug use, actually it's the
6 Durham-Humphrey Act, and I think it goes back to 1951
7 or '52, and it states that a product can be over-the-
8 counter in essence when the criteria for using the
9 product show that it can be used safely and
10 appropriately and the conditions for use are such that
11 a consumer could use the product themselves. So, in
12 other words, if the product somehow involved having to
13 administer the product intravenously with a drip,
14 something that would be hard to self-administer, that
15 probably would not fit those criteria.
16 Reading a label is not part of those
17 criteria, and part of the decision-making that we have
18 to find a balance for is providing products that are
19 safe and effective for people to use and we give them
20 the information, we can't force people to read
21 everything. We have to decide where paternalism stops.
22 DR. HOWARDS: Thank you.

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1 DR. REIDENBERG: Thank you.
2 Dr. Gellad?
3 DR. GELLAD: I'll just keep talking if no one
4 else has questions. I actually had a question for the
5 -- I'm just kidding -- I had a question about
6 the label and specifically the diabetes portion. I
7 guess I'm trying to get a sense of what the actual
8 current proposed label is, and I think I see it in
9 slide 35, but I guess I'm just wondering, one, or the
10 clarifying question is: What is a history of diabetes
11 in the immediate family something that really should be
12 on the label as opposed to symptoms? I'm just
13 wondering medically. That will be like 20 percent of
14 the population probably. So I guess the justification
15 for that being on the label.
16 DR. HEMWALL: We're quite willing to respond
17 to some of these questions if it helps the committee's
18 deliberations even though they're directed at the FDA
19 contingent.
20 The reason it's there is because when we
21 discussed the development of this project with FDA,
22 there was a concern that I think we've agreed that it

1 may not be as great a concern as might have been
2 originally thought, that symptoms, early symptoms, of
3 diabetes might be confused with OAB, so we took a very
4 conservative approach that even if you have a risk
5 factor for diabetes, you should talk to a doctor before
6 you use the product. But it may be a little
7 overconservative.
8 On the discussion of whether or not consumers
9 read labels, I think that's a common conception, in
10 fact, I'm guilty of it myself, of products that I've
11 used over and over, I probably don't read the labels
12 very often, but a recent survey has shown, and fielded
13 with 1,000 over-18 adults, that 9 out of 10 do read
14 their labels of the products, and it's especially
15 important that they read the label of the product that
16 they're using for the very first time.
17 So I want to be real clear that I think we
18 all have the same sort of point of view that Dr. Farber
19 was expressing, but when you really look at consumer
20 behavior and try to put some facts around it, there is
21 a lot more careful reading of labels than one might
22 expect, and especially for products that are new and

1 being used for the first time.
2 DR. REIDENBERG: Okay. Sure.
3 DR. LEONARD-SEGAL: Dr. Gellad, I can also
4 embellish a little bit. And I think that we were
5 trying to be very conservative when we were talking
6 about the development of this product. It has been
7 going on, from our perspective, at least about 4 years,
8 probably longer from Merck's side. And we were trying
9 to find a way to capture people who did not have a
10 diagnosis of diabetes but might be experiencing
11 symptoms for the first time to try to avoid an undue
12 delay in diagnosis, but it's a clinical decision as to
13 how important putting that information on the label is
14 or isn't, and we're open to hearing your thoughts about
15 that today.
16 Thank you.
17 DR. HEMWALL: We have with us Dr. Stan
18 Schwartz (ph), who is an expert in this area, and I
19 think he could provide some additional perspective if
20 you would be willing.
21 DR. GELLAD: I'm happy to discuss it later if
22 you want to -- I'll leave it to the Chair.

1 DR. REIDENBERG: Let us go on with the
2 additional clarifying questions now, and then we'll see
3 how much time we have afterwards.
4 Dr. Parker.
5 DR. PARKER: So I wanted to focus very
6 specifically on the elderly cohort size as I try to
7 understand exactly what we know and don't know from the
8 studies that were presented. So I just wanted clarity
9 on -- since the prevalence of the condition is higher
10 among the elderly. I wanted to know specifically if
11 you could help me to identify for self-selection and
12 also for actual use, what was the size of the
13 population of people over 65 in the self-selection
14 studies and also in the actual use? How many people do
15 we have data on that are 65 or older? So I want to
16 know the size of that.
17 And then I also want to know the prevalence
18 of low literacy among those that are 65 and older since
19 in the general population low literacy is more common
20 among the elderly, the condition is more common among
21 the elderly, so in these studies that we have available
22 to help us decide, I want to know how well that

1 population is represented.
2 That would be my first question.
3 DR. HEMWALL: You're talking about the
4 CONTROL study or --
5 DR. PARKER: Yeah. What I'm going to call
6 actual use just because I know that term, but yes, I
7 want to know that.
8 And then I understood from your early
9 presentation that you had three studies done that were
10 considered self-selection studies, and I'm assuming --
11 I'll get to that.
12 Start with CONTROL, tell me the numbers
13 there, but I do want to know in those self-selection
14 studies, because I assume I'm supposed to look at
15 those, to help me understand whether people can
16 adequately self- select. So I want to know how many
17 elderly were represented in those studies as well.
18 DR. HEMWALL: Okay. And did you want a
19 break- out of low literacy within those subsets?
20 DR. PARKER: Yes.
21 DR. HEMWALL: Okay. I don't think we have
22 the breakout of the low literacy within the subsets,

1 but we can show you the age breakouts from the CONTROL
2 study.
3 DR. PARKER: Right. So two-thirds were below
4 65, as I recall, yeah. So the population is
5 predominantly under 65, and you've got --
6 DR. HEMWALL: Well, yeah, it's --
7 DR. PARKER: Right. Of the total.
8 DR. HEMWALL: It's one-third over 65 and two-
9 thirds under basically.
10 DR. PARKER: Okay. So a third are over 65,
11 two-thirds are under. And you don't have any data on -
12 - so the 12 percent low literacy, do you happen to know
13 how that breaks out by age? So you've got overall 12
14 percent low literacy among users.
15 DR. HEMWALL: Yeah. That's a slide we don't
16 have, it has low literacy breaking out by age. We
17 could get that for you after the break.
18 DR. PARKER: That would be useful to know
19 because it should reflect if there are more low
20 literate people among that elderly cohort to reflect
21 the general population --
22 DR. HEMWALL: Yes.

1 DR. PARKER: -- also reflect the target
2 population. It's already been commented that that's a
3 low number?
4 DR. HEMWALL: That's right. That --
5 DR. PARKER: That's really important given
6 the target population for the drug in question. So I
7 just wanted to get clarity around that. So that was
8 one question.
9 And then the other one is I'm trying to get
10 my hands around what the best way for me to understand
11 self-selection by male or female because this would be
12 brought to over-the-counter in a pink box with a woman
13 who is not leaning backwards and potentially looking
14 pregnant by the stick figure and now looks, from the
15 beginning, on the front cover, so those modifications
16 were made to try to make this appeal to or make it
17 clearer that it's for a female.
18 So give me the best way to look at self-
19 selection because I understood when we talked about the
20 actual use we were told that that was not a self-
21 selection -- don't judge self-selection based on actual
22 use. Am I interpreting this correct, to go back and

1 make judgment on self-selection made on the three self-
2 selection studies that you talked about earlier?
3 DR. HEMWALL: Right. That's right.
4 DR. PARKER: So help me with the best way to
5 understand, how good is self-selection by male versus
6 female? How many males self-select thinking they can
7 use this product?
8 DR. HEMWALL: Well, we looked at that
9 specifically, and I'll ask Steve Neumann to review that
10 with you. And as you saw --
11 DR. PARKER: And I also want to know if we
12 know how many of those are over 65.
13 MR. NEUMANN: Yeah. We might have to take a
14 look to see if we can get that after the break.
15 DR. HEMWALL: We have a separate study in
16 women over 65, but we probably have to break out the
17 men's study to see which men were over 65.
18 MR. NEUMANN: So just to go back to the self-
19 selection studies that we did conduct, Dr. Parker, the
20 initial self-selection study had two cohorts, a normal
21 literate and a low literate cohort. I'll have to look
22 to see what the age distribution is there. That study

1 was a very interesting study because basically it was
2 an all-comers approach. So we advertised in the mass
3 media and we advertised just the symptoms of overactive
4 bladder and we cast a very wide net, and in that net we
5 basically enrolled women who believed that this product
6 would be right for them, and that's what they indicated
7 after reading the label. Actually, they read the label
8 and then they indicated that. Then their results were
9 compared to that of a physician who also read the label
10 and then examined the women.
11 So in that study what you see is the
12 appropriate self-selection, as we defined it, both a
13 response that was consistent with the physician --
14 which was about 82 percent of the normal lit cohort,
15 and I believe it was slightly higher, 85 percent, of
16 the low lit cohort, something like that -- were
17 absolutely consistent with the doctor, and then there
18 were two other categories that we also categorized in
19 that study as being appropriate self-selection, and
20 those were if the woman said that the product was --
21 that she couldn't use it, but the doctor said she
22 could, that's essentially what we would call a lost

1 opportunity. And then another mitigated response was
2 around stress incontinence.
3 In that study also there was a cohort of men,
4 172 men, and as you recall, the label that was used in
5 that study, or I should say the primary display panel
6 in that study, was a blue box, and so men, about 29
7 percent of men, self-selected to use the product and
8 inappropriately -- I'm sorry, 71 percent appropriately
9 self-selected, 29 percent inappropriately self-selected
10 to use the product.
11 So that led us to the follow-up study among
12 men, which we did after the box redesign, which led to
13 the 90 percent result. And then we also conducted, as
14 I indicated, a study among pregnant women with a result
15 of 92 percent. I think I would have to look to see
16 what the breakdown would be by --
17 DR. PARKER: Age.
18 MR. NEUMANN: -- by age. Let me see, I think
19 I have it for --
20 DR. PARKER: So can I just restate that? So
21 with the new box, 10 percent of men -- 10 percent were
22 men that self-selected that it was okay for them to

1 take the product.

2 MR. NEUMANN: That is correct. That is

3 correct. So the self-selection by age breakdown that I

4 have is under 65 was 184 subjects, over 65 was 34

5 subjects in the general population cohort, and in the

6 low literate cohort, it was 111 under 65, and 26 over

7 65.

8 DR. REIDENBERG: Thank you.

9 Dr. Burnett.

10 DR. BURNETT: Thank you. So I would like to

11 talk about safety, certainly in the CONTROL trial. I

12 guess what I'm trying to get a handle on is, how does

13 the CONTROL safety compare to the prescription use in a

14 couple areas? And perhaps both for the FDA and the

15 sponsor to comment.

16 So, for example, in the anticholinergic side

17 effects, I'm trying to get a handle on the extent of

18 the discontinuation effects, and does that compare?

19 does that look similar? The skin reactions

20 look high with the CONTROL trial, but again I'm a

21 simple urologist, so I'm trying to get a handle on the

22 extent of that problem. Maybe because of the trial,

1 you're capturing more problems than would likely be in
2 the real world, but I don't know.
3 And then finally with retention, I'm just
4 curious whether that was truly clinically evaluated in
5 those several patients that at least had some report of
6 that.
7 MS. COHEN: Yeah. I just want to clarify
8 something that was mentioned because I may have just
9 misheard this, but perhaps other people did, too. If
10 the question was the label that was used in the self-
11 selection for men study, that was the old label with
12 the woman in the tent. So as a result of that, the
13 label was changed, you know, based on those results,
14 which were pretty good, but the label was further
15 changed as a result of the box, that and the other
16 research to have the woman with the narrow-waisted
17 silhouette. So, again, I may have just misheard that,
18 but I just wanted to clarify that.
19 DR. REIDENBERG: Okay.
20 Dr. Burnett, I don't think your questions
21 were answered yet.
22 DR. RAFFAELLI: No, that was for the previous

1 one. So for the CONTROL trial, I might defer to the
2 sponsor just to comment on how they populated their
3 groupings of adverse events that they monitored, be it
4 anticholinergic effects, disorientation and confusion,
5 that sort of thing. But I will say that overall both
6 the adverse events overall, the serious adverse events,
7 the discontinuations, everything was pretty consistent
8 with what we found in the postmarketing safety
9 databases. So, again, most people who discontinued,
10 discontinued due to application site reactions. Some
11 of them who reported anticholinergic effects and
12 discontinued, the majority of them who discontinued, it
13 was due to things like dizziness or dry mouth. These
14 were sort of the bigger anticholinergic effect items
15 that we monitored.
16 But, again, the preferred terms or the
17 adverse events that we look at when we look at safety
18 databases, they were pretty vast. I mean, the sponsor
19 sort of grouped together lots and lots of adverse
20 events that they then sort of kept under an umbrella of
21 disorientation, confusion, anticholinergic effects, and
22 that sort of thing. I don't know if you guys want to

1 speak to that a little bit more.
2 DR. HEMWALL: Yeah, it's a standard grouping
3 of specific adverse event terms that are condensed down
4 into groupings of overall symptom disorder terms that
5 gives more of an umbrella look. But I think that we
6 are entirely in agreement with Dr. Raffaelli in that
7 what was seen in CONTROL is entirely consistent with
8 the safety profile of the product that has been seen in
9 postmarketed use and in controlled studies, and
10 obviously it's not a placebo-controlled study, it's an
11 open-label study. There are no new trends seen by the
12 use in the CONTROL study.
13 DR. REIDENBERG: Thank you.
14 Dr. Hanno?
15 DR. HANNO: Thank you. I just have two brief
16 questions or a comment and a question for FDA. One is
17 there is kind of a disconnect or a validity question on
18 its face when 78.5 percent of thee patients who self-
19 selected for the drug were ineligible by the label, so
20 either something is wrong with the label or something
21 else is wrong, but that, on its face, sounds terrible.
22 And my second comment is, does the FDA have

1 any interest in looking at efficacy in the over-the-
2 counter compared to efficacy in the prescription not to
3 look at efficacy per se but to see whether the
4 populations self-select properly and whether it's the
5 same population taking the drug? Because I think that
6 would be a very important factor when you're deciding
7 whether something should go OTC.
8 Thank you.
9 DR. RAFFAELLI: I'll address the first part.
10 I might defer to my colleagues for the second.
11 As to the first part, yes, I agree, that the
12 number seems a bit scary, you know, that this product
13 would be out in the OTC realm and that almost 80
14 percent of people might have some label ineligibility.
15 If the committee wants to discuss items on the label
16 that they feel would help or deter people from using
17 the drug appropriately or inappropriately, that would
18 be welcome, we would love to hear some discussion
19 there.
20 As to the importance of it, I tried to make
21 the point at the end with my conclusions that, again,
22 we didn't see any significant delay diagnoses, we

1 didn't see any significant safety trends or safety
2 signals. A lot of these, quote/unquote, label
3 ineligibilities, I mean, they really span the gamut.
4 You know, somebody who reported a family history of
5 diabetes, it has been commented that we have a large
6 percentage of the population who has that. These
7 people would have been included in having a label
8 ineligibility. So we have to keep that in mind, that a
9 lot of the serious ones, the possible symptoms of UTI,
10 some of the other diabetes symptoms, be it excessive
11 hunger, thirst, that sort of thing, if people had true
12 urinary retention, which nobody did, that these are
13 things that we were able to capture and look at, and
14 that again there weren't any delayed diagnoses, there
15 weren't any really new findings over the course of the
16 trial except for the one user who was diagnosed with
17 diabetes, but it doesn't seem likely that she would
18 have had a delay in the diagnosis just because she was
19 using oxybutynin. I don't know if --
20 DR. HEMWALL: Yeah. It's one of these
21 situations that maybe falls under the heading of, "No
22 good deed goes unpunished," and I think it needs to be

1 made clear because not everyone in the room is familiar
2 with how these studies are done.
3 We showed very good self-selection and label
4 comprehension in the earlier studies, but the criticism
5 that always follows is, well, there is still 10 percent
6 of the people that didn't do proper self-selection or
7 didn't understand the label. So we designed a study
8 that permitted a whole range of people that might not
9 be exactly according to label to enter the study, and
10 so it shouldn't be characterized as poor self-
11 selection. It was not a self-selection study, because
12 if it was, we would have interviewed them and learned
13 that most of their decisions would have been mitigated.
14 But, rather, let's follow these people, let's see what
15 happens, and in this naturalistic setting, and set a
16 checkpoint, did they discontinue within the 2 weeks or
17 within a reasonable time after the 2 weeks if they
18 really do develop these other symptoms or don't respond
19 to the drug? And that was the endpoint that was looked
20 at.
21 And so we actually think that's a very
22 valuable and sort of an enriched look at the way people

1 might use the product in the marketplace, but we don't
2 believe that -- and I don't think in general that that
3 is a representative population that was in CONTROL, it
4 was more a population of people that just thought they
5 were in a clinical trial to use a product but not being
6 told that they had to make a decision based on their
7 own health concerns. That's what a self-selection
8 study does.
9 DR. REIDENBERG: Thank you.
10 Dr. Parker, I cut you off before when you
11 still have a third question. I promised you would get
12 a second chance.
13 DR. PARKER: Okay. So I'm back to the
14 elderly and the use of anticholinergics as baseline. So
15 could you sort of frame what we know about the use of
16 anticholinergics among the elderly as background noise,
17 and also specifically in the studies we've looked at,
18 what do we know about the cohort, people over 65 and
19 their baseline use of anticholinergics and the ability
20 to self-select this wouldn't be a good idea to take
21 this or that it might increase your risk of having an
22 adverse event? And do we have data that can help us

1 think about that? And what are the thoughts about
2 that?
3 DR. LEONARD-SEGAL: Okay. I'm going to try
4 to tackle two questions. First I'll take yours, Dr.
5 Parker, and then I'll take yours, Dr. Hanno, on the
6 efficacy.
7 I think that we don't have specific new data
8 on the anticholinergics for this application, but in
9 the context of what is OTC, I think that it's important
10 to recognize that we have a lot of antihistamines that
11 are strong anticholinergics that are over-the-counter
12 and have been over-the-counter for way before 1972, and
13 we do not see a lot of problems related to their use in
14 any particular population. So I think that that might
15 give a context within which to think about
16 anticholinergics at least.
17 Regarding efficacy, when we think about
18 bringing a product over-the-counter and we have
19 efficacy established for the population that we are
20 targeting, we generally don't revisit that efficacy for
21 the over-the-counter population. What we're concerned
22 about is whether or not they will use the product

1 properly so that they will derive the efficacy that we
2 know that the product is capable of providing.
3 The thing that's complicated about this --
4 and Dr. Reidenberg brought it up before when he also
5 talked about context -- is that in the prescription
6 setting, patient behavior is seldom assessed prior to
7 approval, and it is assumed that if a prescription is
8 given to a patient by a physician in what these days
9 could be a 5-minute or a 10-minute visit, that they
10 will use the product well, but we don't study it
11 generally.
12 In the OTC environment, we find ourselves
13 studying this behavior and, in fact, as Dr. Ganley and
14 I were just sidebaring about this, the standard is
15 probably higher for OTC because we are looking at the
16 behavior and we learn things that may or may not be so.
17 So we may not have known about the Rx, but we don't
18 have the reference to determine it.
19 As I sit here, I recall an advisory committee
20 meeting many years ago where we were looking at a
21 product for chronic use, and the data was presented
22 that, in fact, in the Rx setting people didn't use the

1 product, at least I think it was 50 percent of them
2 didn't use the product, for more than 6 months, and we
3 had similar data that was presented in the OTC setting,
4 but we would not have known this as a comparator if
5 someone had not looked at the Rx environment.
6 So I hope that that provides a context for
7 you.
8 Thank you.
9 DR. REIDENBERG: Dr. Gellad.
10 DR. GELLAD: Another clarifying question.
11 Again this is about the elderly and the anticholinergic
12 issue. Was there anything in any of the studies about
13 patients with dementia or the caregiver aspect here,
14 especially for over-the-counter medicines, whether
15 people are going to buy this to use for other people
16 and not themselves?
17 DR. LEONARD-SEGAL: All right, I don't see
18 anyone running up, so I'll try that one as well.
19 The over-the-counter marketplace does not
20 limit who uses the product. Often over-the-counter
21 products are brought home, and they could be used by
22 different members of the household and they could be

1 purchased by one member of the household for another
2 member of the household or for someone else. So this
3 is why our products are labeled and we provide the
4 information that one needs hopefully to use the product
5 properly, safely, and for the proper person to use the
6 product.
7 DR. RAFFAELLI: I would also just like to add
8 that these are things that obviously we would love to
9 hear discussion about this afternoon as far as our
10 warnings on the label for sleepiness, dizziness, blurry
11 vision, I don't know how much of a quagmire it gets
12 into, but drug interactions, these sort of things could
13 be discussed, and we would love to hear what the
14 committee has to say about, are these things that could
15 be labeled appropriately for safe use in the OTC
16 setting?
17 And just as one additional piece, I don't
18 know if I fully answered Dr. Burnett's question as far
19 as the urinary retention patients. All I can say is
20 from my review of the case report forms, subjects who
21 did see their doctors, there was one subject who had a
22 history of incomplete bladder emptying prior to

1 entering the study. That subject spoke with her doctor
2 because the incomplete bladder emptying continued. Her
3 doctor cleared her to continue use. Another subject
4 did report, quote/unquote, retention, and a lot of
5 these subjects sort of confused incomplete bladder
6 emptying with what you would consider true acute
7 urinary retention, and that subject was asked, advised,
8 to stop using the drug as per her doctor's
9 recommendation. But from my review of the case report
10 forms, there wasn't any clinical diagnosis of acute
11 urinary retention. No subjects had acute urinary
12 retention during the trial.
13 DR. FARBER: Perhaps somebody can answer this
14 for me. The diagnosis of overactive bladder syndrome,
15 basically it's a constellation of symptoms that conform
16 to a syndrome, and that syndrome is with the exclusion
17 of some other conditions. I would like to know if any
18 of the studies or the label addresses that and what
19 percentage of the women in either the label study or
20 the CONTROL study were actually diagnosed by their
21 physician as having overactive bladder as opposed to
22 something else.

1 DR. HEMWALL: We can provide that number for
2 the CONTROL study. I think we showed some of that data
3 when we showed that the people who were previously
4 diagnosed -- or were not diagnosed were far more
5 cautious in their use of the product than the ones who
6 were previously diagnosed.
7 MS. REPLOGLE: In the CONTROL study, 433 of
8 the users had been previously diagnosed with OAB; 265
9 did not have the diagnosis; and there were 29 that we
10 didn't have that data, whether or not they had been
11 diagnosed by their physician.
12 DR. FARBER: So the majority were actually
13 diagnosed?
14 DR. REIDENBERG: Dr. Koff's turn next,
15 please. And then we have to break for lunch. And then
16 we can continue afterwards.
17 DR. KOFF: Actually, my question is similar
18 to Dr. Farber. As a doctor who sees people with
19 overactive bladder, it really is a work of exclusion
20 that involves an exam and screen urine and a long talk
21 about their medical history and their voiding habits.
22 So how did we get to the point where the patients can

1 do that themselves now?
2 And the second comment or question, would you
3 consider having on the label, "This is a product for
4 people who have been diagnosed with overactive bladder
5 by their health care provider"?
6 DR. LEONARD-SEGAL: I'll take the second part
7 of that. The Durham-Humphrey Act is about self-
8 diagnosis. So there is one exception to that kind of
9 language that currently exists on one class of OTC
10 drugs, but that's from a long, long time ago, the
11 vaginal anti-fungal products, but generally we would
12 try to promote the idea that self-diagnosis is within
13 the OTC paradigm.
14 DR. REIDENBERG: Okay. We have another
15 minute or two before lunch.
16 Dr. Farber, I apologize for cutting you off.
17 You can follow up.
18 DR. FARBER: I just wanted to clarify, did
19 that mean that the majority of women in the CONTROL
20 study were the users who had been diagnosed by their
21 physician? Is that what you're saying?
22 DR. HEMWALL: That's right. And, in fact,

1 it's important to remember that a lot of these women
2 have been coping with the condition for months or years
3 without seeing a physician, and what we're trying to do
4 with the label is provide a bit of a diagnostic
5 approach by having the symptoms for at least 3 months
6 and having at least two of the symptoms. But what this
7 also does for the women who have been coping on their
8 own, it gives them a lot more information about to go
9 to their doctor where a full workup can occur.
10 Otherwise, they're still out there on their own, which
11 is what they're doing right now.
12 DR. REIDENBERG: Thank you.
13 We will now break for lunch. We will resume
14 precisely at 1:00 with the Open Public Hearing. And I
15 suggest anyone take their personal belongings they want
16 to take with them. And again to the panel members, we
17 don't discuss any of the subject of this meeting during
18 lunchtime. We'll resume at 1:00.
19 (Lunch break from 11:59 a.m. to 12:59 p.m.)
20 Open Public Hearing
21 DR. REIDENBERG: Everybody, welcome back. I
22 call our session to order.

1 Both the Food and Drug Administration and the
2 public believe in a transparent process for
3 information-gathering and decision-making. To ensure
4 such transparency at the Open Public Hearing session of
5 the advisory committee meeting, FDA believes that it is
6 important to understand the context of an individual's
7 presentation. For this reason, FDA encourages you, the
8 Open Public Hearing speaker, at the beginning of your
9 written or oral statement, to advise the committee of
10 any financial relationship that you may have with the
11 sponsor, its product, and, if known, its direct
12 competitors. For example, this financial information
13 may include the sponsor's payment of your travel,
14 lodging, or other expenses in connection with your
15 attendance at this meeting. Likewise, FDA encourages
16 you at the beginning of your statement to advise the
17 committee if you do not have any such financial
18 relationships. If you choose not to address this issue
19 of financial relationships at the beginning of your
20 statement, it will not preclude you from speaking.
21 The FDA and this committee place great
22 importance in the Open Public Hearing process. The

1 insights and comments provided can help the Agency and
2 this committee in their consideration of the issues
3 before them. That said, in many instances and for many
4 topics there will be a variety of opinions. One of our
5 goals today is for this Open Public Hearing to be
6 conducted in a fair and open way where every
7 participant is listened to carefully and treated with
8 dignity, courtesy, and respect. Therefore, please
9 speak only when recognized by the Chair.
10 I thank you for your cooperation to the
11 speakers. I will say that you have 5 minutes. And the
12 microphone is set to turn off at the end of 5 minutes.
13 For the members of the committee, if you have
14 very specific clarifying questions to ask a speaker,
15 let me know. Otherwise, we'll have the speakers go
16 through their presentations and at the end of that
17 time, we then have a committee discussion and you can
18 discuss or raise any questions that you want.
19 So with those ground rules, I would like to
20 invite our first speaker to come up.
21 DR. MULLER: Good afternoon. I'm Dr. Nancy
22 Muller, and I'm Executive Director of the National

1 Association for Continence. NAFC is a nonprofit whose
2 mission provides education and advocacy for those who
3 have bladder and bowel control problems, retention, and
4 pelvic organ prolapse. We're broadly supported
5 privately. Over 50,000 people visit our website
6 monthly.
7 I'm here representing patients, our
8 constituency. My travel expense is fully funded by
9 unrestricted revenues and paid for ourselves.
10 Recently, Merck became an industry council
11 member of NAFC and provided a research grant for our
12 national survey of women with mild to moderate
13 overactive bladder, or OAB. Similar studies since 2000
14 have been sponsored by grants to us from Pfizer, Lilly,
15 Kimberly-Clark, Watson, and Medtronic. I'm here in
16 support of giving Americans retail access to a safe
17 established drug for OAB.
18 About 17 percent of women and 16 percent of
19 men have OAB. This translates into an estimated 33 to
20 34 million Americans of which an estimated 12 million
21 have urge incontinence. In other words, about two-
22 thirds don't have urine loss accidents due to urgency.

1 Most can thus be classified as having mild to moderate
2 symptoms of urinary urgency and frequency even if a
3 large portion also leak urine associated with stress
4 urinary incontinence due to weakened pelvic floor
5 muscles, as many postmenopausal women do. In fact,
6 women are three to four times more likely than men to
7 actually leak urine for any reason, mostly due to
8 pregnancy and childbirth.
9 Our research in 2009 reveals that baby-
10 boomers to less likely to feel stigmatized or
11 embarrassed like earlier generations than they are
12 frustrated and annoyed with OAB symptoms. Despite the
13 number of prescription drugs available, one in four of
14 those who have never sought treatment explain that it's
15 because they don't really know much about options.
16 Frustration abounds among those in treatment as 28
17 percent complain that the options are too costly. One
18 in four stop because of unwanted side effects, such as
19 dry mouth, and worse, there are clear signs from our
20 research that the overworked family doctor isn't
21 engaging the female OAB patient, as only 19 percent of
22 those ever treated were consulted and advised in

1 behavioral strategies, such as bladder retaining.
2 Combination therapy, including toileting
3 habits, weight loss, diet, and Kegels, to control those
4 sudden urges has been demonstrated more effective than
5 medication alone. Noncompliant patients who quit in
6 less than 6 months of being prescribed a drug are
7 throwing money away for their drugs and doctor visits.
8 Patients remain discontent, as one-third of
9 all OAB respondents to our survey report
10 dissatisfaction with how they're managing their
11 symptoms. Even worse, according to our research,
12 patients are twice as likely to be juggling multiple
13 medications for other conditions like hypertension,
14 high cholesterol, and depression. They are two to
15 three times more likely to forego regular physical
16 exercise, worsening their problems with weight control,
17 and they're more likely to feel guilty about missing
18 precious occasions with family and friends compared to
19 those who don't have OAB symptoms.
20 Tomorrow's solution to today's soaring health
21 care costs is to engage the patient, respond to her
22 needs, and prepare her for directing her own wellness

1 and make the retail pharmacist part of that value
2 proposition. Let PharmDs counsel shoppers who need
3 facts and assurances; help them with the labeling.
4 Allow us, as health educators, to supply details on
5 behavioral strategies and the motivation to stick with
6 a plan, a woman's own health care plan, so she can
7 regain freedom to travel, sit through a movie, enjoy an
8 intimate moment, and to exercise and stay healthy.
9 Open an exciting new chapter in tomorrow's
10 health for women in this country, granting them greater
11 control over the answers they choose for themselves. I
12 encourage you to permit retail access to a safe and
13 proven drug for self-diagnosed symptoms of OAB with
14 over-the-counter approval of Oxytrol for Women.
15 Thank you very much.
16 DR. REIDENBERG: Thank you.
17 May we have speaker number 2, please?
18 MS. LAGRO: My name is Elizabeth LaGro,
19 Director of Communications, commenting on behalf of the
20 Simon Foundation for Continence about the Rx-to-OTC
21 switch of Oxytrol.
22 The Simon Foundation for Continence is a U.S.

1 nonprofit 501(c)3 organization devoted to
2 bringing the topic of incontinence out into the open,
3 removing the stigma surrounding it, and to providing
4 help and hope to people with incontinence, their
5 families, and the health professionals who provide
6 their care.
7 Begun in 1982, the Foundation is known
8 globally for its educational projects and tireless
9 efforts on behalf of people with loss of bladder and
10 bowel control. The Foundation receives revenues from
11 contributions, memberships and grants from foundations
12 and industry. My presence here today is independent of
13 any sponsor, and the Foundation has made my appearance
14 possible.
15 Over our 30 years, we have continually sought
16 to promote innovative and efficacious solutions to
17 widespread but largely underrecognized aspects of
18 incontinence. Overactive bladder is not only an
19 underrecognized problem with a far-reaching impact into
20 the life of its sufferer, but is underreported and
21 undertreated with the majority of women waiting about 7
22 years before seeking professional help, usually when

1 symptom severity is increasing and urinary leakage
2 begins to occur. During the years of waiting, OAB has
3 usually taken a tremendous toll on their lives.
4 Women with OAB cope by altering their daily
5 routines and restricting activities in order to remain
6 close to their bathroom. Listen to them and you will
7 hear, "I used to," all the time, "I used to go to
8 concerts, meet friends, for lunch, play golf, go on
9 walks with my husband, go out to dinner." Normal
10 activities stop when one must always take into account
11 how long a queue might be for a woman's bathroom or
12 when one must always calculate the time and distance to
13 the next available bathroom.
14 OAB symptoms restrict vacation travel,
15 accepting invitations to events, and participation in
16 loved activities, leading to isolation and depression.
17 OAB disturbs and disrupts sleep, it curbs sexual
18 activities and intimacy. Like other chronic illnesses,
19 OAB may result in anxiety, lowering of self-esteem,
20 self-blame, embarrassment, and shame.
21 There is an added dimension to this struggle
22 for younger women with OAB who may be employed outside

1 the home or have young children. The self-limiting
2 behavior that I just spoke about may strain marriages
3 to the breaking point and leave children puzzled as to
4 why their family can't go on hikes or outings like
5 others do. A young woman with OAB may bypass career
6 opportunities and avoid an intimate relationship with
7 her spouse or partner, further straining the family
8 unit.
9 We've been told by individuals with OAB that
10 they have avoided seeking a specialist's help whose
11 office might be at some distance from their home or to
12 participating in self-help groups because it means
13 risking being in a car or bus for too long without
14 assured access to a bathroom when they need it. The
15 fear of an incontinent episode in public and the stigma
16 associated with it is incapacitating. Whereas
17 conditions like cancer and AIDS have lost much of the
18 stigma surrounding them, incontinence has not.
19 The financial impact of OAB is enormous.
20 Personal costs of untreated OAB can include the use of
21 absorbent products and protective skin care products,
22 laundry and cleaning costs, and psychosocial costs.

1 A 2010 study published in the Journal of
2 Urology entitled, "Economic Costs of Overactive Bladder
3 in the United States," found that in 2007 the average
4 annual per capita costs of OAB were $1,925 with an
5 estimated national cost of $65.9 billion. Also needing
6 to be considered are the indirect costs, worker
7 productivity losses, and unemployment. This staggering
8 economic impact could be lowered if more effective and
9 safe treatments were available.
10 Currently OAB may be treated with multiple
11 modalities, but many women lack the knowledge on how to
12 seek help or that they should be seeking help.
13 We are committed through our programs,
14 publications, direct communications with patients, and
15 websites to provide education about OAB, promote a
16 dialogue about it, and all types of incontinence, and
17 to encourage them to take action and report their
18 symptoms to a health care provider.
19 While the Simon Foundation does not endorse
20 any product, device, or treatment modality, we believe
21 that every new addition to the marketplace that is safe
22 and effective should be made available to the millions

1 who could benefit from it. We believe that offering
2 women new alternatives such as an OTC treatment for OAB
3 will help make many take the first step to managing
4 their condition rather than simply coping with it.
5 Thank you.
6 DR. REIDENBERG: Thank you.
7 May we have speaker number 3, please?
8 MS. HELLER: My name is Linda Heller. I'm a
9 special education advocate, and I'm a woman with OAB.
10 First of all, thank you for allowing me to be
11 here to testify before you today. I very much
12 appreciate the opportunity. I also want to tell you
13 that although my travel expenses to attend this meeting
14 are paid for my Merck, the sponsor company, I have
15 never received any funds from Merck or any other
16 pharmaceutical companies.
17 I'm here to tell you about my experience with
18 overactive bladder and to explain how Oxytrol has
19 impacted me personally on my life. I've had overactive
20 bladder for as long as I can remember, from when I was
21 a very young child. I was always the one who needed to
22 run to the bathroom, and I was always told to hold it.

1 As I got older, I learned not to complain and just to
2 locate all the bathrooms wherever I was.
3 I have always worked in situations where I
4 have had to attend meetings with groups of people, and
5 I lived in dread that I would not be able to make it
6 through the meetings without having to get up and go to
7 the bathroom, or that I would start squirming or leak
8 into my underwear and through my clothing. After my
9 pregnancies, things became even worse. I started
10 wearing pads to avoid such situations, and I began to
11 really lose self-esteem. I felt like a baby in
12 diapers, peeing in my pants with no control over my
13 bladder. It was mortifying.
14 Finally, I spoke to my internist about my
15 problem during a regular physical exam, and she sent me
16 to a urologist, who recommended that I see a nurse
17 practitioner in his office for biofeedback, and she
18 started working with me on exercises. I had been told
19 after pregnancy to do my Kegle exercises but nobody had
20 explained to me how to do them correctly before. The
21 nurse practitioner guided me through, and I finally
22 began to understand.

1 She also recommended that in conjunction with
2 the exercises and biofeedback that I begin using the
3 Oxytrol patch. I started using it immediately and it
4 brought excellent results. I continued using pads, but
5 the pads I bought began to be smaller and smaller, and
6 I didn't need to change them so often. I was able to
7 sit through meetings without tension because I didn't
8 feel the need to pee all the time. I practiced my
9 exercises regularly in all settings, and the patch kept
10 me from having the urge to pee every 15 minutes. It
11 was a godsend.
12 At some point, I tried stopping the Oxytrol
13 to see if the exercises would work by themselves, but
14 the urgency started to return and the tension came
15 back. I found that I really needed the combination of
16 exercises and Oxytrol in order to function like a
17 normal human being.
18 As long as I continued to use the Oxytrol
19 regularly, I was okay. It took me a very long time to
20 trust in my new system to the point where I finally
21 went cold turkey and stopped using the pads. I was so
22 afraid of leaking from the years of negative

1 experiences that I needed my crutch. However, once I
2 got rid of the pads, I felt an enormous sense of
3 relief, as if a cloud had been lifted from my
4 shoulders. The Oxytrol helped me to become an adult on
5 a par with everyone around me.
6 I remain dry now since starting the Oxytrol.
7 I can now sit through meetings without squirming or
8 leaking. I can go to lunch or dinner with friends or
9 associates, and often I'm the one sitting at the table
10 while others excuse themselves to go to the restroom.
11 It's an exhilarating feeling for me, although I know
12 that sounds silly.
13 I could not have accomplished this without
14 Oxytrol. I would really like this product to be made
15 available to women who might not have the courage to
16 take the first step with their doctors because of the
17 shame associated but who are desperate to find a
18 solution and would be willing or eager to try something
19 to ease the suffering from overactive bladder if the
20 product were readily available over-the-counter.
21 I hope you will make that possible. Thank
22 you very much.

1 DR. REIDENBERG: Thank you.
2 May we have speaker number 4, please?
3 MS. RYAN: Hi. My name is Kate Ryan. I'm
4 with the National Women's Health Network. It's an
5 advocacy and membership-based organization that brings
6 the voices of women to regulatory and decision-making
7 bodies like this one. We are supported by our members
8 and don't take financial contributions from drug
9 companies, medical device manufacturers, insurance
10 companies, or any other entity with a financial stake
11 in women's health decision-making.
12 There is no doubt that both frequent
13 urination and urinary incontinence are real problems
14 for women and they want real solutions. Having to run
15 to the bathroom 10 times a day or change clothes
16 several times because you wet yourself is incredibly
17 disruptive to a woman's life and damaging to her
18 dignity. However, making Oxytrol available over-the-
19 counter will not meet the needs of women struggling
20 with these symptoms, and there is a significant
21 potential for misuse of this drug that will be
22 exacerbated without a prescription requirement.

1 The FDA requires a sponsor seeking OTC status
2 to demonstrate that women will be able to accurately
3 self-diagnose and self-select by reading and
4 understanding the proposed OTC label. However, as
5 stated in the FDA briefing document on the Oxytrol
6 submission, there is no specific symptom, physical
7 finding, or lab result to establish a diagnosis for
8 overactive bladder. In fact, the diagnosis is made by
9 excluding other causes of these symptoms, sometimes
10 very serious conditions.
11 Yet in the material submitted by the sponsor,
12 the research shows that people with symptoms of these
13 conditions, whether it's kidney disease or liver
14 disease or symptoms that might be caused by those
15 conditions frequently purchased Oxytrol demonstrating
16 that people without medical training are generally
17 unable or unlikely to be able to exclude serious
18 conditions without the help of a health provider. This
19 is problematic because it could lead women to
20 misdiagnosis of OAB and result in delayed treatment of
21 a serious condition, and it could also result in women
22 who don't necessarily have OAB using this drug and

1 experience potential side effects, some of which have
2 been discussed today.
3 Both the actual use and label comprehension
4 studies demonstrate that there is a significant
5 potential for misuse in an OTC setting that's been
6 talked about. The sponsor's actual use study, nearly
7 80 percent of women who bought the drug didn't meet the
8 eligibility criteria, and as discussed, there were a
9 range of reasons for this, but it ranged from issues
10 such as not having two or more of the symptoms for at
11 least 3 months or having things that were potentially
12 contraindications and still choosing to purchase this
13 drug.
14 We very much agreed with Dr. Hanno that
15 that's serious, that's a serious number, and as the
16 sponsor had said, actually your study is, well, that's
17 actual use, that's what we're likely to see if Oxytrol
18 is OTC. In the study, 80 percent was 839 women;
19 however, if this drug was available over-the-counter,
20 80 percent could be as many as hundreds of thousands of
21 women taking this drug that don't need it or shouldn't
22 be taking it.

1 We also agreed with Dr. Howard that patients
2 don't -- people buying in a retail setting don't always
3 read the label. It would be great if they did, but
4 that's just not necessarily always the case. And
5 having a health intermediary is important. The
6 decision to use a medication to treat OAB or use any
7 medication requires balancing risks and benefits. It's
8 one thing for women to make an informed decision to
9 expose herself to side effects of a drug; it's an
10 entirely different thing for women who don't have OAB
11 to be exposed unnecessarily or for women who have
12 another condition to go untreated.
13 We also wanted to address a concern that Dr.
14 Farber had raised, which is that a lit review conducted
15 by an expert in the field and cited by independent
16 leaders in medical care, such as the Mayo Clinic, found
17 the benefit of antimuscarinics, including oxybutynin,
18 over placebo is small, and significant peripheral
19 adverse events may limit drug tolerability. The lit
20 review concluded that available data show behavioral
21 methods can be at least as effective as drug therapy or
22 work best in conjunction with drug therapy.

1 And the sponsor's briefing document states
2 the availability of Oxytrol as an OTC product will not
3 present any greater risk than already being incurred by
4 women who self-manage OAB. While it's true that women
5 who self-manage rather than seek help for their OAB
6 wouldn't have underlying conditions diagnosed, it's
7 also true that the statement disregards the risk and
8 side effects that women who use this drug with a
9 prescription can talk about with their doctor.
10 The last thing I want to discuss is the
11 importance of these non-pharmaceutical solutions such
12 as lifestyle changes and behavioral therapies because
13 they are effective, they don't expose women to the
14 risks that come with drug treatment, and they do need a
15 learned intermediary, as the previous speaker had
16 addressed. You don't always know how to do a Kegel
17 exercise right. It is important to have that
18 interaction with a health provider.
19 And non-pharmaceutical solutions are
20 recommended by organizations such as the American
21 Urological Association as the first-line treatment for
22 women who struggle with these symptoms. Making this

1 drug available over-the-counter will decrease the
2 likelihood that women will seek help from a provider
3 and be informed about all of these different pieces of
4 treating OAB and OAB symptoms.
5 In conclusion, we don't believe the sponsor
6 has adequately demonstrated it can be safely and
7 appropriately used in an OTC setting and we really urge
8 the committee to recommend against switching this
9 product from prescription to OTC.
10 Thank you.
11 DR. REIDENBERG: Thank you.
12 May we have speaker number 5, please?
13 DR. VISCO: Hello. My name is Anthony Visco.
14 I am the President of the American Urogynecologic
15 Society. I have no conflicts of interest. I have
16 slides to summarize the written comments that we've
17 submitted. We appreciate the opportunity to comment on
18 Oxytrol's potential for going over-the-counter.
19 AUGS is a nonprofit organization that
20 represents over 1,500 members. It is the largest
21 professional organization for female public medicine
22 and reconstructive surgery, and it promotes the highest

1 quality patient care through a combination of
2 education, research, and advocacy.
3 Overactive bladder, or OAB, is highly
4 prevalent in the United States in both men and women.
5 The significant proportions -- the prevalence increases
6 with age, which has been discussed, about 30 percent in
7 women over 65. And while that's true, I think it's a
8 myth to consider that it's a normal part of aging, and
9 we recognize that it significantly and negatively
10 impacts quality of life.
11 So OAB symptoms include the range that we've
12 spoken about: urgency, urinary urgency, frequency,
13 nocturia, as well as urgency incontinence. The typical
14 evaluation would include ruling out urinary tract
15 infections, anatomic abnormalities, voiding
16 dysfunction, and bladder pain. And treatment options,
17 there are several, and some can be used separately,
18 some in combination, and that includes dietary and
19 fluid modifications, bladder retraining, pelvic floor
20 exercises, as well as pharmacologic therapy.
21 So our feeling is that Oxytrol is well
22 studied and has had documented efficacy and that the

1 safety is also well documented with generally low rates
2 of common side effects such as dry mouth, constipation,
3 somnolence, urinary tract infections, and visual
4 changes. There have been some cardiac events noted,
5 they're generally rare and they have also been reported
6 in the placebo groups in some of these trials.
7 The labeling concerns that we wanted to
8 address is, first of all, that while OAB symptoms often
9 will lend themselves to self-diagnosis, even an
10 experienced provider can sometimes have difficulty in
11 talking to patients and differentiating between stress
12 and urge.
13 So I think we would really want to look at
14 the stress incontinence and how that's described
15 because really anticholinergics are not indicated for
16 stress incontinence: leaking with coughing, laughing,
17 sneezing.
18 The twice weekly patch probably limits
19 significantly the risks of overdosing.
20 And clear labeling is probably reasonable to
21 both confirm reasonable expectations of the product,
22 warning for women of childbearing years, not just for

1 the risk to the fetus potentially but also because I
2 think pregnancy alone results in a lot of symptoms that
3 could be characterized as OAB to the consumers with
4 just the gravid uterus pushing down on the bladder.
5 Warning to discontinue if bothersome side
6 effects and also some other of the typical
7 contraindications to anticholinergic therapies such as
8 narrow-angle glaucoma and gastric retention.
9 Additional labeling considerations is to
10 consult a physician with sudden onset of pain,
11 difficulty voiding, blood in the urine, and even
12 abnormal vaginal bleeding we thought would be
13 important. And also that additional treatments exist
14 in refractory situations. We certainly don't want the
15 message that if Oxytrol is tried and it doesn't work
16 that the patient has no other alternatives because
17 there are other alternatives that are fairly effective.
18 And then another concern or consideration is
19 whether or not some information could be provided to
20 patients who wanted to track their symptoms to
21 objectively measure things like voided volume, voiding
22 frequencies, with bladder diaries.

1 So in summary, for transdermal oxybutynin, we
2 feel that the safety is well established, the potential
3 benefit outweighs the potential risks, though there are
4 some considerations in this area, that appropriate
5 labeling would be helpful and is recommended, and
6 patient education is needed for both trying to maximize
7 the accurate diagnosis of the condition as well as
8 regarding alternative options that exist.
9 Thank you for your attention.
10 DR. REIDENBERG: Thank you.
11 Since there are no clarifying questions on
12 the part of the panel, the Open Public Hearing meeting
13 at this meeting has now concluded and we will no longer
14 take comments from the audience. Questions to the
15 Committee/Committee Discussion
16 DR. REIDENBERG: The committee will now turn
17 its attention to address the task at hand: the careful
18 consideration of the data before the committee, as well
19 as the public comments.
20 So we will now proceed to the questions to
21 the committee and the panel discussions. I would like
22 to remind the public observers that while the meeting

1 is open for public observation, public attendees may
2 not participate, at the specific request of the panel.
3 Now, one issue that has come up is the issue
4 of the apparent discordance between the number of
5 subjects appropriately self-selecting in the self-
6 selection trial and the number of subjects presumably
7 inappropriately selecting to purchase in the actual use
8 study, and I wonder if we can get that clarified a bit,
9 so that for this, I would like to ask Dr. Hemwall if he
10 will comment.
11 DR. HEMWALL: I would like slide 430, please.
12 Thank you, Dr. Reidenberg. It's easy to see
13 how this can get confused, and so I thought at first we
14 would go with just kind of a brief review of the types
15 of studies that we did, and Mr. Neumann went through
16 these earlier. And I think very quickly the label
17 comprehension and self-selection studies we all agree
18 on, most can agree, that they showed good results,
19 point estimate are lower bound, and that we're
20 essentially in agreement with what Ms. Cohen reported
21 from the FDA side as well.
22 What's confounding people I think is the

1 actual use study where we want to observe the product
2 use and discontinuation according to OTC labeling. And
3 as I mentioned earlier, even though we were able to
4 achieve these good scores in the label comprehension
5 and self-selection studies, there could be a lingering
6 doubt that that smaller subset that didn't quite
7 understand the label or didn't self-select
8 appropriately would be a group that would actually end
9 up using the product.
10 So if I could go back one slide in the core,
11 30, or 29, yeah.
12 So we've seen through what we call our self-
13 managing labeling safeguards that the label is well
14 understood and guides appropriate self-selection. And
15 the question has always been, well, what happens,
16 though, in the real world when people may not read the
17 label as carefully or otherwise be marginally not
18 appropriate according to label, like they have a family
19 history of diabetes, but they don't really have
20 diabetes and they do have OAB?
21 So we set up this study to actually allow
22 people to participate, purchase the product, who might

1 not be according to the label, and that's why you see a
2 high number of individuals that on examination, if you
3 go through each and every element of the label, there
4 will be something that they're not exactly according to
5 label on, and that's by design, and that's to allow FDA
6 and the panel to see what would happen if people who
7 weren't quite according to label actually used the
8 product.
9 And so it sounds like that there was poor
10 self-selection in the actual use study, but it really
11 wasn't designed to examine self-selection. And when we
12 examine self-selection, what we do is we look and we
13 ask the patient after they have made their decision
14 about why they made the decision, and we don't go on to
15 an actual use phase, we generally separate the self-
16 selection so we can interview them, and by doing so, we
17 bias their actual use, so that's why we don't do that.
18 So the results of CONTROL then showed that
19 even with this sort of more open-ended enrollment, that
20 with all those seemingly possibly inappropriate users,
21 that they did in fact stop, discontinue, or did not
22 really end up having the condition that the label

1 warned against, and that was defined by the primary
2 endpoint that was achieved, and then many, many
3 subanalyses that also looked at other elements of use,
4 how many used a patch for longer than 4 days, used more
5 than one patch, or how long it took them to actually
6 stop if the product wasn't working for them and they
7 wanted to give it a little more time. And you saw that
8 the people that were previously diagnosed with OAB or a
9 little bit more experienced with OAB tried the product
10 for longer than the people who did not have a
11 diagnosis, they were much more conservative and stopped
12 earlier.
13 And if I'm not being clear, I'm really open
14 to more questions in that regard.
15 DR. REIDENBERG: All right. Thank you.
16 Would anyone from the FDA care to comment on
17 that? I'm trying to give time to each side here.
18 DR. GANLEY: Ed, can you just clarify then --
19 and this question came up before, did the people
20 enrolling in this study, did they actually read the
21 label then to self-exclude themselves?
22 DR. HEMWALL: They came to the study site

1 thinking they were going to be enrolled in a study to
2 study a product on OAB, and they were given the product
3 and asked if they wanted to purchase the product, but
4 they were not put through the normal steps that a self-
5 selection study would be. So some may have been more
6 careful than others, but it was a fairly perfunctory
7 look at the label.
8 What we did want them to do is read the label
9 and use it according to the label when they got home,
10 and that's what we saw.
11 DR. REIDENBERG: Thank you.
12 Now, we have all been given the opportunity
13 to see the actual box with the label. We have to
14 return this, we can't keep it with us.
15 (Laughter.)
16 DR. REIDENBERG: So I would like everybody,
17 before you leave today, to bring it up here on the
18 front table so that these can be collected and
19 returned.
20 Now, I would like to start our discussion. We
21 will have one vote today. I will read the question we
22 are asked to vote on.

1 "Does the totality of the data support that
2 consumers can appropriately self-select to use the
3 oxybutynin transdermal system in an over-the-counter
4 setting? In your answer, please discuss how the study
5 participants in the actual use study who had
6 ineligibilities should be viewed bearing in mind the
7 safety data from the actual use study."
8 Now, I would welcome comments, discussions,
9 questions. I'll ask Minh to record the people, and I
10 will call on you in order as she sees them.
11 Dr. Farber.
12 DR. FARBER: So basically I think what women
13 are being asked to do in the use of this product is to
14 basically self-diagnose. The definition of overactive
15 bladder syndrome is one in which there are a number of
16 symptoms that are compatible with a particular
17 syndrome, and that syndrome has had other conditions
18 excluded. There are warnings granted on the label that
19 indicate that if you think you have these particular
20 syndromes or other illnesses, that you should consult
21 your doctor instead, but we're asking women to be able
22 to think whether they have any of those other illnesses

1 or not.

2 If one looks at an analogous situation, there

3 is something called situational awareness that occurs

4 in other individuals like fighter pilots and astronauts

5 and actually probably occurs in physicians as well

6 where we have sort of the expertise and training over

7 the years to be able to have a gestalt of a situation

8 where we think that the patient has one particular

9 diagnosis or not, and we use probabilistic reasoning to

10 assess them in order of importance. I don't think that

11 women would be able to do that. I would feel more

12 comfortable, and I understand we can't do this, but I

13 would feel more comfortable if there was something on

14 the label that said, "If you've been diagnosed by your

15 physician with overactive bladder syndrome, here is a

16 product over-the-counter." That I think I could live

17 with. It would also allow women to see their physician

18 and start with some behavioral modification and

19 physiologic attempts to control the symptoms, which

20 should be the first-line treatment, we all agree on

21 that.

22 I think because of those things, I think at

1 this point I have concerns about allowing this over-
2 the-counter.
3 DR. REIDENBERG: Thank you.
4 Dr. Gellad?
5 DR. GELLAD: I guess I'll just give my
6 viewpoint as well, that I think for me the real
7 question, the real issue here, is that there are
8 treatments available for this condition. So the
9 question for me is: Is over-the-counter use really
10 going to improve access to treatment? And my opinion
11 is sensitive to the real burden this has on many women,
12 but I guess my feeling is I'm not convinced that this
13 is going to increase access as much as has been said. I
14 think there are several reasons why. The first is
15 cost, which was mentioned by one of the public speakers
16 as being a barrier for many people, and these are going
17 to be expensive drugs, and you could see from the
18 CONTROL trial that cost was a factor. So whether or
19 not it increases access, I'm just not sure.
20 So the question is: Do the potential
21 benefits outweigh the risks, assuming that it does
22 increase access? And I think the risks are higher than

1 we're thinking. There are drug-drug interactions,
2 there are effects on cognition. We're adding yet
3 another anticholinergic drug to the over-the-counter
4 regimen, of which there are many. And so I think there
5 are many risks.
6 And I think the benefits, even though we're
7 going to say this is efficacious, I think the efficacy
8 of these drugs is low, we just have to be honest. This
9 is not the cure to overactive bladder, this is part of
10 the treatment, and I think the efficacy is low, and
11 there is a risk that people are not going to engage in
12 other treatments that they need.
13 So I think those are the questions that I
14 have related to the over-the-counter use of this drug.
15 DR. REIDENBERG: Somebody else?
16 Oh, sure. Dr. Moffitt?
17 DR. MOFFITT: I have concern with the
18 elderly, 65 and older I guess is what we're terming
19 them, although I'm in that age bracket and don't
20 consider myself elderly.
21 My concern is if this is an anticholinergic
22 drug -- right? -- or has those adverse effects, are the

1 consumers out there who are in that category or even
2 younger going to know that this drug is going to
3 counteract with another drug that they're taking that
4 may be an OTC and is going to increase those adverse
5 events? I mean, how do I know personally what other
6 drugs falls into this line that would have an adverse
7 event against it, that they're not going to mix, these
8 two drugs that I'm taking aren't going to mix? How do
9 I know as a consumer that this is safe for me to take?
10 And that would be my concern, especially with people 65
11 and older, without the aid of a pharmacist or a
12 physician helping them in making that decision whether
13 or not this is actually going to be safe in the long
14 run. Are there going to be too many adverse effects
15 for them to handle at their age?
16 DR. REIDENBERG: Thank you.
17 Well, let me give some different sort of
18 comments. Firstly with respect to the anticholinergic
19 issue, I agree completely. I think we have a real
20 problem with the class of drugs that have
21 anticholinergic effects whether as the intended or
22 unintended effects that we ought to address

1 irrespective of what we do or what we recommend with
2 this particular one.
3 With respect to the issue of seeing a doctor
4 first, what we've heard is that women with this
5 condition will go months, years, without seeing a
6 doctor but self-managing it, so whether adding an over-
7 the-counter option would influence their seeing a
8 doctor is something that's hard for me to predict. One
9 could say it would delay it, one could also say if this
10 also doesn't work, maybe that will be the motivation to
11 see a doctor depending on what the educational program
12 is and what's present.
13 With respect to reading labels, I think there
14 are studies that show that when people buy over-the-
15 counter drugs they don't read labels, but my anecdotal
16 impressions are that when patients don't get the
17 desired effect from the over-the-counter drug, they'll
18 read the label, they'll read whatever they can get
19 their hands on, and then they will seek some
20 professional advice.
21 And then the other thing that concerned me
22 with the studies was that so many of the violations

1 were medically not meaningful. In the labeling of the
2 prescription drug there is a beautiful chart showing
3 that you maintain a level for 5 days, it goes down a
4 bit, but the level is still there. And so why not
5 terminating it after 4 becomes a violation may well be
6 an arbitrary violation, but I don't see that it has any
7 clinical or medical meaning.
8 We've already talked about the issue of
9 family history of diabetes and the idea that, well, if
10 somebody doesn't stop after 2 weeks of no benefit, it's
11 a violation and they shouldn't go on to the third,
12 again that seems awfully arbitrary to me. So that I
13 find that a lot of the issues that we have raised with
14 respect to these particular studies are relevant to the
15 studies, but I have difficulty determining that they
16 actually have relevance to real world use. I only wish
17 that we had some data on what's actually going on now
18 in the prescription world to see how different these
19 projections for over-the-counter use would be to how
20 many of these same so-called violations are occurring
21 now and whether this would be worse or not.
22 So those are my thoughts at the present time.

1 And I'm delighted to call on Dr. Howards for his
2 comments.
3 DR. HOWARDS: I am conflicted. I strongly
4 believe in self-treatment and allowing patients to take
5 an active role in their health care. It has
6 dramatically changed the long-term outcomes for
7 diabetic patients with much less retinopathy since
8 people started taking care of themselves. I also
9 realize that dermal oxybutynin, transdermal oxybutynin,
10 has a significantly lower incidence of side effects
11 than the oral drug.
12 However, I have several concerns. First, I
13 think many men will take this drug without prior
14 evaluation, which they need, by a urologist. Second,
15 no urologist I know would prescribe oxybutynin without
16 a urinalysis and a post-void residual.
17 Third, I worry that those that would be
18 helped by behavioral therapy will not have that option.
19 Fourth, I'm very worried about the elderly-
20 related effects on mental function, although I
21 understand there is no real data on this particular
22 preparation, so it may be perfectly okay, but we don't

1 know that. The AUA, that's the American Urologic
2 Association, and the Canadian guidelines both say that
3 anticholinergics should be used with caution in the
4 elderly, and the Beer's criteria of the Geriatric
5 Society says they should not be used in the elderly.
6 A concern that hasn't been raised but is a
7 concern of mine is that carcinoma in situ of the
8 bladder, although uncommon, typically presents with
9 urgency and frequency without hematuria, and it's a
10 very serious disease for which the diagnosis and
11 treatment could be delayed. Indeed, on the American
12 Board of Urology exam, it's not unusual to present to
13 the candidates a patient with urgency and frequency and
14 downgrade them severely if they don't check for
15 carcinoma in situ. Of course, they would do a
16 urinalysis and they would probably see some blood, but
17 in the over-the-counter setting, that would not be
18 done.
19 I also think that missed stress incontinence,
20 although clearly not a health risk at all, could delay
21 treatment and in some cases prevent seeking medical
22 care, which, as the sponsor has pointed out, affects

1 the quality of life.
2 Finally, I fully understand after today that
3 the FDA -- well, I always understood -- the FDA cannot
4 force people to read labels, but I now understand that
5 the law does not address the label issue basically. But
6 for the reasons I just articulated, I think for some
7 individuals this could create serious problems.
8 Finally, I have no comment at this time on
9 the question the Chair asked us to address.
10 DR. REIDENBERG: Dr. Parker?
11 DR. PARKER: So ditto. That was very well
12 said. Thank you very much. That included several of
13 the thoughts I had, but I wanted to add to that list
14 just a couple of other things that we haven't
15 discussed.
16 There is definitely a public perception that
17 when something is available over-the-counter, right or
18 wrong, that it is probably safer because it's over-the-
19 counter and there is not a need for a learned
20 intermediary, so safety is obviously a huge priority
21 because in making it available, we have said that it is
22 safe.

1 So around that, I have a couple of thoughts.
2 One is the term itself, "overactive bladder." I don't
3 know what the general public thinks an overactive
4 bladder is. I can envision a lot of things, some of
5 which are kind of funny, and I'm sure we could find out
6 that overactive bladder has multiple definitions on the
7 ground to different types of people, but one of them
8 might relate to even though it says for women, children
9 who have enuresis and have bedwetting. And so I think
10 when we make the product available and it's for a term
11 that may have different meaning to different people, we
12 have to think about that, because once it's available
13 over-the-counter, anybody can buy it. That did not
14 come up in the studies, but I would raise the question
15 of if this is available over-the-counter, whether or
16 not it would be picked up and used for enuresis, for
17 bedwetting, for what some people say, "My child has an
18 overactive bladder," and whether or not that is a
19 concern from a safety standpoint given the dose and the
20 ages of children who have enuresis, and the
21 accessibility of going online and seeing though it may
22 not be the main or the number one drug of choice for

1 treating that, there are certainly studies available
2 online that people can access that do refer to this
3 chemical compound in treatment of enuresis. So I think
4 just from a safety standpoint I raise that just for
5 consideration. I don't know the answer, but I think
6 it's worth bringing up.
7 And then the other one is I don't see
8 anything on here about PRN use, so I'm assuming that
9 the marketing of this would be if you have this, you
10 take it, you take it forever, you take it and you keep
11 taking it, if you see that it's working. But I would
12 wonder about what it means to have PRN use when there
13 is something that's over-the-counter and also whether
14 or not, though we do have data on other anticholinergic
15 drugs that have been available for a long time, whether
16 or not there are any safety concerns that relate to it
17 that might be relevant, particularly the use of
18 multiple drugs with anticholinergic pharmacologic
19 impact, people who are on SSRIs and other classes and
20 also taking diphenhydramine and other things, and
21 whether or not there can be a cumulative impact from a
22 safety standpoint.

1 So though on the surface it feels pretty
2 good, I start asking some other questions when I think
3 about broad implications from a population standpoint
4 of making it, and again it boils down to a
5 risk/benefit, and I have questions.
6 DR. REIDENBERG: Thank you.
7 Dr. Hanno.
8 DR. HANNO: Thank you. I have some of the
9 same concerns that been expressed here this afternoon.
10 I think what we're looking at is: What is
11 the marginal benefit of making this over-the-counter?
12 It's not as if the drug is not available or a
13 whole variety of drugs like this. So it's: What's the
14 marginal benefit of making it OTC versus the risks of
15 that? And I think that's the question that we really
16 have to look at. I'm still concerned. I don't think
17 that we have shown that patients can appropriately
18 self-select. We haven't shown that they can't. But
19 the 80 percent number sticks in my mind, and I think
20 it's still a problem.
21 And the fact that 60 percent of the patients
22 on the CONTROL study had already been diagnosed with

1 overactive bladder by their physician means that we're
2 looking at a very small number of patients who hadn't
3 already been diagnosed.
4 So to draw a lot of conclusions from those
5 260 patients is kind of a leap of faith. The risk of
6 misdiagnosis, and like Dr. Howards points out, I had on
7 my list carcinoma in situ. It's small, but it's real,
8 and when you multiply this by millions and millions of
9 patients -- people taking this, it's probably not
10 insignificant.
11 And the drug-drug interaction point is very
12 important because so many people are on so many
13 prescription drugs and over-the-counter drugs that
14 could interact with this.
15 So I'm just not sure that this is a great
16 addition to the over-the-counter, and I'm not sure that
17 the benefits would outweigh the risks at this point.
18 Those are the thoughts going through my mind, a little
19 bit different than when I first walked into the
20 meeting.
21 DR. REIDENBERG: Thank you.
22 Dr. Rogers?

1 DR. ROGERS: My concern is for those women
2 who don't generally go to the doctor or wait until the
3 last minute or even though they have urinary
4 incontinence, they may think that's just part of the
5 process of aging, and so they are going to go and get
6 the medicine, and really the diagnosis should be
7 diabetes, and especially amongst the Latino population,
8 and if they think that this is going to take care of
9 their urinary problems when it really is something else
10 that they have, that really concerns me that that would
11 be available.
12 Secondly, I'm not sure that in the samples
13 that they showed us, I couldn't tell how many people,
14 how many women, were from a minority population in
15 terms of Latinos in particular, and it's worrisome to
16 me that -- and I mentioned and I thought about this
17 when I saw this, I could see one of the older children
18 going up and saying, "Look, Mom, you have this problem,
19 take this," and really their problem is diabetes or
20 some other disease.
21 DR. REIDENBERG: Thank you.
22 Dr. Gellad?

1 DR. GELLAD: This is a question for the FDA.
2 I already mentioned my thoughts. But I guess
3 overactive bladder, by what we read and what we know,
4 is defined as a disease and a condition based on the
5 exclusion of other conditions, and that's impossible to
6 do in the outpatient setting. So in effect this is
7 treating a symptom, it's not really treating a
8 condition.
9 So I think that's still what's sticking in my
10 craw a little bit, is that there is no way to treat
11 overactive bladder without -- to diagnose it without
12 ruling out these other conditions, so what are we
13 treating with this medication? And so I guess I want
14 to hear a little bit from the FDA.
15 DR. LEONARD-SEGAL: Okay, well, I'll start
16 and maybe others will chime in. I'm trying to think of
17 any products that are over-the-counter right now that
18 don't treat symptoms, they all treat symptoms, with the
19 exception of the vaginal yeast infection products
20 perhaps, which actually cure an infection, I can't
21 remember what that label looks like specifically as we
22 speak, but I'm sure that there are symptoms that are

1 listed on that label as well. And all of our products
2 that treat symptoms generally have language on them
3 that say if your symptoms persist beyond this period of
4 time, stop use and do this. So this is a standard OTC
5 paradigm in terms of relief.
6 There isn't any symptom that we treat that
7 couldn't be caused by something terrible, even
8 headaches, which are very, very common and almost are
9 never caused by a brain tumor, or sometimes caused by a
10 brain tumor, sometimes they're caused by meningitis,
11 and we've got products out there that treat headache
12 and fever, but they say if your fever goes on for more
13 than 3 days or your headache persists beyond this
14 period of time, see a doctor, stop use, see a doctor.
15 So this is, I think, a dilemma that we always
16 face when we consider self-treatment and self-care and
17 where we're going to do good and where we won't do
18 good. I think that we need to be considering when we -
19 - I mean, this is a discussion that we've had
20 internally over the years as we've been considering the
21 product here in different stages of development, what
22 kind of a delay in diagnosis is significant in terms of

1 a clinical impact? And I think that OTC labeling has
2 basically said that if you have a headache for 10 days
3 and it goes on longer than that, maybe you need to get
4 some assistance with that. So I guess that we've
5 decided that if you have a brain tumor, you generally
6 can wait up to 10 days if the OTC analgesic is helping.
7 I don't know what the threshold is from the
8 clinical perspective when one thinks about something
9 like diabetes or when one thinks about carcinoma in
10 situ of the bladder. I think it would be helpful for
11 us to hear from the perspective of the urologists and
12 the internists at the table what those consequences
13 might be from your perspective and whether you think
14 that this product would mask those symptoms such that
15 people would go on taking it for a really long time and
16 think that they are in fact getting better because I
17 think that most of what we've seen is that if people
18 use a product and it doesn't help them, they stop
19 taking it, that generally happens, especially when
20 there are side effects involved.
21 So I think that that would be an interesting
22 discussion for us to hear.

1 Anybody else want to chime in?
2 DR. RAFFAELLI: Just also I will add to that
3 and just say that was part of our discussion with the
4 sponsor as far our safety concern about how long we
5 should let people go on with this, and this became one
6 of the misuse rate endpoints that we looked at where we
7 looked at people who used it beyond 2 weeks. Most of
8 the people, when they were interviewed at week 3, week
9 7, week 12, it appeared like a lot of the people were
10 having improvement in their symptoms, so the idea that
11 people who use the product for 2 weeks maybe decided,
12 "This is working for me," or, "Maybe it's not and I
13 need to just use it for a little bit longer," but then
14 a lot of those people reported improvement at week 7.
15 I'm thinking about a 60 percent, 70 percent number of
16 people who reported improvement at those time points as
17 the duration of the trial went on. And again, as Dr.
18 Leonard-Segal commented, people who don't have
19 improvement, they're going to stop using it and they're
20 either going to try to use something else, maybe
21 they'll pursue behavioral therapies or maybe they will
22 finally see their doctor and get the treatment that

1 they need or the diagnosis that they need. But we
2 found that that 2-week time window was what seemed
3 appropriate to make sure that we are protecting the
4 safe use of the product.
5 DR. REIDENBERG: Dr. Howards?
6 DR. HOWARDS: I don't want to overstate this
7 because carcinoma in situ is an uncommon disease.
8 However, you might get relief of symptoms with an
9 anticholinergic if you had urgency and frequency from
10 carcinoma in situ. It is not necessarily true that it
11 wouldn't be at all effective, and a delay of 2 weeks in
12 diagnosis is trivial, but a long-term delay is very
13 serious for this particular disease. Again, it's a
14 rare disease, so I don't know if it's appropriate to
15 even bring this up, but it occurred to me, so I brought
16 it up.
17 DR. REIDENBERG: Let me comment that I think
18 it is quite appropriate to bring up anything that's on
19 anybody's mind relevant to the topic, so that, as the
20 Chair, I will say, yes, it is appropriate to bring it
21 up.
22 Dr. Farber.

1 DR. FARBER: So my concern is that there were
2 a few specific diseases that were listed and that were
3 looked for as to the use study, but I think I can list
4 several other diseases that are uncommon but can
5 present this way that could be masked by the use of
6 oxybutynin for a prolonged period of time and that
7 would be disastrous if they were missed. For example,
8 right frontal lobe brain tumor can present this way,
9 can be masked to some degree by oxybutynin, can
10 progress obviously.
11 I'm torn because of the fact that these are
12 uncommon, and are we saying either we're going to allow
13 this to be over-the-counter and say to those women,
14 "Well, too bad," or are we going to say we're not going
15 to allow this over-the-counter because we have concerns
16 about these women who could have something else and
17 then say a lot of women might not get that benefit?
18 But the other thing I'm thinking of is the
19 whole issue of alternative treatments and actual
20 diagnosis. And I think that basically the mix-up is
21 the fact that basically we're talking about, as it
22 says, this is for women with overactive bladder, and

1 the only way really of diagnosing overactive bladder is
2 in a physician's office, and that's some of the concern
3 I have. I don't know how women can self-diagnose other
4 than having symptoms compatible with it, which are
5 compatible with a number of other diagnoses.
6 DR. REIDENBERG: As I think about it, I
7 continue to be concerned about additive anticholinergic
8 effect, and my concern there is largely in the elderly
9 both because they're more susceptible and secondly
10 because they are more likely to be taking other
11 medicines with anticholinergic effect.
12 I'll ask a question of the urologists. My
13 impression is that some of these other serious but
14 uncommon diseases that we're concerned about are also
15 more frequent in the elderly than in the young so that
16 I wonder if we were to urge an upper age limitation to
17 deal with the problem of anticholinergic delirium and
18 the increasing prevalence of these other diseases,
19 whether having it available for the younger women would
20 be better because, again, as people go for years
21 without seeing a doctor, then I question whether adding
22 this would delay diagnosis of anything much more that

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1 needs to be diagnosed early or whether on
2 epidemiological grounds an upper age limit will deal
3 with most of the problems that we're concerned about.
4 DR. LEONARD-SEGAL: Dr. Reidenberg, if I
5 could just -- we've been chatting over here about the
6 fact that a lot of OTC labels contain drug
7 interactions. One thing that we've been talking about
8 internally is which ones maybe would go on this product
9 label. We have not sorted that through, and I think
10 that we would be interested if you were contemplating
11 that, what recommendations you might make and whether
12 you might want to see specific classes or whether you
13 would like to see a consumer information leaflet like
14 which is the equivalent for our prescription
15 colleagues, the patient package insert for an OTC
16 product, whether you would like to see something along
17 those lines. We have many P450 products that are
18 currently approved over-the- counter, probably the
19 prototype would be cimetidine, but there are many
20 others.
21 DR. REIDENBERG: Thank you.
22 Dr. Burnett.

1 DR. BURNETT: I don't know if I have anything
2 terribly profound to offer at the moment, but I can see
3 all sides of this, and I think I'm conflicted as well
4 to try and synthesize all this because I can see both
5 sides of this.
6 Let me just kind of run through some of my
7 thoughts. I think that on one hand, positives, this
8 offers an option that doesn't preclude other options,
9 so it's an option, it's optional, and so consequently
10 in some respects just that thought suggests that for
11 those who might have the opportunity to use this, this
12 may be something that still is for them, and that
13 doesn't preclude other options.
14 I think there has been, at least well-
15 demonstrated today I think by the sponsor with a very
16 nice presentation, and I congratulate them, a
17 demonstration of safety, and I do concur that there is
18 this number that seems very concerning with regard to
19 how individuals select using it, but in the end, did
20 they still make decisions to stop it when it was
21 appropriate? It looks like it's largely so. And in
22 the final outcomes, what were the complications?

1 Yes, I think there is always the worry here
2 that there could be a misdiagnosis. For those patients
3 who have carcinoma in situ, yeah, we fear that, as
4 urologists. The issue here, I guess, is that patient
5 who has those kind of symptoms, whether use of this
6 medication would change that patient's outcome if they
7 were not inclined to go to the doctor anyway. If they
8 were going to have burning symptoms and they were still
9 never going to see a physician, would this just be a
10 matter of just a delay for some or change the eventual
11 outcome in those who otherwise would never have gone to
12 see a physician anyway with the extent of the burning
13 symptoms that might be consistent with an insidious
14 bladder tumor? So I think that's kind of an unknown.
15 These are things we're certainly grappling with.
16 I think we have had concerns with the actual
17 study, on the downside, with regard to elderly and
18 anticholinergics. The proportion of individuals who
19 have been already seen by a physician and then
20 diagnosed with overactive bladder, those who already
21 have primary physicians and perhaps had the opportunity
22 to follow through on some of their symptoms, and I

1 think the actual use study does have some limitations.
2 So again I'm conflicted, the dilemma here,
3 issues on both sides, and I think it comes down to here
4 whether we think there are enough safety concerns and
5 unknowns that we make a decision just because of that
6 that we just can't move forward or whether we still
7 think this has some potential benefit, and I'm still
8 wrestling with that in my own mind.
9 I do believe that educational campaign is
10 key, and I think the sponsor should be congratulated to
11 consider that and to develop that. So I think that's
12 certainly very purposeful. As to whether another
13 actual use study could be done with select populations
14 65 years and older, I think that's also an idea. All
15 these things are expensive, though, and take time, so a
16 challenge with all of that.
17 So at this moment I'm still a little bit
18 conflicted, but these are some of my thoughts.
19 DR. REIDENBERG: Thank you.
20 Dr. Gellad?
21 DR. GELLAD: Just in response to some
22 comments about the label. I do actually like the box a

1 lot. I think what they've done is great. I think the
2 "For Women," it's large, it's pink. I mean, I
3 certainly wouldn't buy it myself --
4 (Laughter.)
5 DR. GELLAD: -- but I may not be the normal
6 consumer.
7 But I think there are a couple things -- and
8 I mentioned these before -- about the label. The first
9 is the issue of asking a doctor before use if you have
10 a family history of diabetes, which again I'm not sure
11 -- I know you all have been studying it for a long
12 time, but there doesn't seem to me to be any reason why
13 anyone would need to ask me first unless they're having
14 symptoms.
15 The other is a history of kidney stones. If
16 they're not currently having the symptoms of kidney
17 stones, I'm not sure whether that is required, only
18 because there is a lot on here, and so if you really
19 want people to understand this, there is just a lot on
20 here.
21 The other parts were about asking a doctor or
22 pharmacist before use if you're taking a prescription

1 medication for overactive bladder. Shouldn't that be a
2 contraindication rather than asking them? I mean, I
3 don't think people, the -- I've never put people on two
4 anticholinergics for overactive bladder. And I didn't
5 quite get the issue about taking a diuretic, why that
6 would require asking a doctor.
7 But I guess my overall impression is I think
8 if there were less on the label and you made it
9 absolutely clear that this is one of many treatments
10 for overactive bladder, this is not the only treatment,
11 if your symptoms do not go away, you really should talk
12 to a doctor, making those more prominent, I think that
13 might allay at least the concerns that I have.
14 DR. REIDENBERG: Thank you.
15 Dr. Koff?
16 DR. KOFF: A couple things I think, as a
17 urologist, I mean, carcinoma in situ is rare, but
18 bladder cancer is not that rare, I mean, it's one of
19 the most common cancers, and, as a urologist, I feel
20 much better giving people medications for overactive
21 bladder, just being able to screen their urine for
22 microhematuria. So that's the one thought.

1 I mean, I don't really have an inherent issue
2 with making this over-the-counter, but I have an issue
3 with self-diagnosis or if we're going to call it self-
4 selection. And I think a lot of the argument in favor
5 of doing this is because the women are having shame, as
6 a couple people said, and also they didn't know about
7 their options, and I think having it available at CVS
8 and then going online is not necessarily going to meet
9 helping them with their shame or knowing what their
10 options are. I think having a compassionate
11 interaction with a health care provider is a good way
12 to allay the shame that they feel about incontinence,
13 and although I think the educational part is very good,
14 I think going over treatment options is not going to be
15 met by making this over-the-counter.
16 DR. REIDENBERG: Thank you.
17 And now, Dr. Hutchinson-Colas?
18 DR. HUTCHINSON-COLAS: Yes. I just have one
19 quick question regarding the age limit for the use of
20 Oxytrol. Currently, is there an age limit for the use
21 of Oxytrol? I'm asking that of probably Merck. Okay.
22 And just to comment is: How often have we

1 seen an association with delirium in the elderly with
2 the current use of Oxytrol?
3 DR. HEMWALL: I think we can address a lot of
4 the questions and the suppositions and conjecture
5 that's been brought about here today because we've
6 thought about some of these things ourselves, we would
7 have a chance to do that. We have --
8 DR. REIDENBERG: Since you've been asked a
9 direct question, you can certainly respond.
10 DR. HEMWALL: Yeah. Okay. Well, I'm going
11 to have Dr. Gary Hoel respond to this question because
12 there have been studies done with elderly patients and
13 patients in nursing homes, and the product is in fact
14 safe in this population. It provides a very low
15 anticholinergic burden, as we've tried to get across in
16 some of our earlier slides.
17 DR. HOEL: My name is Gary Hoel, Vice
18 President, Clinical Research, Watson Pharmaceuticals.
19 To answer the first question, there is not an
20 upper age limit for the use of Oxytrol, it's 18 years
21 and older, so that's the age group that it's approved
22 for.

1 I think some of the safety concerns -- and
2 I'm not going to address all of them at this point in
3 time, but I would like to talk a little bit to more the
4 CNS and cognitive function that might impact the
5 elderly. There is a fair amount of evidence to suggest
6 that Oxytrol does have a fairly low incidence of CNS
7 effects relative to other anticholinergic agents. Part
8 of that is, as Dr. Hemwall mentioned, there is lower
9 DEO formed -- that's the active metabolite -- and so
10 there is a lower overall anticholinergic burden.
11 The second part is that Watson has actually
12 done a nonclinical study in rats in which we've
13 measured brain concentrations of DEO and oxybutynin and
14 do find that when you avoid first-pass metabolism, you
15 do get less DEO accumulating in the brain.
16 Third, I think when you look at the overall
17 safety profile from the Phase 3 controlled studies, you
18 do see that although dizziness and somnolence has been
19 reported, it is at low rates and it's very, very
20 similar to placebo.
21 And, finally, Watson actually has done a
22 study, a clinical study, looking at cognitive function

1 in older adults. In this particular study -- I've got
2 a slide here, I can show you kind of the design of the
3 study -- essentially Watson conducted a double-blind,
4 double-dummy, placebo-controlled trial. We had three
5 treatments in this study. We used the gel formulation
6 of oxybutynin, Gelnique, that delivers the same amount
7 of oxybutynin as Oxytrol, in fact, it was designed to
8 mimic that product. We also used an immediate-release
9 oxybutynin product and placebo gel, and it was a
10 double-dummy study, so it was sufficiently blinded. One
11 hundred fifty-two subjects were included, 60 to 79
12 years of age. One week of treatment was given so they
13 could get to steady state, and a variety of generally
14 memory type tests, but psychometric assessments, were
15 performed. A name/place association test was the
16 primary endpoint. We also looked at secondary
17 endpoints such as visual working memory, misplaced
18 object tests, et cetera.
19 Well, in this particular study the outcome
20 was if there was no significant difference on the
21 primary or the secondary endpoint for seeing a negative
22 cognitive effect. So essentially there was no

1 difference between the oxybutynin gel product and
2 placebo on any of these assessments. And obviously
3 there are limitations in what the study can tell us. I
4 think it's only measuring one aspect of psychometric
5 functioning. However, it was done in an older
6 population. It also does give us some reassurance. I
7 think given the totality of the information, that the
8 expectation of significant CNS problem is minimized
9 with this dosage form.
10 DR. REIDENBERG: Dr. Farber.
11 DR. FARBER: So I want to first commend Merck
12 for wanting to do an educational piece for patients. I
13 think that's vitally important, and regardless of
14 whether oxybutynin patch goes over the counter or not,
15 I think you should do that because I think it's
16 necessary and important.
17 I will speak as a physician in San Diego for
18 the last 5 years, and that population is very different
19 than any other I've encountered, but I will say that
20 basically I encounter two types of patients. And as a
21 physician who has studied patient-physician
22 communication for many, many years, my interest is in

1 how we not only communicate with patients but how
2 patients can manage their own health in a lot of
3 different ways.
4 Generally I find that patients do one of two
5 things in terms of medications overall. One is either
6 they look for any medication they can that will fix
7 whatever they have immediately. And I have concerns
8 about that in terms of having this over-the-counter in
9 terms of somebody looking to fix their symptoms whether
10 or not they've been diagnosed, whether or not they have
11 the particular syndrome in mind.
12 On the other hand, there is the other
13 population that I see who want nothing to do with any
14 kind of medication that isn't "natural." And there is
15 sort of a backlash, if you will, the more medications
16 that are available, the more there is publicity about
17 that, and sometimes these patients don't avail
18 themselves of medication that really would help them.
19 So that's the population I've encountered,
20 and I've seen it elsewhere, but it's especially
21 prevalent in Southern California. But anyway, I have
22 concerns about both sides of those issues.

1 DR. REIDENBERG: If there is nothing more to
2 discuss, we can vote. There are a number of discussion
3 questions. Since it's still early, is there anybody
4 who wishes to comment further? I thought that we would
5 vote on the question and then give additional advice to
6 the Agency as relevant. But I'll welcome any further
7 comments of anybody before we vote on the question.
8 (No audible response.)
9 DR. REIDENBERG: Okay. We shall be using an
10 electronic voting system for this meeting. Once we
11 begin the vote, the buttons will start flashing and
12 will continue to flash even after you have entered your
13 vote. Please press the button firmly that corresponds
14 to your vote. If you are unsure of your vote or you
15 wish to change your vote, you may press the
16 corresponding button until the vote is closed. After
17 everyone has completed their vote, the vote will be
18 locked in. The vote will then be displayed on the
19 screen. The DFO will read the vote from the screen
20 into the record. Next we will go around the room and
21 each individual who voted will state their name and
22 vote into the record. You can also state the reason

1 why you voted as you did if you want to. We will
2 continue in the same manner until all questions have
3 been answered or discussed.
4 DR. LEONARD-SEGAL: I'm sorry, Dr.
5 Reidenberg, can I just ask one more thing? We've been
6 having a chat over here. We might also like to hear a
7 discussion, maybe before this vote, on the notion of
8 putting behavioral information into the OTC packaging
9 akin to the kind of thing that we have with nicotine
10 replacement products or the orlistat weight loss
11 product where information is provided to the OTC
12 consumer about other things that they can do to help
13 them with their condition. This is not something that
14 we put into the questions earlier, but we would be
15 interested to hear a discussion about that.
16 DR. REIDENBERG: In that context, as we keep
17 suggesting more information for the consumer, either
18 the print will get smaller and smaller or we will need
19 some sort of a supplementary patient package insert.
20 DR. LEONARD-SEGAL: That's right.
21 DR. REIDENBERG: What is the Agency's view?
22 DR. LEONARD-SEGAL: Well, we're interested to

1 hear what you have to say. In the OTC world, we call
2 it a consumer information leaflet, it goes inside the
3 package. For the orlistat, there are little booklets
4 on calorie counting and different kinds of things like
5 that. We would like to hear a conversation about it.
6 DR. REIDENBERG: So that we can suggest
7 additional information to go to the purchaser without
8 it meaning that the print will get unreadable.
9 Now I see that the vote buttons are still
10 blinking, and I will ask that they be turned off and
11 that we haven't yet voted, so whatever numbers I saw I
12 will declare are artifact at this time.
13 Does anyone wish to discuss?
14 Dr. Farber.
15 DR. FARBER: You bet, but with a caveat. I
16 think that behavioral techniques and physiologic
17 techniques like biofeedback and all need some guidance.
18 I don't know if you can put that into a booklet form
19 because patients need to be shown sometimes how to do
20 some of the issues. Some of the things like bladder
21 training and stuff like that is probably able to be put
22 into a booklet form.

1 What I would suggest is that the package
2 contain something about the fact that patients first
3 need to treat their overactive bladder symptoms with
4 behavioral forms of treatment and that to do this
5 effectively, they should really see a physician, and
6 that would also allow them to be diagnosed by chance,
7 which would also then be a more specific way of
8 eliminating some of the other things that we have
9 concerns about without saying on it, "You must be
10 diagnosed with overactive bladder syndrome before using
11 this product."
12 DR. REIDENBERG: Dr. Hanno.
13 DR. HANNO: Yes. I think Dr. Leonard-Segal's
14 point is very well-made. I think that would be a great
15 addition, and the way I would think of doing it is
16 having a coupon in the medication that they could send
17 away for a CD that details how to do behavioral
18 modification and how to do exercises. That's one of
19 the things that we do in our center, and it's extremely
20 effective. And I think it would also make patients a
21 little more patient taking the medication for the first
22 week or two while they're waiting for the CD to come in

1 the mail and they wouldn't keep sending for more CDs if
2 they like the medication. So I think that's the way I
3 would think about it, and I think that would be a good
4 addition.
5 DR. REIDENBERG: Dr. Hutchinson?
6 DR. HUTCHINSON-COLAS: I think Dr. Leonard-
7 Segal's point is well taken, and I think I agree that
8 we should provide some information in the package or
9 somewhere in the box that indicates that at least be
10 observant as to your fluid intake, the type of fluid.
11 It's easy to explain avoiding caffeinated beverages.
12 I'm not sure a CD may be as helpful because we're
13 assuming that many patients would have access to a
14 device to play a CD.
15 And while we are on the subject of provided
16 information to patients, I think the package insert
17 should also be in the other common language that's
18 used, probably Spanish, rather than having to go to a
19 website to get that information. It should be when you
20 buy the packet, it should have some basic information
21 in it.
22 DR. REIDENBERG: Thank you.

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1 Dr. Parker.
2 DR. PARKER: I wish we had it here to look at
3 because I think it's a great idea, but I think the
4 devil is in the details because it's going to be
5 incredibly important that it be, to use a term that's
6 overused, but still not done and patient-centered,
7 consumer-centered, whatever you want to call it for the
8 OTC world, but it really needs to be educational and
9 centered on the need to know to do. And that needs to
10 center on behavioral approaches to taking care of a
11 chronic condition that requires self-management where
12 the evidence supports behavioral intervention as a
13 chronic management and approach to a chronic condition.
14 And it's got to have a very balanced approach to what
15 the role is for pharmacotherapy in this, and that needs
16 to come before and be reviewed because what we don't
17 want to do is use that space and encourage people to
18 spend their limited time paying attention to it if it's
19 not really doing what we want it to do.
20 So, yes, but carefully. That's really
21 important. So I think that needs to come before and be
22 looked at, and there need to be criteria that are used

1 for judging it.
2 Here, above all else, is where the role of
3 the actual people with the condition can help in
4 creating it and making it something that really is
5 useful and meets their needs and truly educates about
6 something that I would be very willing to say that most
7 prescribers don't well understand.
8 DR. REIDENBERG: Dr. Howards.
9 DR. HOWARDS: I have a different question. So
10 has everybody completed their statements on this topic?
11 DR. REIDENBERG: Dr. Rogers?
12 DR. ROGERS: Just two comments. I think it's
13 a great idea. One is that most people, regardless of
14 whether or not you're an underserved population or
15 whatever, have a telephone, have some form of
16 communication. Social media is a big way of getting
17 this out in some way or another. The other is that
18 most people do have a DVD or CD player. That is
19 something that we have found -- well, of course, I'm
20 talking about the Latino population -- that we have
21 found that it doesn't matter, even some of our homeless
22 have access to this.

1 DR. REIDENBERG: Dr. Howards?
2 DR. HOWARDS: I don't know what the rules
3 are, but my vote would change if there were in the
4 labeling prominently displayed if you are over X age,
5 you should see a physician first. And I don't know if
6 we can have a vote on with or without that label or
7 not.
8 DR. REIDENBERG: I know that we can certainly
9 recommend very, very strongly that it be there. I was
10 told that we can't modify the question as it's written.
11 DR. HOWARDS: Thank you.
12 DR. REIDENBERG: So I think that the
13 discussion has led to some very, very strong
14 recommendations for what should be in patient
15 information dispensed with the product itself. We also
16 have the strong recommendation that, in addition, a DVD
17 with more educational material be made available on
18 request. I think this has been expressed. I don't
19 know that there is a way to express it with any more
20 vigor than we already have.
21 So that I think that after -- we can vote,
22 and then if we want to continue to discuss the kind of

1 information that should be made available both with the
2 package and as supplementary material, we can do that,
3 but I don't see how we can change the question that
4 we've been asked to vote on.
5 And the other thing, I asked for confirmation
6 -- and I think I know it -- but explicitly you have the
7 authority to require the patient information leaflet
8 within the package. Is that correct?
9 DR. LEONARD-SEGAL: Yeah. A consumer
10 information leaflet is labeling, and that becomes
11 something that we can review and require. So, yes,
12 that's clearly labeling.
13 DR. REIDENBERG: And with respect to the DVD,
14 I assume that we can most strongly request it. Do you
15 have the authority to include that in the legal
16 definition of labeling?
17 DR. LEONARD-SEGAL: Well, we don't have the
18 attorneys here. I believe that if the -- and maybe Dr.
19 Ganley will help me with this -- but I believe that if
20 the CD is in the package, that is labeling. The
21 definitions of what is labeling and what we can require
22 is sometimes morph. If there is a coupon and it's part

1 of the package, that is also something that we look at
2 as labeling, but we can't mandate that somebody send it
3 in and then have their CD come back to them.
4 So whatever is part of the package right now
5 I think we could all call labeling.
6 Dr. Ganley, do you have any other comments on
7 that?
8 DR. REIDENBERG: Just clarification, if the
9 label is part of the package, does the CD that it
10 refers to -- does the content of the CD also come under
11 the purview of the FDA?
12 DR. LEONARD-SEGAL: If the CD is part of the
13 package, yes. If it's a coupon that goes out to get
14 the CD, I don't know that we have that answer. Do we
15 have that answer?
16 DR. GANLEY: I don't think we can necessarily
17 enforce that, that they be required to send a CD out.
18 DR. REIDENBERG: Okay. Thank you for the
19 answers. That makes it very clear.
20 Yes, Dr. Parker.
21 DR. PARKER: Just one other point, and that
22 would be that along with the notion that we're

1 discussing about the education for self-management and
2 behavioral approach being part of the therapeutic
3 approach to overactive bladder, whatever that really
4 is, I think that we have to keep in mind, and we would
5 like to encourage the manufacturer, that the
6 advertising of the product, which is not under the
7 purview of the FDA for an OTC, as I understand it,
8 needs to also reflect this, and there needs to be the
9 intent going forward that this was brought up and
10 discussed by committee as part of strong
11 recommendation, advice, hope, whatever the word is.
12 DR. LEONARD-SEGAL: Yeah. I can clarify that
13 for over-the-counter products. Advertising is covered
14 by the FTC. That's different than for prescription
15 products.
16 DR. GELLAD: I was just going to ask, looking
17 at this product, do we know or do we have any data
18 about how often people actually open the flap as
19 opposed to what's read on the back -- I'm totally
20 serious -- depending on what information is here versus
21 in here?
22 DR. LEONARD-SEGAL: Ed, do you have data on

1 that? We do have many over-the-counter products that
2 have pullouts, flaps.
3 DR. HEMWALL: As part of the actual use or
4 the studies was this actual box was used in those
5 studies. Yeah. And it can be completely read at the
6 store shelf, it doesn't have to be purchased to be
7 opened. And we have a lot of data on some of the other
8 questions that have been talked about today as well.
9 DR. REIDENBERG: We still have time, so if
10 you have more data that we haven't heard before.
11 DR. HEMWALL: Well, I think what we wanted to
12 do for this committee is make sure that they had a full
13 array of approaches to some of the questions that
14 they're asking. We invited some experts from the
15 academic community to be here, and I would like to
16 start with Dr. Roger Dmochowski, who is an expert in
17 the area of overactive bladder and can address some of
18 the concerns that have started to emerge. And we also
19 have an oncologist here who can talk about bladder
20 cancer as well.
21 DR. DMOCHOWSKI: Hi. I'm Roger Dmochowski,
22 and I'm at Vanderbilt University. I am a urologist. I

1 am Professor of Urology and also Obstetrics and
2 Gynecology at that institution, and I run the
3 Fellowship Training Program in Female Pelvic Medicine
4 and then the Section of Female Pelvic Medicine in the
5 Department of Urology.
6 Did you have specific things you wanted me to
7 address or do you want just an open forum?
8 DR. HEMWALL: I think one of the things that
9 the committee is concerned about is that women aren't
10 going to be seeing their doctor if a product like this
11 is available, and I think one of maybe the
12 misconceptions that we created in our presentation
13 about women not seeing their doctor about OAB because
14 of the shame and embarrassment did not mean to imply
15 that these women did not see their doctor. In fact, in
16 the surveys we've done, many of these women have an
17 ongoing relationship with a physician, seeing them up
18 to six times a year for various reasons. It's the
19 nature of the condition that they do not want to talk
20 about it.
21 And then I think it's also the ability to
22 self-recognize and not be confounding with other

1 conditions and the simple difference between an acutely
2 emerging condition, which this is not, or a condition
3 that emerges over a long period of time that a delay in
4 diagnosis such as diabetes for a short time using this
5 product is not necessarily a concern.
6 DR. REIDENBERG: I think we're all aware that
7 women will see doctors even though they hide this
8 information. If there is specific factual information
9 with respect to self-diagnosis that we haven't heard
10 before, I would welcome it.
11 DR. DMOCHOWSKI: I can't give you specific
12 numbers, but I would just like to share there have been
13 I think some concerns raised about what the term
14 "overactive bladder" means specifically to the female
15 population that will be utilizing this agent, and they
16 very much understand that concept.
17 And to add to Ed's point, many of these
18 women, it's not months, it's been years and years, have
19 been dealing with this. So this does give them another
20 method to add to many of the things they're already
21 doing. And we have talked much about behavioral
22 therapy and the need to interject that into these

1 patients' lives. These women are very smart, and even
2 if they don't have a high level of education, they're
3 doing many of the things that we would require them to
4 do behaviorally already to manage their condition. So
5 actually in my experience -- and I would ask Diane
6 Newman also because she sees a lot of these patients --
7 but the majority of patients are already doing some
8 behavioral therapies at this point.
9 I would also like to address one of the other
10 concerns that's been raised regarding the potential
11 coexistence of neurologic symptoms and lower urinary
12 tract phenomena, specifically, quote/unquote,
13 overactive bladder. And there is actually a neurogenic
14 overactive bladder that is recognized as one of the
15 diagnostic codes.
16 The important thing with neurogenic causes in
17 almost causes neurogenically based, the incontinence is
18 a consequence of the disease, it doesn't precede the
19 disease, it comes either at the same time or post the
20 disease, so you certainly see, for instance, stroke is
21 a great example of that. The patient is perfectly
22 fine, they have a hemorrhagic stroke, and then they

1 develop severe refractory incontinence, very similar
2 for brain tumors, as a matter of fact, as well.
3 DR. REIDENBERG: Okay. Thank you. Any
4 further comments?
5 Dr. Farber.
6 DR. FARBER: Two questions. If these women
7 are doing all these things already and seeing a
8 physician, then why can't the physician just prescribe
9 the oxybutynin? Why does it need to be over-the-
10 counter?
11 And the second issue is in terms of the
12 neurogenic causes of, quote, overactive bladder or
13 symptoms of overactive bladder. There are conditions
14 such as brain tumors that can be insidious except for
15 those kinds of symptoms.
16 DR. DMOCHOWSKI: So this is all about access.
17 And, again, the personal impact that these patients
18 experience is significant, and it's not only
19 embarrassment, there are access issues. So you're
20 right, patients can certainly seek a physician, but
21 many don't for whatever reason, whether it's access,
22 whether it's embarrassment, whether it's a combination

1 of both.
2 DR. REIDENBERG: Further questions or
3 comments from the committee before we vote?
4 DR. HEMWALL: We actually have survey data
5 that addresses Dr. Farber's question if you would like
6 to see that.
7 DR. REIDENBERG: If you have data, sure,
8 we'll see it.
9 DR. HEMWALL: Okay. This is from a 2012
10 study when women were surveyed why they have not spoken
11 to a doctor about OAB, and it repeats what we've been
12 saying here, but at least it provides some real
13 numbers. The main reason, of course, is that they just
14 thought it was a normal part of getting older, the
15 embarrassment factor you've already heard, "My doctor
16 never asked me and I didn't think anything could be
17 done." This is all stuff we've said, which may seem
18 more just word-of- mouth, but this is actually out
19 there in the world, and this is shown in the survey.
20 DR. REIDENBERG: Thank you.
21 Dr. Parker.
22 DR. FARBER: I was just going to ask, so that

1 was of 245 women who did not speak to the physician.
2 What percent of women did speak -- I mean, out of what
3 population, how many women did speak to their
4 physician? I mean --
5 DR. HEMWALL: We see about 20 percent.
6 DR. FARBER: Twenty percent don't.
7 DR. HEMWALL: Do.
8 DR. FARBER: Twenty percent of women do.
9 DR. HEMWALL: Yes.
10 DR. FARBER: And the 80 percent you're saying
11 do not.
12 DR. HEMWALL: That's right.
13 DR. REIDENBERG: Charlie?
14 DR. GANLEY: Yeah. I just wanted to follow
15 up on the cognitive function study in the elderly. And
16 you mentioned that there was no significant difference
17 between the patch and placebo. There was another arm
18 in there that was immediate-release formulation. Was
19 there a difference with that group?
20 DR. DMOCHOWSKI: In this particular study,
21 there was not a significant difference in the immediate
22 release on the primary endpoint. Numerically, the

1 score was worse in the immediate-release formulation,
2 and in general in all the secondary endpoints, the
3 numerical scores were different.
4 There was one other secondary endpoint in
5 which there was a significant difference between the
6 immediate release and placebo.
7 DR. REIDENBERG: If I can add to that, on
8 page 75 of the FDA booklet, there is the study, a small
9 randomized, double-blind, controlled trial, 12
10 subjects, comparing oral oxybutynin, and nearly 50
11 percent of cognitive tasks tested oral oxybutynin and
12 decreased performance, and so we were told that the
13 oral gives you higher systemic anticholinergic activity
14 than the patch, but this is in the reference material
15 that we were given on page 75.
16 DR. HEMWALL: I can put some perspective on
17 that as far as how that shows up in other
18 anticholinergics, if we have A2, and this was actually
19 put together over the break in response to a question
20 we had earlier in the morning, and I wasn't sure if we
21 were going to get a chance to present it.
22 But from a recent review of the literature,

1 in 2010, put together a look at the side effect profile
2 from oxybutynin in immediate release, oxybutynin in
3 extended release, and then the transdermal system, and
4 if you look at the levels of dry mouth across the three
5 there, the constipation levels, and somnolence,
6 nervousness, much higher obviously. These are not
7 direct head-to-head comparisons, so you have to be
8 careful about what conclusions you draw. Dizziness,
9 again you see the difference.
10 This is again not a head-to-head comparison,
11 these are taken from product labels, but nonetheless, I
12 think this is again what we're trying to get across
13 about the much lower anticholinergic side effect
14 profile of this product, which I think we can agree is
15 indicative of what might extend to other situations and
16 certainly was not seen in that cognitive impairment
17 study that Dr. Hoel just talked about.
18 DR. REIDENBERG: Thank you.
19 Dr. Farber, did you want to comment further?
20 (No audible response.)
21 DR. REIDENBERG: Anybody want to say anything
22 before we vote?

1 (No audible response.)
2 DR. REIDENBERG: "Does the totality of the
3 data support that consumers can appropriately self-
4 select to use the oxybutynin transdermal system in an
5 over-the-counter setting? In your answer, please
6 discuss how the study participants in the actual use
7 study who had ineligibility should be viewed bearing in
8 mind the safety data from the actual use study."
9 Well, as I read it, the vote is: Can they
10 appropriately select it and use it or not? And then
11 everything else is discussion after that.
12 Do I have confirmation?
13 (No audible response.)
14 DR. REIDENBERG: Okay. Last chance, any
15 comments? Further discussion?
16 (No audible response.)
17 DR. REIDENBERG: Okay. I will read it again.
18 "We will be using an electronic voting system
19 for this meeting. Once we begin the vote, the buttons
20 will start flashing and will continue to flash even
21 after you entered your vote. Please press the button
22 firmly that corresponds to your vote. If you are

1 unsure of your vote or you wish to change your vote,
2 you may press the corresponding button until the vote
3 is closed. After everyone has completed their vote,
4 the vote will be locked in. The vote will then be
5 displayed on the screen. The DFO will read the vote
6 from the screen into the record. Next we will go
7 around the room and each individual who voted will
8 state their name and vote into the record. You can
9 also state the reason why you voted as you did if you
10 want to. We will continue in the same manner until all
11 questions have been answered or discussed."
12 Now I have read the question. I trust that
13 there is nothing further to speak, and so let us vote.
14 (Voting.)
15 DR. DOAN: The vote is five yes, six no.
16 DR. REIDENBERG: Okay. We will now go around
17 the room for the voting members. State your name and
18 how you voted. And I'm happy to go first. And I voted
19 yes. Reidenberg.
20 DR. GELLAD: Walid Gellad. I voted no.
21 DR. ROGERS: Norma Martinez Rogers, and I
22 voted yes.

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1 DR. HANNO: Phil Hanno. I voted no. Are we
2 supposed to say something about why?
3 DR. REIDENBERG: You may or we can discuss
4 after --
5 DR. HANNO: Okay. We can discuss it?
6 DR. REIDENBERG: We'll have time to discuss
7 the questions.
8 DR. HANNO: Sure.
9 DR. MOFFITT: Pam Moffitt, and I voted yes.
10 DR. BURNETT: Arthur Burnett, yes.
11 DR. HUTCHINSON-COLAS: Juana Hutchinson-
12 Colas, yes.
13 DR. PARKER: Ruth Parker, no.
14 DR. FARBER: Neil Farber, no.
15 DR. KOFF: Stacey Koff, no.
16 DR. HOWARDS: Stuart Howards, no.
17 DR. REIDENBERG: Thank you.
18 Now, I think, Dr. Hanno, you wanted to
19 comment?
20 DR. HANNO: Well, I was just going to say, I
21 mean, I don't think the data shows it does or doesn't.
22 I think the numbers are very small, so many of the

1 patients had already been diagnosed in the study by
2 their doctors that I don't think there is data to say
3 that patients can self-diagnose, and that is probably
4 my biggest concern with this, is the self-diagnosis
5 aspect of it. I think it's a very safe drug and I use
6 it a lot in my practice, but I just don't know that we
7 have shown that patients are able to self-diagnose.
8 DR. REIDENBERG: Dr. Howards?
9 DR. HOWARDS: I already articulated my
10 concerns. My main concerns were related to the
11 potential unproven mental effects on the elderly and
12 the missing of the diagnosis of carcinoma in situ,
13 which would admittedly be rare. So I would have voted
14 differently, and it would have swung the vote, if there
15 were an age limit to be determined in the labeling.
16 DR. REIDENBERG: Dr. Farber.
17 DR. FARBER: And I, too, would have voted
18 yes, and that would have swung it even more, if it had
19 not only an age limit but two other things, or maybe
20 one other thing, and that would have been a caveat that
21 said that behavioral treatment should be tried first,
22 and here is the information to do so, and/or see your

1 physician to do so, which would allow the patient to be
2 diagnosed because I, too, have the concern about how a
3 patient could self-diagnose this condition.
4 DR. REIDENBERG: I suspect that these
5 comments we're stating now would be more helpful than
6 the specific discussion questions that we're asked, so
7 let us continue the way we're currently going and then
8 we'll go to the discussion questions.
9 So would anybody else like to comment on --
10 I'm sorry, Dr. Parker.
11 DR. PARKER: I would really reiterate that.
12 My concern was really with the self-selection and also
13 with the behavioral component being addressed up front
14 and also being a part of the approval.
15 And I still have concern about it being,
16 though it's pink and targeted for women, that I believe
17 I'm interpreting correctly that we still had 10 percent
18 of men in self-selection who felt like it was okay for
19 them to take it. That seems high for me.
20 And the anticholinergic, the Beers criteria
21 that was mentioned before, prescribing patterns for the
22 elderly and that not being addressed up front seems to

1 me that it's in conflict with evidence.
2 DR. REIDENBERG: I would like to explain, and
3 that is, firstly, the natural course of this seems to
4 be so prolonged that it was hard for me to see trying
5 something else among all the things that women may try
6 for this for a few weeks is a key to delay in
7 diagnosis. So that didn't weigh as heavily on me as it
8 did on others. I think this anticholinergic matter in
9 the elderly is a very important issue. I think it's a
10 generic issue related to far more than just this
11 particular product. I think very strongly that we need
12 a consumer leaflet, whatever you call a patient package
13 insert, for over-the-counter with appropriate
14 consideration of a number of these issues that we have
15 discussed repeatedly at this meeting, and so we're
16 talking specifically about various forms of bladder
17 training, we're talking about anticholinergics, and the
18 relevance of age and multiple drugs a patient may be
19 taking to this issue which in fact is even in the label
20 but rather superficially. And so I think that these
21 are some of the keys that with our earlier discussion I
22 was hoping would be dealt through education and

1 therefore we could do it.
2 I would like Dr. Burnett next.
3 DR. BURNETT: Well, I went with yes because
4 while I struggle with this issue of proper selection,
5 and I'll try not to use the self-select studies as a
6 way to qualify the thinking, but how patients ended up
7 using this I think is problematic, but in the end I
8 think there is a pretty good safety profile, I thought,
9 with what I was able to see, particularly with this
10 formulation of it. And I think about how we've come
11 forward in my area where I do a lot of work in sexual
12 medicine, how with the availability of some of the oral
13 medications, it actually has improved, I think, the
14 care of men with sexual dysfunctions, they're more
15 informed, they come in the door, they're able to pursue
16 the right options and move forward properly, and I
17 think this is potentially an opportunity with
18 education, proper package labeling, to actually perhaps
19 improve management.
20 And I know this is a big unknown, and there
21 are unknowns out there, and maybe we'll never have all
22 the studies done, we always grapple with that. "Is it

1 sufficient enough?" "No, let's do another study." "Is
2 that enough?" "No, let's do another study." But I
3 just wonder whether we still at least have enough
4 safety data to move forward, and I would say yes.
5 DR. REIDENBERG: Thank you.
6 Dr. Gellad?
7 DR. GELLAD: Just to explain my vote, I voted
8 on the literal question here, and I just think the data
9 does not support the appropriate self-selection. The
10 self-selection study aside, I think I'm still just
11 stuck and I would welcome more comments from Merck if
12 they're able to convince me otherwise. But it was this
13 issue that 80 percent of patients who decided to
14 purchase the drug were not supposed to based on the
15 label, and that 17 percent of patients who should have
16 stopped, based on what's on the label, did not. So I
17 think that's what's really getting me and the main
18 reason why I answered this question, which I view is
19 separate from whether or not I think this should be
20 over-the-counter.
21 DR. REIDENBERG: Thank you.
22 Dr. Rogers.

1 DR. ROGERS: In spite of going back and forth
2 about it, I voted yes for it, and the reason I voted
3 yes for it is because in the label it does say, "If
4 this medication is not helping you in 2 weeks, see your
5 physician," and that's clearly stated on the label.
6 DR. REIDENBERG: Okay. I think we can go to
7 the discussion questions now. And so we'll go to
8 Discussion Question 1, which is item 2.
9 "Given that some of the pre-specified
10 endpoints were not met in the Label Comprehension
11 Study, which concepts, if any, are you concerned about
12 in the Label Comprehension Study data? And please
13 discuss your concerns."
14 I welcome anybody's comments.
15 DR. FARBER: So I have two concerns about the
16 Label Comprehension Study. One is the number of men
17 who opted to use the product. And I realize that there
18 was a change in the packaging, but you still have some
19 percentage of men who would use the product, and I have
20 some concerns about that.
21 The other concern I have is the picking the
22 85 percent threshold for diabetes as being adequate

1 because it was not a significant side effect or
2 problem. I mean, I can't believe that diabetes
3 undetected would be an insignificant problem. I'm not
4 sure why you picked 85 percent instead of 90 percent.
5 And, in fact, they did not meet 90 percent. So I have
6 some concerns about that as well.
7 DR. REIDENBERG: Thank you.
8 Any other comments on item number 2?
9 (No audible response.)
10 DR. REIDENBERG: Okay. Supposing we take a
11 break now for 15 minutes. It's 5 minutes of 3:00, and
12 we resume at 10 minutes after 3:00. So we'll recess
13 for 15 minutes.
14 (Break from 2:56 p.m. to 3:13 p.m.) Questions
15 to the Committee/Committee Discussion
16 DR. REIDENBERG: And we will go to item 3.
17 "The data show that some subjects' symptoms
18 did not improve or worsened during continued oxybutynin
19 TDS beyond the 2 weeks proposed in the labeling in
20 order to see if it needed more time to work. Please
21 discuss your level of concern regarding consumers not
22 stopping use of the product if their symptoms have not

1 resolved."
2 I welcome comments.
3 Dr. Farber.
4 DR. FARBER: I guess my concern about this
5 would be similar to the concern about a patient who had
6 not seen their physician and been diagnosed; that is,
7 do they have a condition that needs to be treated
8 differently? And basically if you have a percentage of
9 patients who even after being advised of not continuing
10 the drug and seeing their physician, if they continue
11 to have symptoms, that they still continue to use the
12 drug, I think that reinforces my concern about the fact
13 that some patients who are using the oxybutynin patch
14 have not originally been diagnosed, have not been
15 diagnosed when they're continuing to have symptoms and
16 instead are continuing to use the patch.
17 DR. REIDENBERG: Thank you.
18 Anyone?
19 Dr. Howards.
20 DR. HOWARDS: I'm not very concerned about
21 this because all the studies on these types of drug
22 show an enormous placebo effect, all the controlled

1 studies. So if we're concerned about people who don't
2 get better, why aren't we concerned about people who
3 get better because of the placebo effect? I just --
4 I'm not worried about it.
5 DR. REIDENBERG: Dr. Rogers?
6 DR. ROGERS: I would go back to -- I'm not
7 worried about it either because I'm going to go back to
8 the label, and it says, "Condition does not improve
9 after 2 weeks of use, stop use and seek a doctor."
10 DR. REIDENBERG: Dr. Gellad.
11 DR. GELLAD: Well, just to make the literal
12 answer to the question, I'm very concerned that if
13 consumers are not going to go see their doctor after 2
14 or 3 weeks of using the product and it hasn't improved.
15 So I'm concerned. Now, whether or not that's a
16 realistic concern, I don't actually know, but if that
17 were to happen, I think that's very concerning because
18 they have not had the workup prior to starting the
19 medication to rule out some of the other things.
20 And I just go back, especially this issue of
21 having a urinalysis. I think that's something that
22 should always be done when these symptoms are present,

1 and that's really what's bugging me on the diagnostic
2 side.
3 DR. FARBER: I just want to respond to Dr.
4 Rogers' comment. Although the label says that, we know
5 that at least 17 percent of patients either didn't read
6 or completely ignored the label. That has me
7 concerned. I mean, no matter what, I mean, I don't
8 know whether there are other label studies to show that
9 that's about usual for any medication or not, but at
10 least in this medication, just because the label has a
11 warning on it does not mean that it's safe.
12 DR. REIDENBERG: And I'm not very concerned,
13 and the reason is where this condition has generally
14 gone on for a long time before people would go to OTC
15 medication, I don't know what all other things they've
16 been trying on their own. And so I really have a
17 question whether one more intervention that didn't work
18 would make a particle of difference in the timing that
19 these women have for when they finally see a doctor or
20 an independent practicing nurse or even ask the
21 pharmacist about what to do for their urinary trouble,
22 and with luck, if they ask anybody, they'll get

1 directed to the right thing.
2 Dr. Moffitt?
3 DR. MOFFITT: I go back to the premise that,
4 okay, after 2 weeks it hasn't worked, and as a
5 consumer, I'm thinking, okay, I'm going to give it a
6 little bit more time, I've put up with this for 6
7 years, I haven't talked to my doctor, and they're
8 offering me something that might work.
9 We don't want to have to live with this
10 disease or condition, we don't want to have to wear
11 diapers, we don't want to have to have surgery, so the
12 2 weeks doesn't bother me in the aspect that I don't
13 think physically taking it after 2 weeks is detrimental
14 to their health, number one. Number two, they're going
15 to want to give it a try, they're going to want to give
16 it a little bit more time because, like I said, we
17 really don't want to have to live with this, and if
18 this is something that's going to work, that's fine.
19 And Merck themselves said it takes us 6-plus
20 years to get the courage to go see our doctor about
21 this. If I can take something OTC that offers me an
22 option when I wasn't even aware there was an option out

1 there, then I'm going to try it and I'm going to try it
2 for more than 2 weeks.
3 DR. REIDENBERG: Dr. Rogers?
4 DR. ROGERS: Just a comment. I mentioned
5 this earlier to one of the FDA people. I have a family
6 member that has this problem that does wear Depends. We
7 went to the urologist for another type of problem. And
8 so he asked her -- she's 75 -- he asked her, "Do you
9 have a bladder problem?" and she says, "No," and I'm
10 like staring at her and saying, "Uh, yeah." And we're
11 primarily nurses, and she's a retired nurse, and she
12 says, "No." So I said, "Yes, you do," and I give the
13 symptoms. We come out of the doctor's office and she
14 said, "I'm so mad at you. Why did you tell him that? I
15 am not going to tell a man that." And that's the
16 issue, it's the cultural issue. Would she have loved
17 to have this? Of course she would.
18 DR. REIDENBERG: Dr. Hanno?
19 DR. HANNO: Yeah, I'm not overly concerned
20 about the 2 week or 3 week or 4 week that they stay on
21 it if it's not effective. What concerns me more along
22 that line is I really think there should be something

1 on the label that says, "If you have failed two
2 anticholinergic drugs prescribed by your doctor, this
3 product is not for you," because what I can see
4 happening is since so many people fail anticholinergics
5 and since the Oxytrol patch is hardly used at all now -
6 - as a share of the market, I don't know what it is,
7 but it's minimal -- there are going to be a lot of
8 people who have failed these other drugs, VESIcare or
9 whatever, and they're going to go on this and it's not
10 going to help them. And most people -- and Dr.
11 Dmochowski I think can back me up on this -- who have
12 failed two more anticholinergics are not going to
13 respond to another one, especially this one. So I
14 think that's important.
15 DR. REIDENBERG: Dr. Burnett?
16 DR. BURNETT: Thank you. I think in the
17 ideal world we would like to try and work everybody up
18 and counsel them well. I think that's what we would
19 all want to do, but I just know that in the real
20 situations that doesn't happen. And I like to do
21 urinalysis, I like to do a scan, I do this and that.
22 But I'm hearing these real world experiences and I

1 think that things just are somewhat different.
2 Am I concerned that after 2 weeks this would
3 be a problem? I am somewhat concerned if somebody
4 wants persistent therapy, but I don't think that delay,
5 if we're thinking about the issue of delayed diagnosis,
6 is going to be that big a deal. Either they were going
7 to come in and get sorted out or they weren't, and I'm
8 not sure this is going to either change their way of
9 thinking one way or the other, at least in my mind.
10 DR. REIDENBERG: Dr. Hemwall, did you have
11 something to add to this discussion?
12 DR. HEMWALL: Thank you. I just wanted to
13 add a little bit more perspective around some of the
14 things that Dr. Hanno was saying. I think he probably
15 recognizes this, too, as well. The way managed care
16 works is that the first thing you have to give a
17 patient is generic oral oxybutynin, and oftentimes they
18 go off that because of the side effects and they don't
19 stay with it whether or not it was working, and the
20 Oxytrol patch is at best second tier and usually third
21 tier with a large copay. So a lot of people don't
22 actually get to try the Oxytrol patch in the Rx

1 situation.
2 And when you were talking about access and
3 cost earlier, the OTC version would actually be a lot
4 cheaper than what they would have to pay to get it Rx,
5 and it would be something that they wouldn't have to go
6 through a series of other products before they would be
7 allowed to use it in a managed care situation. That's
8 all.
9 DR. REIDENBERG: Thank you.
10 Dr. Farber.
11 DR. FARBER: So I think all of us have
12 anecdotes, and you're right, I've seen anecdotes of
13 women who don't talk about their overactive bladder and
14 I have seen anecdotes of women who do talk about their
15 overactive bladder and are treated for it without being
16 adequately diagnosed and die of sepsis or some other --
17 or HHNK.
18 The use studies in this didn't show a lot of
19 problems, but there were a small number of women, you
20 know, there were only 700 women who were active users.
21 I think if we expand it into millions of users, you're
22 going to see a fair number of women who would have

1 problems long term. So I still have concern. I hear
2 what you're saying about the anecdote, and, as I said,
3 I think we all have them, but I have concerns about a
4 woman who is not being adequately diagnosed.
5 DR. REIDENBERG: Thank you.
6 Dr. Gellad.
7 DR. GELLAD: I guess my concern is less about
8 missing a particular diagnosis, but it's just that it's
9 not necessarily the way to treat a problem, is to take
10 a medicine and then see what happens in 2 weeks or 3
11 weeks if it doesn't work. I don't think it's going to
12 be the majority of -- let me say it this way, it's not
13 going to be all the patients who are going to have
14 symptoms for 6, 7 years and have not been willing to
15 see a doctor and then all of a sudden this comes on and
16 they buy it. I mean, this is going to be people might
17 have symptoms for 1 week, they might have symptoms for
18 1 month, they might have symptoms for a month and a
19 half. So I think there are going to be a lot more
20 women that are going to be using this than just the
21 people that we, as physicians or clinicians, think have
22 overactive bladder. I think we've seen in the studies

1 that not all women are able to properly diagnose
2 themselves as overactive bladder and you can't actually
3 diagnose overactive bladder without a urinalysis. So I
4 guess it's less about missing a diagnosis of diabetes,
5 but it's more about, what is the proper way to treat
6 this condition?
7 And the idea that there is stigma, I
8 understand there is stigma. There was a lot of stigma
9 at erectile dysfunction, and now every patient that
10 sees me asks me for this drug. So I think that putting
11 something over-the-counter does not necessarily have to
12 be the only solution to overcoming stigma. There are
13 risks, there are risks of putting something over-the-
14 counter.
15 And again I'll just bring up this issue again
16 about cost, that cost is going to be a barrier to many
17 women who you want to have access because this product
18 is on the market, especially if you're talking about
19 long-term use.
20 DR. REIDENBERG: Thank you.
21 I think that if I can summarize our
22 discussion of point 3, some of us continue to have

1 concerns about improper diagnosis or about missing
2 disease that requires different treatment and that
3 others have not been concerned about that. So we don't
4 appear to have a consensus, but we have fully expressed
5 each point of view in detail.
6 Now, I will go on to question number 4, or
7 item number 4, and let me again ask that we try to
8 focus on what we haven't already said because we have
9 discussed the safety concerns for each of our things.
10 If there is something new or if you would like to
11 emphasize something again, that would be just fine.
12 And so, "Please discuss any safety concerns
13 about the potential delay to diagnosis of conditions
14 with similar symptoms."
15 I welcome any comments.
16 Dr. Farber.
17 DR. FARBER: I guess the only one I would
18 mention, I mean, we touched upon, but I would like to
19 emphasize, are some of the neurologic conditions that
20 can occur that may be quite insidious and display only
21 things like incontinence and/or overactive bladder
22 syndrome first before exhibiting some of the other

1 neurologic symptoms that they might have. That would
2 be my concern in terms of delay in diagnosis.
3 The other one would relate to diabetes since
4 the threshold was set low.
5 DR. REIDENBERG: Thank you.
6 Walid?
7 DR. GELLAD: I guess I would curious to hear
8 from the FDA. When I was reading this material, I was
9 trying to think, what other over-the-counter products,
10 if you take it, could be masking serious illness? And
11 then I was thinking about Prilosec, for example. There
12 are a lot of very serious illnesses that could present
13 with the symptoms similar to Prilosec. So I guess
14 that's -- I don't know if you -- I know you're hear to
15 listen to us, but I'm sure in your internal discussions
16 you've talked about, is there anything to bring to bear
17 from the Prilosec lesson about this issue of masking
18 serious conditions or delay the diagnosis of serious
19 conditions?
20 I mean, it's different, ibuprofen and pain
21 medications are to treat pain. When I think about
22 Prilosec, I think of something more similar to this,

1 where it's treating a set of symptoms that is supposed
2 to be characteristic of a particular diagnosis but may
3 not necessarily be that diagnosis in some cases.
4 DR. LEONARD-SEGAL: I think that anytime you
5 have a treatment for a symptom, symptoms can be due to
6 lots of different things. It's hard for me to think of
7 any one symptom that anyone has that is not possibly
8 representative of a lot of possible conditions, some
9 not serious and some serious. We have certainly got
10 medications over-the-counter that can treat heartburn,
11 as you're bringing up, and certainly those symptoms
12 could potentially be confused by someone and represent
13 something else. They could even represent a myocardial
14 infarction, which could be an acute event that one
15 would not even want to delay 15 minutes in terms of
16 diagnosing.
17 The thing that we grapple with in our
18 internal discussions is, how do we make decisions where
19 we could benefit many and how do we figure that out
20 when we consider the potential for a serious adverse
21 event where something might be missed for a few? And
22 this clinical decision-making and it's never perfect,

1 but I hope that that has helped to answer your
2 question.
3 DR. GELLAD: It does, but then it brings back
4 to me the issue that the real benefit, the real and
5 only benefit, to putting this over-the-counter then is,
6 how is this going to improve access or treatment for
7 women that have these conditions? And I guess there is
8 no way to get data for that maybe.
9 So I don't know how you can answer
10 definitively whether that's going to be the case or
11 not. I think there are a lot of reasons why it
12 wouldn't be the case and there are a lot of reasons why
13 it would be the case. But if it's not going to be the
14 case that it's going to significantly improve access,
15 then it seems to be there is no reason to even talk
16 about over-the-counter use.
17 So it's this issue of, why do we think it's
18 going to improve what we think, and we know that women
19 are going to go and use this -- I guess that's, why do
20 we know that women are going to go use this?
21 DR. GANLEY: I think the Prilosec example is
22 a great example. When the advisory committee that

1 discussed that, if you're familiar with Prilosec and
2 the other PPI drugs, it's a 14-day limit, and you can
3 use it I think three times in a year, and the obvious
4 concern was that you may be masking something similar
5 to Barrett's esophagus or something like that with
6 repeated use of the product.
7 And I guess it gets down to when do you, as
8 Dr. Leonard-Segal had said, when do you -- does having
9 that product available OTC make it better for consumers
10 with the risk that some people will ignore the
11 directions and just take it all the time for their
12 symptoms realizing that if they go off it, that the
13 symptoms return, and, in fact, maybe if they didn't
14 have a doctor or something, that they would be self-
15 treating and actually preventing Barrett's esophagus? I
16 don't know. We don't know the answer to that.
17 I think in this situation, if the statistics
18 are accurate that only 20 percent of the women who have
19 these symptoms are bringing it up to their doctor,
20 well, there is a problem there. Okay. So if it's
21 readily available OTC, does that change that? We're
22 not going to know the answer to that, but the challenge

1 for us is if this drug could be -- we have a company
2 that wants to bring it OTC, we're required to look at
3 that and see what the hurdles are for them to get over,
4 and if the data they provide shows that they are able
5 to get over those hurdles for whatever reason, through
6 labeling or the consumer leaflet that may be included
7 or other mechanisms, then it may actually increase
8 access. And so I think that's how I sort of look at
9 it.
10 DR. GELLAD: I understand what you're saying,
11 and it's difficult, and the answer you need to know is
12 whether it's going to improve access is not knowable, I
13 mean, until you allow for access and then see what
14 happens, I mean, I guess in the end. I guess when
15 Prilosec went over-the-counter there were side effects
16 for those that used the prescription products in terms
17 of what was available to them, what formularies
18 covered, et cetera. And so there may be other risks
19 for the folks who are on prescription medications if
20 this goes over-the-counter.
21 DR. GANLEY: I think the challenge for us,
22 too, is that's an issue of cost and who pays for it.

1 Ultimately, the consumer and the patient pay for these
2 things whether they are prescription or OTC, it's just
3 a question of whether it increases your copay, it
4 increases the amount that's taken out of your check
5 every month to pay for your insurance, and so
6 realistically it becomes an issue of cost-shifting that
7 we don't really take into account when we're trying to
8 think these things through.
9 The issue is, is this something if you self-
10 diagnosed, used appropriately, can be labeled that
11 people will use it appropriately? And those are the
12 issues we grapple with. I think the things you raise
13 are very legitimate questions, but we generally don't
14 factor those into our decisions.
15 DR. LEONARD-SEGAL: I would just also add, as
16 a reminder of what Dr. Reidenberg reminded me to talk
17 about this morning, is that the regulations are
18 supportive of the list that Dr. Ganley just provided to
19 you. The regulations do not support our discussion
20 thinking in terms of cost and what third-party payers
21 will do.
22 DR. REIDENBERG: Any further comments on item

1 number 4?

2 (No audible response.)

3 DR. REIDENBERG: Well, to summarize, I think

4 that there have been a number of safety concerns that

5 have been mentioned throughout our discussion and the

6 concerns having to do with erroneous self-diagnosis

7 with delay in diagnosis and management of a different

8 and more serious condition is the one that most people

9 are concerned about. And the intensity of that concern

10 varies from member to member of the committee.

11 Now we shall go to item number 5.

12 "Based on the information included in the

13 briefing materials and presented today, please discuss

14 whether the content of the proposed package label is

15 acceptable for OTC marketing. If you think the content

16 of the label should be improved, please discuss

17 additional concepts that should be conveyed to the

18 consumer on the package label and the current labeling

19 or in the appendix of the FDA briefing book."

20 And I think we have already most strongly

21 urged that there be a purchaser insert, that there be a

22 description of the various behavioral methods of

1 addressing the problem that this medicine is supposed
2 to address, that we think the issue of concurrent
3 anticholinergic drugs particularly in elderly people is
4 a major one that must be addressed in this form of
5 labeling. And these are the only two themes that I
6 think we have general consensus and virtual unanimity
7 about.
8 Dr. Farber, please.
9 DR. FARBER: I would have been the first that
10 it be not only that there be an insert about behavioral
11 techniques, but that there should be something on the
12 label that says behavioral techniques need to be tried
13 first, that that's the first-line treatment, and that
14 the patient should see their physician to be able to go
15 over what these behavioral techniques are.
16 DR. REIDENBERG: Are you going to make a
17 recommendation to Merck that they should consider this
18 in their advertising even before somebody purchases the
19 product for the first time?
20 DR. FARBER: It should be in the advertising
21 and it should be on the label, both.
22 DR. REIDENBERG: Dr. Parker.

1 DR. PARKER: So I'm not 65 yet. God willing,
2 I will be one day, it won't be too far off, but I would
3 posit that a need to know for an informed consumer is
4 the complexity that is under recommendation like the
5 Beers recommendation, that anticholinergics not be used
6 in the treatment of overactive bladder among the
7 elderly. That exists. I didn't write it. It's out
8 there. As a practicing clinician in an academic
9 center, I ding my residents when they do it.
10 So I'm conflicted. If I'm supposed to be
11 dinging, and I might even get dinged by somebody
12 someday if I'm not following those kind of guidelines,
13 and this is sitting out on the market available for all
14 comers, I see confusion in that. And if I am to be an
15 informed consumer and you're my public health agency,
16 my guardian, my tax-supported guardian, of my public
17 health, I need you to help me understand the complexity
18 of this, and I'm confused.
19 So I see that as something that's got to be
20 addressed in labeling. I can't understand it without
21 it. I can't understand how I weave through that.
22 Age restrictions? What do I really do when

1 I'm 65 about this? Do I go to my doctor and let my
2 doctor explain to me why I'm an exception to that, and
3 even though it's out there, I've got these little Ruth
4 Parkers in the hospital telling her residents not to do
5 it, or whatever that is? I need some guidance on it.
6 This is how complex it is to figure out what to really
7 do, but I see that as a myth and one that we've got to
8 figure out what to do with.
9 So I put the anticholinergics in the elderly
10 prescribing patterns based on best evidence as
11 something that we need to be able to have clarity
12 ourselves on if we are going to help the public be
13 informed consumers. So I think we've got to be very
14 clear on that.
15 A couple of other things that we've already
16 discussed, just to highlight: the behavioral approach,
17 the fact that the evidence supports the use of it and
18 how that's communicated, the inclusion of that, the
19 review of that, and then I think a black box remains --
20 and we all know it -- that advertising and the
21 oversight of advertising for an OTC product is left to
22 the FTC, there are different regulations, there are

1 different guidelines, it's not the same as an Rx, and
2 so there has to be an understanding about that that
3 goes forth in goodwill.
4 I do want to applaud Merck for the work
5 they've done on this, and I see a lot of progress
6 that's been made in the work to try to improve labeling
7 and try to improve all of this, but what's difficult is
8 that this is really tough and hard to figure out, and
9 so it takes a lot of partners to figure out, what is
10 the essential need to know to do given the fact that we
11 all want to live to be as old as possible and in good
12 health and as dry as possible at that age, I think? We
13 have to figure out how we put the essential information
14 out there in a way that we can use it. Big challenge.
15 DR. REIDENBERG: Dr. Gellad?
16 DR. GELLAD: I would agree. I looked up the
17 Beers. The Beers redid their list, they just redid it
18 this year, and I think oxybutynin was not on the list
19 except as a drug disease contraindication for patients
20 with dementia, but someone should double-check that.
21 But nonetheless, it was on the list before, and so the
22 question is, are we -- now, there is already

1 diphenhydramine over the market, but we're putting
2 actually a specific product on the market that an
3 expert panel has deemed is too risky for those over the
4 age of 65 with certain conditions. So I think if
5 that's the case, that at least has to be very
6 specifically mentioned on the label. I'll have to
7 double-check that when I get home.
8 DR. REIDENBERG: Dr. Totman?
9 DR. HEMWALL: Can I interject for a minute?
10 DR. REIDENBERG: Oh, sure.
11 DR. HEMWALL: It's interesting, on the Beers
12 list there are a couple places where it does list
13 oxybutynin as one of the anticholinergics to be aware
14 of, but then when you look at some of the symptom
15 areas, like the gastric area, it says in parentheses
16 "oral."
17 DR. REIDENBERG: Go ahead.
18 DR. TOTMAN: And I wanted to point out that
19 the prescribing information for the Rx product says
20 that 49 percent of Oxytrol-treated patients in the
21 clinical studies were at least 65 years of age, no
22 overall differences in safety or effectiveness were

1 observed between these patients and younger patients,
2 and other reported clinical experience has not
3 identified differences in response between elderly and
4 younger patients. And I understand when you start
5 talking about polypharmacy, but the product itself,
6 there is evidence to allay some of our concern.
7 DR. REIDENBERG: If I can comment on that,
8 it's extremely difficult in normal social or clinical
9 interactions to detect mild delirium or dementia, and
10 in the absence of formal mental status testing, it's
11 hard to accept that there wasn't an effect or may be,
12 so that without actual formal study of elderly people -
13 - and we were given one example where it has been
14 formally studied -- I'm not willing to accept clinical
15 observation of lack of effect as meaning the effect was
16 not there.
17 DR. GELLAD: And I think the real issue is
18 the interaction with the other drugs. I see the data
19 that's convincing about oxybutynin itself transdermal,
20 but it's about the interaction with other meds that are
21 easily available over-the-counter, you know, it's
22 diphenhydramine, cold medicine, and Oxytrol, all the

1 things I'm going to put together.
2 DR. TOTMAN: So that would mean that instead
3 of putting just a limit that anyone over 65 should not
4 use without seeking advice of a doctor, you would put
5 in drug interaction information?
6 DR. GELLAD: I'm not an expert in label, it's
7 just these are the reasons I think this is -- these are
8 the things that people who prescribe think about and
9 look at, and the pharmacist as well, and you're taking
10 all of those steps out when you put it on the shelf. No
11 longer can a pharmacist run this next to all the other
12 medicines someone is taking, you know, like they
13 typically do with a prescription. So it's just taking
14 away all the checks that happen, and so I think --
15 whether it goes on the label or not is not my area of
16 expertise, but it's the interactions that are most
17 worrisome.
18 DR. REIDENBERG: And if I can comment, I
19 think that we have identified a major problem of a
20 class basis, and that is, over-the-counter medications
21 that have anticholinergic activity, whether intended or
22 unintended, I hope that this will get back to the FDA

1 and they will think about this particular issue as the
2 population ages, as dementia and delirium get more
3 common, and as the use of over-the-counter drugs
4 continues in a variety of ways along with prescription
5 drugs that also have anticholinergic activity.
6 So I think there is a general issue here that
7 needs to be addressed irrespective of whether specific
8 action is taken for this particular product. On the
9 other hand, I think we all agree that because we're
10 aware of it, we want the labeling to address this
11 general problem because this particular drug enters
12 into the picture.
13 Other comments?
14 Sure.
15 DR. GELLAD: And I would just make one more
16 comment, that these are not necessarily studies --
17 these are small studies, everything I've seen. And we
18 all know the history about safety and small studies. So
19 I guess I would just make that caveat. I don't want to
20 base our decisions on whether -- ultimate decisions
21 about the safety of these on the studies that have been
22 presented.

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1 DR. REIDENBERG: Does anybody have any
2 further comments on any issues that we have discussed
3 today, any last words from anyone?
4 (No audible response.)
5 DR. REIDENBERG: Well, let me thank
6 everybody, the various presenters, and the committee
7 members for sticking to the topic, to being objective
8 and explicit. Let me ask that the boxes be returned to
9 the front table so that they can be collected. And if
10 there are no further comments of anybody, the meeting
11 stands adjourned. Thank you very much.
12 (Whereupon, at 3:48 p.m., the Meeting of the
13 Nonprescription Drugs Advisory Committee
14 (NDAC) was adjourned.)
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1,000 52:11 126:18 166:13
1,069 138:22
1,218 52:9 138:10
1,230 138:10
1,500 210:20
1.8 137:19
1:00 190:14,18
10 38:16 50:22 75:15 103:9 166:13 174:21 181:5 205:15 237:2,6 278:17 283:12
10:00 103:10
10:10 103:14
103 8:12,13,18
105 154:14
10903 1:16
10-minute 184:9
11 6:4 17:13 31:20 32:4,16 54:13 106:21 107:19 108:16 110:9 141:14,19 144:10
11:59 190:19
111 9:6 175:6
12 6:8 32:2 52:1,4 70:6 136:11 137:5 141:16 170:12,13 193:20 238:9 272:9
12:59 190:19
12-week 106:17 110:8 136:8
13 141:12
13,700 156:11
133 9:12
138 141:14
141 101:22 145:14 147:19
14-day 298:2
15 53:16,21 67:9 103:12 107:12 149:18 203:10 283:11,13 296:15
150 109:1
1503 1:15
152 146:8
154 59:4 149:10
155 146:9
15-minute 103:9
15-week 50:21
16 6:15 129:20 193:18
160 9:13
17 57:16 101:14 102:18 155:22 193:18 281:15 286:5
17.7 143:17
172 174:4
17th 18:5 20:3
18 12:19 13:2,14 21:3 50:22 56:18 61:4 137:18 146:18 147:10 249:20
184 175:4
185 153:21
186 154:5
187 82:15 89:6 139:9 145:20 146:1
18th 18:5 20:3
19 54:11 107:10 155:22 194:21
190 9:15,16
192 9:18
1951 164:6
196 10:3
1972 12:10 183:12
1982 197:7
1990 65:19

2

2 28:22 49:10 56:11,18,22 108:20 110:10 118:1 120:22 135:21 142:12 144:8,14 146:1 147:8 181:16,17 196:17 226:10 238:7,11 239:11 282:4,8 283:8,19 285:9,13 287:4,12,13 288:2,20 290:2 292:10
2,700 138:9
2,731 90:1
2.7 150:8
2:56 283:14
20 24:11 145:15 149:10 165:13 271:5 298:18
2000 193:13
2002 104:10
2003 20:22 26:1 31:12 35:20 65:20 100:13 104:7 106:10
2004 156:12
2007 37:22 200:3
2009 19:14 20:2 194:9
201 10:5
2010 17:20 200:1 273:1
2011 16:11 18:5,20 20:3
2012 1:12 18:7 19:4 270:9
2013 17:13
202211 1:9 13:21
205 10:7
208 12:19 13:3,14
21 145:2 146:7
21.5 140:22
210 10:10
21-351 8:15
214 10:12 82:13 139:6
22 141:16 146:10
23 6:16,19 57:13

23.5 158:20
24 116:17 117:6 119:6
24.3 87:19
245 271:1
25 41:16 99:12 102:2,3 154:18
26 51:1 135:1 149:17 175:6
260 149:10 233:5
265 57:8 188:8
27 82:21 105:6 139:12 147:20
270,000 35:14
276 158:16
28 194:16
283 10:13,15
29 146:19 174:6,9 188:9 216:11
29th 20:1
2nd 18:7 19:4
2-week 56:15 119:17 239:2

3

3 26:9 31:17 33:1,5 35:3,6 36:2,4 52:4 60:4 80:12 100:2 101:12 106:16 108:21 109:11 110:4,9 116:15 117:6,20 118:16 120:7 132:12 135:19 137:5 138:14 140:21 142:3,11,13 144:5,9 146:2,15 150:4,14 154:9 155:22 162:3 190:5 201:7 207:11 236:13 238:8 250:17 283:16 285:14 288:20 292:10 293:22
3.4 55:5 143:4
3.9 20:19 106:13
3:00 283:11,12
3:13 283:14
3:48 310:12
30 25:21 41:16 75:14 95:8 146:2 197:15 211:6 216:11
30th 20:2
31 1:14 7:5
310 10:16
33 150:8 193:19
34 175:4 193:20
35 55:16 57:1 165:9
36 7:11
37 109:6
38 144:17 158:17
3-month 26:9

4

4 26:14 33:1,7 36:7 55:21 100:2 115:12 119:4 136:3 144:22 145:9 146:7 149:19 167:7 205:2 218:4 226:5 288:20 294:6,7 301:1
40 95:8 156:13 157:8
40-year 61:4
428 108:22
43 105:6 140:12
430 215:11
433 57:6 188:7
45 34:12 57:12 90:1 136:21
47 109:7
49 306:20

5

5 34:9 52:19 55:6,8 100:2 121:17 135:22 142:3,13 143:6 144:20 145:18 146:4,16 158:14 192:11,12 210:12 226:3 252:18 283:11 301:11
50 7:15 16:14 65:16 95:16 185:1 272:10
50,000 193:5
501(c)3 197:1
52 164:7
54 58:19
58 139:2
5-minute 184:9

6

6 129:18 185:2 195:6 287:6 292:14
60 127:11,14 137:12 232:21 238:15 251:11
600 108:21
60-plus 127:11
61 70:15
63 7:22 109:4
643 146:3
65 47:2 49:18 97:14 127:7 146:19 147:3,5 158:20 168:13,15,18 170:4,5,8,10 172:12,16,17 175:4,6,7 182:18 211:7 223:18 224:10 245:14 303:1 304:1 306:4,21 308:3
65-plus 118:14 120:12 121:1 122:3,17 123:12 127:9,15 129:1 130:8
66 146:21 150:18
69 8:6
6-plus 287:19

7

7 52:4 100:14 105:6 137:5 157:10 197:21 238:9,14 292:14
7.5 48:18
70 139:3 158:22 238:15
700 291:20
703 140:3
71 48:3 56:16

174:8
727 52:12 139:2
74 8:9 48:16
74-percent 118:17
75 89:12 146:20 272:8,15 288:8
78 8:10 88:21 155:7
78.4 89:2
78.5 88:19 141:7 178:18
785 89:9 139:1
79 155:6 251:11

8

8 100:14 116:17 117:6
8.5 55:17 57:4
80 26:19 54:9 121:3 123:11 128:22 159:1 179:13 207:7,18,20 232:19 271:10 281:13
80s 84:20
81 120:14
812 70:5
82 122:15 137:13 173:14
83 121:22
839 207:18
85 49:19 67:17 115:3 117:11,19 121:14 127:16 128:2 145:3 173:15 282:22 283:4
855 138:22
85-percent 122:1
88 49:17 62:5,14 122:3 123:15 136:10
89 154:15
8-percent 118:9

9

9 1:12 31:20 32:4,14 105:6 106:20 107:5 108:6,16 110:8 119:5 166:13
9:54 103:14
90 41:5 43:7 47:15,17 48:3 61:14 62:4 67:17 115:1 122:5 125:4 174:13 283:4,5
90s 84:20
91 128:1
92 46:17 48:9,17 109:3 174:15
93 49:15 61:4 62:13 127:22
94 49:17 123:15
95 76:18
95-percent 114:11
96 145:4 157:9
96.6 55:3

A

a.m 103:14 190:19
A2 272:18
abbreviations 115:6
abdomen 26:13
abdominal 140:18
ability 24:15 119:13 152:6 182:19 266:21 312:5
able 19:22 20:5 54:16 81:22 84:7 131:22 136:10 151:8 180:13 202:5 203:6 206:2,17 216:3 220:21 221:7,11 247:21 256:21 277:7 280:9,15 281:12 293:1 299:4 302:14 304:11
abnormal 35:11 109:16 213:12
abnormalities 211:15
abounds 194:16
absence 67:19 307:10
absolute 40:14 128:22
absolutely 91:7 173:17 247:9
absorbent 25:11 70:13 71:18 199:21
academic 16:16 19:16 265:15 303:8
accept 26:22 78:14 161:9,11 307:11,14
acceptable 45:9,10 53:9 101:2 102:10 142:16 158:15 301:15
accepted 105:10
accepting 198:15
access 68:13,17,21 74:16 77:5,15 84:1 86:12 193:16 196:12 199:14 222:10,13,19,22 231:2 258:13 260:22 269:16,19,21 291:2 293:17 297:6,14 299:8,12,13
accessibility 162:18 230:21
accidents 27:8 119:7 155:2,20 193:22
accomplish 74:9
accomplished 204:13
according 30:8 37:15 42:7 54:15 67:4 76:16 84:15 85:8 88:20 117:15 121:20 122:12 125:3 181:9 195:11 216:2,18 217:1,4,7 219:9
account 71:2 198:10 300:7
accumulating 250:15
accurate 214:7 298:18 311:6
accurately 206:2

Acetaminophen 18:6 20:2,5
achieve 216:4
achieved 49:14,16,19 101:3 108:12 218:2
achieves 59:21
across 134:22 249:15 273:4,12
Act 11:14 12:10 164:6 189:7
acted 59:10 61:19
acting 2:2 3:3 5:18 6:4,8 15:3
action 200:17 309:8 312:7,8
active 25:20 33:18 68:9 75:19,20 227:5 250:9 291:20
activities 198:5,10,16,18
activity 272:13 308:21 309:5
actual 7:12 14:7 21:16 30:7 37:13 38:6,16,21 50:6,9 77:1 80:18 83:13 84:13 90:4,7,15 113:9 130:17 133:16 134:2,20 135:2,5,11 163:20 165:7 168:12,14 169:6 171:20,21 207:3,6,17 215:7 216:1 217:10,15,17 219:13 220:5,7 240:19 244:16 245:1,13 260:3 265:3,4 274:6,8 307:12
actually 82:18,19 84:8 85:3 88:6,16 92:16 94:5 95:7,10 98:16 99:1 100:5,6 101:3 102:16 120:17 121:5 129:19 131:8 138:11,22 152:19 160:8 164:5 165:4 173:7 181:21 187:20 188:12,17 194:7 207:16 216:8,21 217:7 218:5,20 221:5 224:13 226:16,17 235:20 245:22 250:11,21 264:18 268:5,13 270:4,18 272:18 280:13,18 285:16 290:22 291:3 293:2 298:15 299:7 306:2
acute 26:11 150:12 153:3 187:6,10,11 296:14
acutely 267:1
ad 90:20
ADA 67:4
adapt 27:10
adapted 156:21
add 133:8 186:7 229:13 238:2 267:17,20 272:7 290:11,13 300:15
added 44:13 46:5 60:5 131:12 198:21
adding 223:2 225:6 241:21
addition 49:11,15 71:21 72:20 138:5 142:18 149:17 156:15 200:21 233:16 257:15 258:4 261:16
additional 30:18 38:10 53:3 66:19 78:2 98:18 109:22 125:22 142:19 158:7 167:19 168:2 186:17 213:9,13 254:5 256:7 301:17
additionally 16:22 27:12 65:2 67:8 91:22 137:20 140:14 155:19
additive 241:7
address 23:13 30:17 72:10 113:16 123:19 179:9 191:18 208:13 212:8 214:17 224:22 229:5,9 249:3 250:2 265:17 266:7 268:9 302:2 309:10
addressed 46:17 112:8 121:15 124:15 209:16 278:13,22 302:4 303:20 309:7
addresses 59:19 187:18 270:5
addressing 112:6 302:1
adequate 135:3 136:9 137:6 282:22
adequately 158:12 169:16 210:6 291:16 292:4
adhesive 100:6
adjourn 22:4
adjourned 310:11,14
Adjournment 10:16
adjudication 40:7 53:7
Adjunct 99:9
administer 164:13
administration 1:5 12:7 17:8 22:19 33:21 191:1
administrative 82:6,15,16 89:7
administratively 139:10
admittedly 277:13
adopt 64:10
adopted 104:9
adult 26:6 28:12 204:4
adults 166:13 251:1
advantages 26:3

162:17

adverse 35:4,9 109:7,8,10 146:22 147:7,13,16,18,20,21,22 153:21 154:2,3,5,7,15,18,20 155:6,9,12,14,17,22 156:1,9,11 157:2,12 177:3,6,17,19 178:3 182:22 208:19 223:22 224:4,6,14 296:20

advertised 173:2,3

advertisements 136:16

advertising 44:20 51:11 52:9 72:18 264:6,13 302:18,20 304:20,21

advice 19:6 59:20 134:14 153:9 158:22 225:20 254:5 264:11 308:4

advise 15:17 23:4,11 191:9,16

advised 97:17 187:7 194:22 284:9

advisory 1:7 2:4,8 3:13 11:13,15 12:9,10 17:8,11 18:5 20:2,4 22:22 184:19 191:5 297:22 310:13

advocacy 193:2 205:5 211:2

advocate 10:5 18:3 201:9

AE 147:9

AEs 157:8

Affairs 2:16 7:4 31:5

affect 24:17,19

affected 26:19 64:2 66:7

affecting 24:8

affects 228:22

afraid 203:22

afternoon 157:19 162:11 186:9 192:21 232:9

afterwards 168:3 188:16

against 29:10 73:19 94:3 114:19 117:11,14 118:19 210:8 218:1 224:7

age 21:4 47:2,4,7 49:14,18 61:3 66:8 81:18 109:4 118:14 120:12 121:1 122:3,17 123:12 127:7,8,10,14 129:1 146:13,18 147:1 170:1,13,16 172:22 174:17,18 175:3 211:6 223:19 224:15 241:16 242:2 248:19,20 249:20,21 251:12 261:4 277:15,19 279:18 303:22 305:12 306:4,21

agencies 12:14

agency 192:1 254:6 303:15

Agency's 13:6 255:21

agenda 13:19 14:14 15:11

agent 267:15

agents 250:7

ages 75:10 81:18 230:20 309:2

aggressive 67:21

aging 27:1 68:16 70:21 71:5 211:8 234:5

ago 21:2 75:15 115:10 184:20 189:10

agonist 106:3

agreed 17:1 82:8 114:1 142:17 165:22 207:14 208:1

agreement 94:10 178:6 215:20

ahead 101:17 103:4 161:4 306:17

aid 72:3 77:12 224:11

AIDS 199:17

airways 99:22

akin 255:9

alcohol 105:16

algorithm 53:19

alike 72:9

allay 247:13 248:12 307:6

all-comers 173:2

allergic 127:21 128:1

allergy 83:2 138:5 139:19 153:21,22

allow 50:15 196:4 216:21 217:5 221:17 240:12,15 257:6 278:1 299:13

allowed 11:10 51:5 85:7 87:4 291:7

allowing 201:10 222:1 227:4

allows 36:7 85:1

alone 73:7 86:11 195:5 213:2

already 15:11 28:6 49:12 59:14 77:6 79:13 84:16 104:17 109:12 110:11 112:6 113:1 121:5 125:20 128:6 171:2 209:3 226:8 232:22 233:3 235:2 244:19,20 261:20 267:20 268:4,7 269:7 270:15 277:1,9 294:8 301:20 304:15 305:22

altering 70:12 198:4

alternative 64:8 214:8 240:19
alternatives 201:2 213:16,17
am 31:4 60:20 63:18 68:12 69:10 78:7 171:22 210:14 227:3 265:22 266:1 288:15 290:2,3 303:14 311:7 312:7,8
America 17:11
American 24:8,11 74:19 105:3 156:8 209:20 210:14 228:1,11
Americans 193:16,20
among 19:18 21:12 38:17 45:21 46:18 47:2,7,14,17 48:1,8 49:2,3,14,18 59:14 62:13,14 63:21 70:4,14 77:6 101:13 121:2 122:5,18 127:13 168:10,18,20 170:14,20 174:11,14 182:16 194:16 279:5 303:6
amongst 234:7
amount 16:21 79:16 118:4 250:5 251:6 300:4
Amy 7:13 30:6 50:7 89:20 92:13 94:21 95:1 101:17
analgesic 237:6
analogous 128:8 221:2
analyses 144:13 159:5
analysis 40:17 53:5 93:6 146:13
analyst 9:5 111:19
analyze 39:12
analyzed 39:22
anatomic 211:15
and/or 162:16 277:22 294:21
Andrea 5:11 6:12 163:3 164:3
anecdotal 225:15
anecdote 292:2
anecdotes 65:20 291:12,14
Angioedema 111:8
angle 130:15
Annandale 3:16
annoyed 194:12
annual 66:18 200:4
answer 30:20 79:9 87:15 160:18 161:10 187:13 220:4 231:5 249:19 263:14,15 274:5 285:12 297:1,9 298:16,22 299:11
answered 85:13 87:17 92:4 176:21 186:18 255:3 275:11 281:18
answering 77:20
answers 70:19 196:11 263:19
Anthony 10:8 210:13
anthrax 18:9
anticholinergic 25:18 33:20 36:8 65:7 66:21 68:7 75:17 79:12 86:9 93:17,22 94:1 99:16 109:15,19 154:14 155:3,21 156:3 157:13 158:5,8 159:13 175:16 177:4,11,14,21 185:11 213:7 223:3,21 224:18,21 231:14,18 239:9 241:7,11,17 249:15 250:7,10 272:13 273:13 278:20 279:8 289:2 302:3 308:21 309:5
anticholinergics 33:13 35:10 65:9 68:2 79:4,17 86:10 154:13 182:14,16,19 183:8,11,16 212:15 228:3 244:18 247:4 272:18 279:17 289:4,12 303:5 304:9 306:13
anticipated 129:7
anti-fungal 189:11
antihistamines 128:5 183:10
antimuscarinic 106:2
antimuscarinics 91:5 208:17
Antonio 3:10,11 18:1
anxiety 24:17 198:19
anxious 11:19
anybody 103:5 230:13 238:1 254:3,7 273:21 278:9 286:22 310:1,10
anybody's 239:19 282:14
anyone 57:21 83:4 102:21 185:18 190:15 218:16 246:13 256:13 284:18 296:7 308:3 310:3
anything 79:2 80:1 102:11 103:11 121:21 122:13 125:3 162:4 185:12 231:8 239:18 241:22 243:1 270:16 273:21 295:16
anytime 296:4
anyway 125:10 244:7,12 253:21
apologize 189:16
apparent 151:10 159:7 215:4

appeal 171:16
appear 28:21 159:13 294:4
appearance 197:13
appeared 145:8 152:3 156:3 238:9
appears 34:22
appendix 301:19
applaud 305:4
Applause 17:16 18:17 19:10 20:12
applicant's 156:21
application 1:9 13:21 21:17 31:18 35:8 106:16 109:12 133:21 147:4,10 148:5 157:5,6 159:12 177:10 183:8
applied 26:13 53:2,14 58:4 102:22 134:9
applies 114:17
apply 54:22 97:12,17,20 98:3,6 100:10 113:7
applying 72:2
appreciate 201:12 210:17
appreciation 6:9 15:22 17:2 18:13 19:8 20:9 77:22
approach 29:18 37:19 40:20 41:4 76:6 82:11 166:4 173:2 190:5 259:13,14 264:2,3 304:16
approached 47:17
approaches 28:7 85:14 259:10 265:13
approaching 34:12 47:15
appropriate 14:9 21:19 27:22 29:4,10 31:8 36:13 41:12 50:2,4,11 54:10 56:15 59:8 64:22 73:17 74:3 76:8,17 77:12 83:14 84:15 85:19 105:19 112:19 113:2 125:16 142:17 173:12,19 214:4 216:14,18 239:3,14,18,20 243:21 279:13 281:9
appropriately 29:21 37:4 39:4 43:18 50:18 59:10 61:19 63:8 73:2 145:6 164:10 174:8 179:17 186:15 210:7 215:5 216:8 220:2 232:17 274:3,10 300:10,11
approval 31:19 36:4 104:6 106:9 109:21 184:7 196:14 278:14
approved 20:22 25:22 75:15 105:20 106:2,5,10,13 242:18 249:21
approximately 108:21 109:2,4 127:4
April 18:6 19:4
arbitrary 226:6,12
ARBOGAST 312:3,11
area 69:5 97:19 167:18 214:4 265:17 280:11 306:15 308:15
areas 19:21 46:15 51:1 175:14 306:15
aren't 224:8 266:9 285:2
argument 248:4
arm 83:20 271:17
array 19:17 265:13
arrived 52:10 92:18
Arthur 4:3 276:10
articles 19:17
articulated 229:6 277:9
artifact 256:12
aside 281:10
aspect 24:13 74:15 185:13 252:4 277:5 287:12
aspects 86:13 124:12 163:15 197:17
assess 18:8 39:7 135:8 221:10
assessed 73:18 130:5 137:2 184:6
assessment 130:6
assessments 251:14 252:2
assigned 120:6 127:20
assistance 237:4
Assistant 2:12,13 4:16 18:20
Associate 99:10
associated 24:6 33:3,13 35:10 45:12 56:4 61:17 80:2,5 155:2 194:3 199:16 204:17
associates 204:9
association 9:18 105:4 140:17 156:8 193:1 209:21 228:2 249:1 251:15
assume 91:14 169:14 262:14
assumed 184:7
assuming 169:10 222:21 231:8 258:13
assurances 196:3
assured 199:14
astronauts 221:4
asymptomatic 65:1 151:1

at-home 137:4
Atlanta 2:20
at-risk 62:15
attained 45:18
attempted 89:18
attempting 70:12
attempts 221:19
attend 41:18 201:13 202:4
attendance 191:15
attendees 215:1
Attending 7:20
attention 29:13 67:19 77:18 110:16,21 136:18 150:7 214:9,17 259:18
attitudes 70:4 71:1 73:17 74:7
attorneys 262:18
attributes 36:12
attuned 120:18 128:10
AUA 228:1
Auburn 7:21 63:17
audible 103:7 254:8 273:20 274:1,13,16 283:9 301:2 310:4
audience 214:14
audio 312:4
Audrey 5:18
AUGS 10:8 210:19
author 16:16
authored 19:17
authority 12:9 262:7,15
authorized 13:3
avail 84:7 253:17
availability 24:20 27:18 30:10 59:13 67:14 74:21 75:22 163:15 209:2 280:12
available 30:19 59:5 64:5 71:22 90:6 96:9 105:22 137:12 168:21 194:13 198:13 200:9,22 204:15,20 205:18 207:19 208:20 210:1 222:8 229:17,21 230:10,12,15 231:1,15 232:12 234:11 241:19 248:7 253:16 261:17 262:1 266:11 298:9,21 299:17 303:13 307:21
Avenue 1:16
average 48:17 107:3,18 109:1,4 118:9 120:12 200:3
avoid 79:5 167:11 199:6 202:10 250:14
avoided 199:10
avoiding 105:15 258:11
avoids 33:21
Award 17:8
aware 11:18 267:6 287:22 306:13 309:10
awareness 28:1 68:19 70:4 71:3 73:21,22 74:1 86:14,16 221:3
away 113:7 116:18 121:19 195:7 247:11 257:17 308:14
awfully 226:12
awkward 92:22
axis 34:7,8

B

baby 194:9 202:11
baby-boomers 97:14
background 81:21 182:16
backlash 253:15
backwards 171:13
bacteriuria 65:1
bad 240:14
balance 162:20 163:10,14 164:18
balanced 259:14
balancing 208:7
Baltimore 4:6
Band-Aid 97:22 98:1,2 100:5
bar 54:18
Barbara 9:4
111:13,18
Barrett's 298:5,15
barrier 222:16 293:16
barriers 25:17 71:10 74:22
base 309:20
based 14:14 23:8 29:11 31:7 34:10 35:14 41:12 43:19 49:21 75:15 89:3 102:17 111:1 113:14 115:2,3 132:11 142:10,11,14 171:21 176:13 182:6 235:4 268:17 281:14,16 301:12 304:10
baseline 32:2,10 70:2 73:19,20 106:20,22 182:14,19
basic 4:4 258:20
basically 95:16 100:4 127:2 137:2 170:9 173:1,5 187:15 220:12,14 229:5 237:2 240:20,21 252:20 284:8
basis 40:1 96:19 113:11 308:20
bathroom 42:6 198:6,11,13 199:14 201:22 202:7 205:15
bathrooms 202:2

bear 81:12 295:16
bearing 220:6 274:7
beautiful 226:2
became 193:10 202:9 238:5
become 204:4
becomes 226:5 262:10 300:6
becoming 61:11
bedwetting 230:9,17
Beers 278:20 303:5 305:17 306:11
Beer's 228:4
begin 23:17 203:2 254:11 274:19
beginning 23:11,14 78:4,13 116:6 171:15 191:8,16,19
begins 27:7 29:22 198:2
Begun 197:7
behalf 15:3 16:5 196:19 197:9
behaved 57:10
behavior 27:22 31:22 37:6,9 39:2,7,10,20 40:2 50:10 53:9 54:4,10 55:2 56:15 59:3,8 60:21 61:21 62:11 85:3 86:10 166:20 184:6,13,16 199:2
behavioral 24:21 71:8 72:21 73:5 83:9,17,19,21 85:14 86:2,7,13,17 99:13 195:1 196:5 208:20 209:12 221:18 227:18 238:21 255:8 256:16 257:4,17 259:10,12 264:2 267:21 268:8 277:21 278:13 301:22 302:10,12,15 304:16
behaviorally 268:4
behaviors 51:6 55:5 57:5 70:3 71:2 73:18
Beitz 5:15
belief 47:20
beliefs 70:3
believe 22:19 125:16 158:12 159:14,18 164:1 173:15 182:2 191:2 200:20 201:1 210:5 227:4 245:9 262:18,19 278:16 283:2
believed 48:6 154:3 173:5
believes 22:22 191:5
belongings 190:15
Belvoir 4:21
benefit 27:17 30:12 32:20 36:4,5 64:6 71:6 77:3 101:2 201:1 208:17 214:3 226:10 232:11,14 240:17 245:7 296:19 297:4,5
benefited 16:19 19:5
benefits 31:13 33:10 77:7 208:7 222:21 223:6 233:17
best 73:9 84:22 117:3 119:20 129:20 171:10,18 172:4 208:22 290:20 304:10 312:4
bet 256:15
beta-3 106:3
Beth 63:17
Betsy 119:5,7
better 34:2,22 46:3,11 68:9 86:4 98:4 107:8 125:10 237:16 241:20 247:20 285:2,3 298:9
beverages 105:15 258:11
beyond 103:1 236:3,13 238:7 283:19
bias 58:11 129:12 217:17
bigger 118:11 177:14
biggest 277:4
billion 200:5
binary 41:3
biofeedback 202:17 203:2 256:17
biomarker 104:12
bit 22:14 80:20 81:10 103:4 104:3 116:10 120:19 122:14 123:22 130:14 133:1 134:2,18 136:14 148:10 167:4 178:1 179:12 190:4 215:8 218:9 226:4 233:19 235:10,14 238:13 245:17 250:3 287:6,16 290:13
black 304:19
bladder 14:3 21:1,3 24:2,3 25:7 27:6 28:12 31:10 42:5 58:6 59:18 60:12 62:3,10 63:21 67:11,12,15,21,22 68:19 69:5 72:10 79:20,21 80:2,5 83:18 86:8 88:9 99:18 104:4,17 105:7,13,16 106:12 115:9 116:14 117:17 120:2 131:22 140:9,16 149:4,5 152:6,13,22 153:5,12,13,15 173:4 186:22 187:2,5,14,21

188:19 189:4 193:3,13 195:1 197:9,18 200:2 201:18,20 202:13 204:19 206:8 211:3,16,19 213:4,22 220:15 221:15 223:9 228:8 230:2,4,6,18 233:1 235:3,11 237:10 240:22 241:1 244:14,20 247:1,4,10,18,21 256:20 257:3,10 264:3 265:17,19 267:14 268:13,14 269:12,13 279:16 288:9 291:13,15 292:22 293:2,3 294:21 303:6

bleeding 213:12

blinded 251:10

blinking 256:10

blistering 154:8

blisters 128:2

blood 42:7 60:10 83:1 123:16 213:11 228:16

blue 34:13,15 46:4 136:18 174:6

blurry 157:15,22 186:10

board 69:15 228:12

bodies 205:7

boiled 70:19

boils 232:4

bolded 28:18 60:2

bolding 46:9

book 32:22 42:21 58:19 89:3 301:19

booklet 256:18,22 272:8

booklets 256:3

boomers 194:10

bother 287:12

bothersome 63:22 96:19 158:10 213:5

bottom 149:9

bought 203:5 207:7

bound 40:18 41:1 55:8 114:11,15 115:7 118:17 119:19 120:13 121:1 122:4 123:15 127:16 215:19

bounds 145:16

bowel 193:3 197:10

box 46:4 83:21 84:3,4 92:20 93:2 96:10 137:17 171:12 174:6,12,21 176:15 219:13 245:22 258:9 265:4 304:19

boxes 90:7 310:8

bracket 223:19

brain 161:5,21 236:9,10 237:5 240:8 250:13,15 269:2,14

break 8:12 10:13 103:9,14 146:9 169:19 170:17 172:14,16 188:15 190:13,19 272:19 283:11,14

breakdown 174:16 175:3

breaking 170:16 199:3

breakout 169:22

breakouts 81:18 170:1

breaks 12:2 170:13

breastfeeding 83:2 137:22

brief 30:16 112:2 178:15 215:14

briefing 32:22 42:21 58:18 88:18 89:3 101:10 206:5 209:1 301:13,19

briefly 31:13 104:5 127:17

bring 113:2 120:15 219:17 239:15,18,20 293:15 295:16 299:2

bringing 112:20 183:18 197:2 231:6 296:11 298:19

brings 27:6 205:5 297:3

broad 16:20 72:14 105:5 232:3

broaden 68:18

broadly 193:4

brochures 84:2

broken 146:5

brought 139:4 171:12 184:4 185:21 203:4 239:15 249:5 264:9

brown 34:8

Brunswick 4:19

bugging 286:1

Building 1:14

bullet 132:5 146:11 147:7 158:6

bulleted 130:13,21 132:3,7

bulleting 131:3

burden 222:11 249:15 250:10

Burnett 4:3 80:16,17 175:9,10 176:20 242:22 243:1 276:10 280:2,3 289:15,16

Burnett's 186:18

burning 60:9 61:22 123:9 244:8,12

bus 199:13

busy 107:4

busyness 154:11

buttocks 26:14
button 254:13,16 274:21 275:2
buttons 254:11 256:9 274:19
buy 91:12 185:15 225:14 230:13 246:3 258:20 292:16
buying 79:5 92:1 208:2
bypass 199:5

C

CA 2:10
caffeinated 258:11
caffeine 105:16
calculate 198:12
California 2:10 19:15 253:21
callers 138:10
calorie 256:4
Cambridge 7:22
campaign 72:20 245:9
Campus 1:14
Canadian 228:2
cancer 59:18 60:12 62:3,10 67:13,15,22 104:18 140:16 149:5 153:12,13,15 199:17 247:18 265:20
cancers 67:21 247:19
candidate 26:5 36:13
candidates 228:13
candy 97:4
capable 184:2
capita 200:4
Capital 1:20
capture 39:21 153:14 167:9 180:13
captured 54:16 82:1 102:21 155:10
capturing 176:1
car 199:13
carcinoma 228:7,15 233:7 237:9 239:7,10 244:3 247:17 277:12
card 26:13
cardiac 212:4
cards 52:2,13
care 6:19 7:5,11,15 8:6 11:15 13:20 19:20 20:20 23:21 26:18 28:17 30:15 31:5 53:11 59:8 64:18 65:15,18 66:12 69:15 70:18 71:12 72:9,16 73:1 74:3 77:13 81:3,21 82:2 96:4 162:22 164:2 189:5 195:21 196:6 197:6 199:21 200:18 208:16 211:1 218:16 227:5,8 228:22 234:8 248:11 259:10 280:14 290:15 291:7
career 16:15 19:16 199:5
careful 166:21 214:17 219:6 273:8
carefully 37:5 44:8 53:7 61:16 93:19 192:7 216:17 259:20
caregiver 185:13
Care's 14:12
carry 41:19 75:3
case 85:5 87:2 108:8 119:20 126:19 148:8 153:6 186:20 187:9 208:4 297:10,12,13,14 306:5
case-by-case 40:1
cases 45:16 59:9 65:2,5 67:17,22 105:18 153:2,13,15 228:21 296:3
cast 173:4
categories 58:18 73:13 155:11 173:18
categorize 39:16
categorized 47:11 173:18
category 58:20,22 66:4,6 110:13 128:8 224:1
caught 66:17
cause 64:21 74:1 94:5 161:5,22
caused 45:22 104:22 206:14 236:7,9,10
causes 71:7 74:14 206:9 268:16,17 269:12
caution 111:10 159:15 228:3
cautious 188:5
cautiously 57:11
caveat 256:15 277:20 309:19
caveats 112:9 129:10
CD 257:17,22 258:12,14 260:18 262:20 263:3,9,10,12,14,17
CDER 1:6 2:5 5:9,13,16,20 6:15 8:20 9:6,12
CDs 258:1
center 1:6,15 3:9 17:12 18:1 63:18 257:19 259:10 303:9
centered 49:5 259:9
Centers 156:9
certain 33:14 40:15 41:20 81:9 161:20 163:22 306:4
certainly 79:9 81:4 84:3 175:11

213:14 231:1 244:15 245:12 246:3 249:9 261:8 268:20 269:20 273:16 296:9,11

CERTIFICATE 311:1 312:1

certify 311:3 312:3

cetera 117:7 251:18 299:18

Chair 17:1 167:22 192:9 229:9 239:20

Chairperson 3:3 6:4 11:11

challenge 126:4,5 129:14 245:16 298:22 299:21 305:14

challenged 126:5

challenging 39:21

chance 182:12 249:7 257:6 272:21 274:14

chances 64:1

change 32:1 41:22 50:19 106:18,20,22 107:2 203:6 205:15 244:6,10 254:15 261:3 262:3 275:1 282:18 290:8 298:21

changed 46:4,11 68:8 93:1 129:9 176:13,15 227:6

changes 33:3 48:4 63:3 68:10 73:17,20 112:11 130:9 209:12 212:4

changing 72:2

chapter 196:9

characteristic 296:2

characterized 24:5 181:10 213:3

charges 162:12

Charles 5:7

Charlie 271:13

Charlottesville 4:14

chart 226:2

chat 255:6

chatting 242:5

cheaper 291:4

check 228:14 300:4

checkpoint 181:16

checks 308:14

chemical 231:3

chest 147:19

chew 116:22

Chief 4:20 10:8

child 201:21 230:17

childbearing 49:14 61:3 212:22

childbirth 65:22 194:8

children 13:13 199:1,3 230:8,20 234:17

chills 138:3 148:14,18 149:14

chime 235:16 238:1

choice 82:17 163:2 230:22

cholecystitis 147:19

cholesterol 195:14

choose 23:13 25:14 26:19 69:22 70:11 75:2 191:18 196:11

choosing 48:2 207:12

chose 70:17 95:12

chronic 24:3,8 65:12 184:21 198:18 259:11,13

cimetidine 242:19

circled 141:12

circulating 93:22

circumstances 77:1 98:11 126:7

cite 132:16

cited 208:15

claimed 70:15

clarification 46:10 80:9 87:7 101:15 103:6 160:2 263:8

clarified 215:8

clarify 80:20 81:10 131:18 133:6 176:7,18 189:18 218:18 264:12

clarifying 8:10 9:13 78:10,12 159:21 165:10 168:2 185:10 192:14 214:11

clarity 38:11 63:2 168:8 171:7 304:11

class 111:1 189:9 224:20 308:20

classes 231:19 242:12

classic 33:14,20 36:8

classification 44:10 110:13

classified 44:7 58:17 194:1

classifying 40:8

clean 25:3

cleaning 199:22

clear 18:11 27:16 28:19 80:10,19 86:7 90:15 92:6 131:10 139:19 148:7 166:17 181:1 194:19 212:20 218:13 247:9 263:19 304:14

cleared 187:3

clearer 171:17

clearly 28:13 59:22 77:13 85:5 228:20 262:12 282:5

Clinic 208:16

clinical 2:9 5:12 6:13 7:2 9:9

16:13,21 17:21 19:14 29:14 30:1 31:2,13,16 33:10 36:4,5 40:7 63:10,18 66:15 69:1 75:16 83:19 99:6,19 109:5,6 110:4 111:20 113:20 114:4,7 133:17,20,22 143:9 155:13 160:19,21 161:16 167:12 182:5 187:10 226:7 237:1,8 249:18 250:22 296:22 306:21 307:2,8,14

clinically 32:19 176:4

clinician 64:3 303:8

clinicians 292:21

clinician's 30:10

close 117:18 120:5,22 122:1 159:1 198:6

closed 39:10 254:16 275:3

closed-ended 43:22 53:6

clothes 205:15

clothing 202:8

cloud 204:3

cloudy 64:15 123:10 138:4 148:15,20

CNS 111:7 156:3 250:4,6 252:8

CNS-related 155:3

codes 268:15

coexistence 268:11

cogent 18:11

cognition 223:2

cognitive 94:4 97:15 250:4,22 251:22 271:15 272:11 273:16

Cohen 9:4 111:13,17,18 152:7 176:7 215:20

cohort 48:9 49:4 110:6 122:6,7 127:4 129:17 168:6 170:20 172:21 173:14,16 174:3 175:5,6 182:18

cohorts 43:7 44:18 45:18 124:3 172:20

coincident 150:16

Colas 276:12

cold 203:21 307:22

collaboration 72:5

colleagues 179:10 242:15

collected 35:14 62:20 219:18 310:9

College 3:6 16:14

color 46:4

column 58:19,22 59:2 142:22

combination 27:20 65:14 70:7 86:9 195:2 203:15 211:1,18 269:22

combine 154:12

combined 86:1

comers 303:14

comes 245:3 268:19 292:15

comfortable 98:2 102:15 221:12,13

coming 45:1

commas 132:6

commend 252:11

comment 85:22 162:22 163:19 164:2 175:15 177:2 178:16,22 189:2 210:17 215:10 218:16 229:8 239:17 248:22 254:4 273:19 276:19 278:9 286:4 288:4 307:7 308:18 309:16

commented 171:2 180:5 238:18

commenting 196:19

comments 19:6 49:6 192:1 210:16 214:14,19 220:8 224:18 227:2 245:22 254:7 260:12 263:6 269:4 270:3 274:15 278:5 281:11 282:14 283:8 284:2 294:15 300:22 309:13 310:2,10

committed 200:13

committee 1:7 2:4,8 3:13 6:2 11:2,14,15 12:1,9,10,12 13:1,10 14:8,15,19 15:17 17:8,12 18:5 20:3,4 21:18 22:4,7,22 23:4,11 78:12 94:11 103:5,10 104:2 110:1 160:2 162:13 179:15 184:19 186:14 191:5,9,17,21 192:2,13,17 210:8 214:16,18,21 264:10 265:12 266:9 270:3 297:22 301:10 310:6,13

Committee/ Committee 10:12,15 214:15 283:15

committee's 12:17 165:17

common 16:22 24:7 37:16 63:22 65:14 74:20 104:15 105:1,12 109:10 123:9 148:4 157:2,5,16 159:14 166:9 168:19,20 212:2 236:8 247:19 258:17 309:3

commonly 35:9 100:21 152:15

157:12
communicate 253:1
communicated 28:13 304:18
communicates 77:11
communication 19:19 71:16 116:12 117:8 118:5 119:22 121:8 124:16 252:22 260:16
communications 113:14,16 123:2,7 127:18 128:12,20 196:19 200:14
community 4:21 17:22 18:3 25:4 265:15
comp 112:4,15,17 113:3,4,13 115:8 118:14,21 119:16 120:13 122:17 124:1
companies 96:4 201:16 205:9,10
company 1:20 15:6 201:14 299:1
comparative 34:3 86:1
comparator 101:20 185:4
compare 175:13,18
compared 32:8,12,14 35:1 45:3 57:8,13 77:3 101:2 108:15,17 110:6 141:5 173:9 179:2 195:18
comparing 32:4 272:10
comparison 83:11 273:10
comparisons 273:7
compass 74:5
compassionate 248:10
compatible 220:16 241:4,5
compensated 30:21
competitors 191:12
compilation 83:3
complain 194:17 202:1
complaint 96:18
complete 138:12 139:10
completed 62:22 136:11 137:13,15 140:3 142:12 144:8 146:2 154:9 254:17 260:10 275:3
completely 58:7 88:9 121:15 224:19 265:5 286:6
completes 111:12
complex 95:18 104:10 304:6
complexity 303:4,17
compliance 12:17 13:1 19:19
complicated 91:2 184:3
complications 243:22
component 71:13 72:5 83:18 278:13
components 73:11
compound 231:3
comprehend 119:14
comprehended 47:5
comprehension 7:7 9:2 14:6 21:15 30:4 36:17,19 37:10 38:2,15,20 41:8,21 42:4,13,18 43:4,12 44:18 46:15,22 47:1,3,8 48:15 49:13,18,22 61:2,13 62:3,13 76:9 84:17,18 111:14,16,21 119:18 121:22 122:14 123:16,19 127:15 129:2,22 130:4,6 181:4 207:3 215:17 216:4 282:10,12,16
comprehensive 30:14 35:19 69:11
comprised 80:22
conceal 26:21 27:11 70:12
concealed 68:17
concealing 25:1
concentration 34:7
concentrations 34:12 250:13
concept 267:16
conception 166:9
concepts 157:19 282:11 301:17
concern 54:13 58:1 60:19 67:20 69:2 80:7 91:4 128:18 153:7 165:22 166:1 208:13 213:18 223:17,21 224:10 228:6,7 230:19 234:1 238:4 240:1 241:2,8 267:5 277:4 278:2,12,15 282:21 283:21 284:4,5,12 285:16 292:1,7 295:2 298:4 301:9 307:6
concerned 135:4 183:21 225:21 232:16 241:7,14 242:3 266:9 282:11 284:20 285:1,2,12,15 286:7,12 288:19 290:2,3 294:3

301:9

concerning 14:21 56:15 150:16 159:10 243:18 285:17

concerns 75:3 101:1 115:11,17 136:9 182:7 212:7 222:1 227:12 231:16 232:9 234:10 240:15 244:16 245:4 247:13 250:1 253:7,22 257:9 265:18 267:13 268:10 277:10 282:13,15,20 283:6 288:21 292:3 294:1,9,12 301:4,6

concerts 198:8

concise 90:14

conclude 30:16 159:17

concluded 208:20 214:13

conclusion 11:22 29:20 49:21 63:5 77:9 158:11 163:17 210:5

conclusions 108:11 109:17 136:7 179:21 233:4 273:8

concomitant 134:11 154:4

concur 127:2 243:17

concurrent 302:2

condensed 178:3

condition 24:4 26:20,22 28:21 50:18 52:18 54:12 58:1 59:2 60:11 62:2 64:2 66:16 68:15 69:21 70:11,17 71:4,20 73:9,22 74:20 75:5 77:1 86:15 91:20 115:19 118:16 119:3 124:18 158:18 168:9,20 190:2 201:4 206:21 208:12 214:7 217:22 222:8 225:5 235:4,8 255:13 259:11,13 260:3 266:19 267:2 268:4 278:3 284:7 285:8 286:13 287:10 293:6 301:8

conditions 24:8 26:10 27:14 28:16,20 29:9,15 45:8 50:10,17 51:7 53:10 59:15,17 60:1,22 61:20 63:22 71:16 74:1 94:4 104:15 115:22 117:6 119:7 124:19 130:12,19 131:1,10 134:11 140:19 141:14,15 150:2 159:8 161:3,16,19,20,21 162:2 164:10 187:17 195:13 199:17 206:10,13,15,18 209:6 220:17 235:5,12 267:1 269:13 294:13,19 295:18,19 296:8 297:7 306:4

condition-specific 33:2

conduct 172:19

conducted 21:17 37:3,8 38:14 42:12,14 45:5 48:1 49:3 50:22 126:17 130:11 156:17 174:13 192:6 208:14 251:3

Conference 1:15

confidence 25:13 40:18 55:8 114:11

confirm 137:8 212:21

confirmation 262:5 274:12

conflict 6:6 12:5,15,18 13:2,8 14:16 279:1

conflicted 227:3 243:3 245:2,18 303:10

conflicts 13:6,11 210:15

conform 187:15

confounding 66:1 215:22 266:22

confused 65:12 67:10 79:20 166:3 187:5 215:13 296:12 303:18

confusing 133:2 150:11

confusion 131:18 155:1,7,16 177:4,21 303:14

congratulate 243:16

congratulated 245:10

Congress 13:3

conjecture 249:4

conjunction 69:6 203:1 208:22

connection 14:17 191:14

consensus 294:4 302:6

consent 82:7,18 139:11

consequence 42:20 47:12,13,14,16 48:20 85:4 268:18

consequences 30:12 68:5 69:2 81:4 113:18 115:2,4 237:12

consequently 243:9

conservative 102:11 105:14 114:14 117:18 120:19 166:4 167:5 218:11

consider 14:8

21:19 26:15 56:11 57:19 66:13,15 155:1 157:20 158:3,7 161:18 187:6 189:3 211:8 223:20 236:16 245:11 296:20 302:17

consideration 31:9 36:14 77:19 132:10 162:5 192:2 213:18 214:18 231:5 279:14

considerations 112:12 113:18 213:9 214:4

considered 41:6 42:10 53:4,12 84:3 94:17 106:15 109:8 139:21 140:1 142:19,21 148:11 152:4 153:20 158:19 161:3 169:10 200:6

considering 57:19 236:18,20

considers 20:7

consistent 29:8 35:15,22 36:7,10 38:9 43:10,13 45:11 138:2 157:13 173:13,17 177:7 178:7 244:13

consistently 105:11

constellation 187:15

constipation 33:15 35:11 109:15 147:4,11 154:16 158:9 212:2 273:5

constituency 193:8

consult 213:10 220:20

Consultant 2:4

consulted 69:13 194:22

consulting 3:15 13:15 15:7 23:6

consumer 3:7 6:19 7:5,10,11,15 8:2,6 9:3 13:20 14:6,12 18:7 20:20 21:14 23:21 31:5 36:22 37:6,9 39:2,6,10,20 46:21 49:10 50:9 60:21 61:21 62:11 69:7,8,14,18 70:3 72:4,18 94:21 95:1,9 111:16,22 112:7 115:18 116:7 117:1 129:22 134:21 164:11 166:19 224:9 242:13 246:6 255:12,17 256:2 262:9 279:12 287:5 299:6 300:1 301:18 303:3,15

consumer-centered 259:7

consumers 14:10 21:21 29:6 30:15 37:3,10,12,14,18 38:1 39:3 43:18 50:15 56:11 60:6,13 73:2 75:6 87:8 91:8 92:15 113:4,7 115:19 119:13,18 135:6 158:4,10 159:15 166:8 213:3 220:2 224:1 274:3 283:21 285:13 298:9 304:13

contact 64:18

contain 72:1 242:6 257:2

contained 56:13

containing 18:8

contemplating 242:10

content 263:10 301:14,15

CONTENTS 6:1 7:1 8:1 9:1 10:1

context 23:1 98:14 134:10 141:10 144:16 156:13 183:9,15 184:5 185:6 191:6 255:16

Continence 9:18 10:3 104:9 193:1 196:20,22

contingent 165:19

continually 197:15

continue 54:3,12 88:12 143:15 187:3 188:16 241:7 254:12 255:2 261:22 274:20 275:10 278:7 284:10,11 293:22

continued 3:1 4:1 5:1 7:1 8:1 9:1 10:1 39:17 53:16 56:4 57:12,15 102:8 103:1 143:18 158:22 187:2 203:4,18 283:18

continues 309:4

continuing 284:9,15,16

contracts/grants/CRADAs 13:16

contradictory 96:21 97:5

contraindicated 45:8 60:18 94:3

contraindication 57:22 247:2 305:19

contraindications 110:17 207:12 213:7

contrast 34:17 39:14

contribute 66:12

contributes 33:20

contributions 197:11 205:8

control 7:12 21:16 30:7 38:7 50:6,9,11,14,21 51:2 55:10 61:9,15,18 62:7,9,15,22 63:5 71:9 73:9

76:14 85:6,19 86:22 88:20 89:17 91:9 101:10 116:20 136:13 146:21 156:9 158:11 160:8 164:5 169:4,12 170:1 175:11,13,20 177:1 178:7,12 182:3 187:20 188:2,7 189:19 193:3 195:3,16 196:11 197:10 202:12 217:18 221:19 222:18 232:22

controlled 36:2 75:16 178:9 250:17 272:9 284:22

CONTROL's 52:14

convened 19:4

convening 12:8

conversation 256:5

conversations 11:16 71:11 74:22

converted 75:20

conveyed 301:17

convince 281:12

convinced 222:12

convincing 307:19

convulsive 155:18

cooperation 192:10

Coordinator 10:6

copay 290:21 300:3

cope 27:11 71:19 198:4

coping 25:1 64:10 70:14 190:2,7 201:4

copy 125:15

core 216:10

Cornell 3:5 16:14

correct 29:6 39:8 40:3,8 41:6 44:10,15 48:10 55:2,5,13 62:4 76:16 79:18 102:19 171:22 175:2,3 262:8

correction 107:9

correctly 37:12 55:19 56:18 61:7 76:11 143:14 149:19 202:20 278:17

correctness 42:11

corresponding 40:16 41:17 254:16 275:2

corresponds 254:13 274:22

cost 200:5 222:15,18 291:3 293:16 299:22 300:20

costly 194:17

costs 195:21 199:20,22 200:2,4,6

cost-shifting 300:6

cough 97:4

coughing 212:16

council 193:10

counsel 196:2 289:18 311:7 312:7

counted 45:10

counter 20:8,22 162:8 163:22 164:8 179:2 205:19 225:15 229:19 242:18 252:14 269:10 293:14

counteract 224:3

counting 256:4

countless 64:6

country 135:1 196:10

couple 112:10 129:10 134:5 163:1 175:14 229:14 230:1 246:7 247:16 248:6 304:15 306:12

coupon 257:16 262:22 263:13

courage 204:15 287:20

course 29:14 66:15 79:9 88:11 123:3 125:5 127:8 152:1 180:15 228:15 260:19 270:13 279:3 288:17

courtesy 192:8

cover 112:1 171:15

covered 12:18 264:13 299:18

craw 235:10

create 29:2 30:5 229:7

created 77:5 266:12

creating 260:4

credit 26:12

criteria 45:17 51:4 88:3 137:16 142:4,7 148:16 149:13 163:22 164:8,15,17 207:8 228:4 259:22 278:20

criterion 58:4 60:5

critical 163:13,14

criticism 181:4

critiquing 117:3

crucial 73:15

crutch 204:1

cultural 288:16

cumulative 231:21

curbs 198:17

cure 223:9 235:20

curious 89:16 176:4 295:7

current 70:3 71:10 131:15 132:22 152:10 165:8 249:2 301:18

currently 24:12 25:17 59:14 69:22 71:17 74:19 75:8 77:7 105:20 106:4 189:9 200:10

242:18 246:16 248:20 278:7

cursorily 91:8

cut 182:10

cutting 189:16

CVS 248:7

cystitis 4:11 79:21 147:6,11 150:19

D

DABT 3:15

daily 32:3,7,13 34:16 74:15 106:22 108:4 198:4

damaging 205:17

dark 34:15

data 13:19 14:3,9 21:13,19 29:19 31:14 33:9 34:10 35:2,3,5,14 36:6,13 39:11,21,22 40:21 41:3 44:4 50:10 53:6 56:16 59:5 60:21 65:16 79:15 81:20 83:9,11 87:1,21 89:10 91:22 98:10,12 100:18 106:6 136:10,12 137:11 146:20 156:5,16,20,21 157:1 159:12 168:15 170:11 182:22 183:7 184:21 185:3 188:2,10 208:20 214:18 220:1,7 226:17 227:21 231:14 264:17,22 265:7,10 270:4,7 274:3,8 276:21 277:2 281:4,8 282:12 283:17 297:8 299:4 307:18

database 8:15 103:18 106:16 109:3 156:7,8,10

databases 155:13 156:16 177:9,18

dating 35:20

day 20:16 21:22 97:22 106:14 107:15,22 108:2,6,7 205:15 303:2

days 26:14 36:8 55:16,17,22 57:1,4,12,13,16 64:19 100:2 109:1 136:3 144:22 145:9 146:7 184:8 218:4 226:3 236:13 237:2,6

Deaconess 63:17

dead 114:9

deal 241:17 242:2 290:6

dealing 27:16 64:2 267:19

dealt 279:22

death 147:13

deaths 109:5

DEBORAH 312:3,11

decade 24:10 26:2 35:13

decades 19:16

December 16:11 17:13 18:20

decide 43:19 164:21 168:22

decided 52:11 89:8 139:5,11,16 141:19 237:5 238:11 281:13

deciding 179:6

decision 29:7 44:3 45:11 48:11 51:18 87:9,18 89:4 93:4 125:18 138:18,21 139:7 140:13 141:1,8,13 149:12 151:17 159:2 167:12 182:6 208:6,8 217:13,14 224:12 245:5

decision-making 22:21 161:12 164:17 191:3 205:6,11 296:22

decisions 134:3 140:5 181:13 243:20 296:18 300:14 309:20

declare 256:12

decrease 32:13 210:1

decreased 272:12

deed 180:22

deemed 83:14 85:18 306:3

defensive 126:8

defer 177:1 179:10

define 149:5 152:7

defined 45:14 52:19 173:12 218:1 235:4

defines 104:11,13

definitely 229:16

definition 104:8 134:10 220:14 262:16

definitions 230:6 262:21

definitively 297:10

degenerative 161:20,21

degree 160:22 164:1 240:9

dehydration 25:9

delay 50:17 60:19 64:22 66:3,12 67:6,9,15,19 167:12 179:22 180:18 225:9 228:20 236:22 239:11,12 241:22 244:10 267:3 279:6 290:4 294:13 295:2,18 296:15 301:7

delayed 27:13 75:4 152:4 153:16 159:8 180:14 206:20 228:11 290:5

delaying 59:15

delays 151:10

deliberately 76:14 84:14

deliberations 20:1 22:4 94:11 110:2 165:18
delighted 227:1
delirium 241:17 249:1 307:9 309:2
deliver 101:4
delivered 71:17
delivering 75:19
delivers 251:6
delivery 26:4 33:12 34:21 36:6
dementia 185:13 305:20 307:9 309:2
demographics 80:21 81:14
demonstrate 37:3 206:2 207:4
demonstrated 31:17 36:3 43:4 47:9 49:11 50:1 54:5 61:3,13 63:5 195:4 210:6 243:15
demonstrates 50:11
demonstrating 30:7 55:7 206:15
demonstration 243:17
Dentistry 4:18
deny 68:21
DEO 33:20 34:1,4,12,15,20 250:9,13,15
DEO-to-oxybutynin 34:20
Department 3:10 17:21 266:5
depending 225:11 264:20
Depends 288:6
depression 24:18 195:14 198:16
depth 29:19
Deputy 5:18
derive 184:1
dermal 227:9
described 118:20 126:4 137:1 212:14
describing 41:10 153:4
description 161:10 301:22
deselect 50:19 63:8
deselected 76:17
deselection 29:11 50:4,12
desethyloxybutynin 33:19
design 28:10 48:13 51:5 82:9 92:19 113:13 134:2 135:3 136:13 143:21 144:1 153:14 217:5 251:2
Designated 2:2 6:8
designed 29:2 37:6 50:14 51:2 57:21 62:9 73:11 158:12 181:7 217:11 251:7
desired 225:17
desperate 204:17
despite 24:20 66:22 74:21 194:12
destination 25:6
detail 31:15 56:16 148:11 294:5
detailed 32:22 42:21 72:1
details 11:21 38:22 196:4 257:17 259:4
detect 307:9
deter 179:16
determination 98:18 136:6
determine 39:3 40:3 44:9 59:12 69:16 99:7 144:4 184:18
determined 12:22 13:6 53:8 54:9 55:4 81:5 102:10 115:3 123:7 136:1 140:22 277:15
determining 94:8 226:15
deterrent 110:14
detriment 27:12
detrimental 68:5 287:13
develop 54:20 63:6 81:3 158:17 181:18 245:11 269:1
developed 23:22 37:1 46:19 52:16 53:14,17 59:1,6 69:6,12 72:7,13 76:5 91:21 101:21 102:1,6 128:2
developing 43:2 69:13 94:7
development 8:4 29:1 36:18 37:5,16,19 39:1 46:14 70:8 111:3 165:21 167:6 236:21
device 200:20 205:9 258:14
devil 259:4
devoted 197:1
DFO 254:19 275:5
diabetes 46:10,12 49:16 58:2,4 59:18 60:15,17,18 62:11,16,19,21 66:13,16,18 67:1,2,6,10 104:17 116:2 121:7,19 122:8 124:18 130:5 132:2,20,21 133:3,7 140:15 149:2,3 151:12,15 152:1 159:10 165:6,10 166:3,5 167:10 180:5,10,17 216:19,20 226:9 234:7,19 237:9 246:10 267:4 282:22 283:2

293:4 295:3

diabetic 122:4,19 227:7

diagnose 235:11 293:1,3

diagnosed 57:7,10,11,14,15,17 58:7 59:7 62:16,18 79:17 121:6 149:15,20 150:1,4,19,21 151:1 152:1 180:16 187:20 188:4,6,8,11,13 189:4,20 209:6 218:8 221:14 232:22 233:3 242:1 244:20 253:10 257:6,10 277:1 278:2 284:6,14,15 291:16 292:4 300:10

diagnoses 62:10 159:8 179:22 180:14 241:5

diagnosing 241:1 296:16

diagnosis 27:14 50:17 59:15 60:19 66:3 67:3,7,9,15,20 75:4 104:4,13 151:10 152:3,11 153:17 167:10,12 180:18 187:10,14 188:9 189:8 206:7,8 214:7 218:11 221:9 228:10 234:6 236:22 239:1,12 240:20 241:22 267:4 277:12 279:7 290:5 292:8 293:4 294:1,13 295:2,18 296:2,3 301:7

diagnostic 190:4 268:15 286:1

dialogue 200:16

Diane 99:3,8 268:5

diapers 202:12 287:11

diaries 137:6 213:22

diary 52:2,13

die 291:16

Diego 2:10 19:15 252:17

diet 195:3

dietary 211:18

difference 33:15 64:4 93:9 107:13,16 108:2 251:20 252:1 267:1 271:16,19,21 272:5 273:9 286:18

differences 127:10 147:1 306:22 307:3

different 21:7 39:9 50:18 72:12 73:4,8,10 80:14 95:8 97:19 124:1 130:19 185:22 208:10 210:3 224:17 226:18 230:7,11 233:19 236:21 252:18 253:3 256:4 260:9 264:14 272:3 290:1 294:2 295:20 296:6 301:7 304:22 305:1

differentiating 212:11

differently 277:14 284:8

difficult 18:10 39:15 40:13 95:18 105:1 144:3 299:11 305:7 307:8

difficulty 212:10 213:11 226:15

dignity 192:8 205:18

dilemma 236:15 245:2

dimension 198:21

ding 303:9

dinged 303:11

dinging 303:11

dinner 198:9 204:8

dip 65:19

diphenhydramine 231:20 306:1 307:22

direct 28:1 78:18 191:11 200:14 249:9 273:7

directed 51:14 52:16 76:22 104:19 118:2 165:18 287:1

directing 195:22

direction 311:6

directions 28:20 42:19 43:14 91:19 159:6 298:11

directly 73:20

Director 4:4,9 5:7,11,15,18 6:12 7:20 9:17 10:2 19:14 63:15 192:22 196:19

directs 29:6,13 52:22 63:7 77:13

disagree 114:3

disastrous 240:7

disclose 14:20 15:1

discomfort 64:18

disconnect 178:17

discontent 195:8

discontinuation 148:4 175:18 216:2

discontinuations 147:22 156:1 177:7

discontinue 181:16 213:5 217:21

discontinued 147:21 153:9 154:1,6,18 155:8 177:9,10,12

discordance 215:4

discourage 26:10 46:2

discriminate 60:6

discuss 19:5 38:22 70:17 74:3 80:8

102:14 104:2 111:14 113:21 114:12 115:16 133:16 134:2,3,6 162:11 167:21 179:15 190:17 192:18 209:10 220:4 254:2 256:13 261:22 274:6 276:3,5,6 282:13 283:21 294:12 301:13,16

discussed 11:4 14:3,13 18:10 38:13 64:10 112:22 115:13 125:12,20 138:20 165:21 186:13 207:2,8 211:6 229:15 255:3 264:10 275:11 279:15 294:9 298:1 304:16 310:2

discussing 11:20 12:2 112:5 133:21 134:16 141:21 264:1

discussion 10:12,15 11:7 13:9,19 20:6 21:9 22:6 78:16 80:10 104:17 134:19 140:2 143:16 151:11 155:4 157:17 166:8 179:18 186:9 192:17 214:15 219:20 236:19 237:22 238:3 254:2 255:7,15 261:13 274:11,15 278:6,8 279:21 282:7,8 283:15 290:11 293:22 300:19 301:5

discussions 15:10 115:15 214:21 220:8 295:15 296:18

disease 104:22 127:12 128:15 141:4 206:13,14 228:10 234:20 235:4 239:7,13,14 268:18,19,20 287:10 294:2 305:19

diseases 79:20 240:2,4 241:14,18

disorder 155:18 178:4

disorders 63:21

disorientation 155:1,7,15 177:4,21

dispensed 51:20 137:14 138:22 151:17 261:15

display 34:6 174:5 294:20

displayed 53:9 55:2,5 56:14 59:8 254:18 261:4 275:5

displays 59:1

disposition 138:8

disregards 209:7

disruptive 205:17

disrupts 198:17

dissatisfaction 195:10

disservice 68:21

distance 198:12 199:11

distinct 34:11

distinguish 46:11

distinguished 16:15 17:10 151:8

distress 74:14

distributed 156:14

distribution 172:22

disturbances 24:16

disturbs 198:17

ditto 229:11

diuretic 247:5

Division 2:4,19 5:11,18 6:13 8:17 10:8 16:13 103:22 111:19 133:19

dizziness 111:7 154:17,19 157:16,21 177:13 186:10 250:18 273:8

Dmochowski 265:16,21 267:11 269:16 271:20 289:11

DNCE 6:14 9:6,12

Doan 2:3 6:7 12:4,7 275:15

doctor 27:4,7 28:20 52:17 53:1,11,18 60:14 61:9 79:4,13 80:3 88:1,11 102:9 103:2 120:3 121:6,10 124:20 125:5 127:22 128:2,14 131:13,17,19,21 132:3 133:9,11 151:19,21 152:20 153:10 158:21,22 166:5 173:17,21 187:1,3 188:18 190:9 194:20 195:7 209:9 220:21 225:3,6,8,11 234:2 236:14 238:22 241:21 244:7 246:9,21 247:6,12 266:10,13,15 270:11,15 285:9,13 286:19 287:7,20 289:2 292:15 298:14,19 304:1,2 308:4

doctors 54:2,3 88:3 141:18 186:21 204:16 267:7 277:2

doctor's 28:17 75:1 187:8 288:13

document 101:10 206:5 209:1

documented 211:22 212:1

documents 88:18

Don 103:21 111:17
Donald 8:16
done 70:22 87:13 95:20 99:7 123:19 169:9 181:2 228:18 245:13 246:1 249:12 250:12,21 252:5 259:6 266:16 270:17 280:22 285:22 305:5
door 280:15
dosage 252:9
dose 106:13,14 230:19
doses 34:14
Dosing 18:6 20:4
double-blind 31:19 251:3 272:9
double-check 305:20 306:7
double-dummy 251:4,10
doubt 205:12 216:6
downgrade 228:14
downside 244:17
downward 65:17
doxycycline 18:9 19:5
Dr 11:3 12:7 15:1,4,6,20,21 16:2,8,10,15,18 17:3,13,15,17,18,19 18:2,4,15,16,18,19 19:11,13,21 20:10,11,13 22:9,11,13,15,17 23:16,19 29:22 30:9 31:1,3,6 32:17 36:20 63:10,13 69:9 74:12,13 77:21 78:5,7,9,11,22 79:1,8,15,18,19 80:4,12,16,17 81:11 83:6,7,16 85:12,20,22 86:5,19,22 87:5,20 88:14,15,16,17 89:14,15,16,19 90:3,8,10,11,12,13 91:6 92:6,12 93:15,16,18,21 94:18,19,20 95:3,14 96:6,8,11,12,13 97:7,11 98:8,10,16 99:3,8 100:16,20,21 101:6,7,8,17 102:13 103:3,4,8,16,17,21 133:15,18 157:22 159:19 160:1,5,6,16,17,20 161:7,15 162:2,4,7,10,14,15,21 163:3,12,19 164:4,22 165:1,2,3,16 166:18 167:2,3,17,21 168:1,4,5 169:3,5,18,20,21 170:3,6,7,8,10,15,18,22 171:1,4,5 172:3,4,8,11,15,19 174:17,20 175:8,9,10 176:19,20,22 178:2,6,13,14,15 179:9 180:20 182:9,10,13 183:3,4,5 184:4,13 185:9,10,17 186:7,18 187:13 188:1,12,14,17,18 189:6,14,16,18,22 190:12,21 192:21 196:16 201:6 205:1 207:14 208:1,13 210:11,13 214:10,16 215:9,11,12 218:15,18,22 219:11,16 220:11,12 222:3,4,5 223:15,16,17 224:16 227:1,3 229:10,11 232:6,7,8 233:6,21,22 234:1,21,22 235:1,15 238:2,17 239:5,6,17,22 240:1 241:6 242:4,21,22 243:1 245:19,20,21 246:5 247:14,15,16 248:16,17,18 249:3,8,10,11,17 250:8 252:10,11 254:1,9 255:4,16,20,21,22 256:6,14,15 257:12,13 258:5,6,22 259:1,2 260:8,9,11,12 261:1,2,8,11,12 262:9,13,17,18 263:6,8,12,16,18,20,21 264:12,16,22 265:3,9,11,16,21 266:8 267:6,11 269:3,5,6,16 270:2,4,5,7,9,20,21,22 271:5,6,7,8,9,10,12,13,14,20 272:7,16 273:17,18,19,21 274:2,14,17 275:15,16,20,21 276:1,3,5,6,8,9,10,11,13,14,15,16,17,18,20 277:8,9,16,17 278:4,10,11 279:2 280:2,3 281:5,6,7,21,22 282:1,6,15 283:7,10,16 284:3,4,17,19,20 285:5,6,10,11 286:3,12 287:2,3 288:3,4,18,19 289:10,15,16 290:10,12,14 291:9,10,11 292:5,6,7 293:20 294:16,17 295:5,7 296:4 297:3,21 298:8 299:10,21 300:15,16,18,22 301:3 302:8,9,16,20,22

303:1 305:15,16 306:8,9,10,11,17 ,18 307:7,17 308:2,6,18 309:15 310:1,5

dramatically 227:6

draw 110:16,21 233:4 273:8

drawing 126:14

drawn 48:9

dread 202:5

dress 126:17

drink 96:20,21

drip 164:13

drive 66:22

drop 97:4 114:8

drug 1:5,6,9 5:7,15 6:14 8:19 12:7 13:20 17:7,12 20:7 22:19 29:5 31:18 37:21 38:8 43:10 44:17 50:15 51:21 54:6 59:18 71:14 77:9 90:4 101:5 105:19 108:7 109:5 111:1 115:13 134:13 135:7 137:14 138:18,19 139:1,5,16 140:13 141:1,8,20 142:12 143:15 144:8,14,21 149:19 151:17 160:9 163:21 164:5 171:6 178:19 179:5,17 181:19 186:12 187:8 191:1 193:17 195:6 196:13 205:8,21 206:22 207:7,13,19,21 208:9,19,21,22 209:8,14 210:1 223:3,14,22 224:2,3 225:17 226:2 227:11,13 230:22 232:12 242:6 277:5 281:14 284:10,12,21 293:10 299:1 305:19 308:5 309:11

drug-drug 223:1 233:11

drugs 25:18 66:6 99:2 110:14 153:18 157:15 158:4 189:10 194:13 195:7 222:17 223:8 224:6,8,20 225:15 231:15,18 232:13 233:13 279:18 289:2,8 298:2 302:3 307:18 309:3,5

drug's 158:3

Drugs 1:7 2:8 3:13 5:8 12:9 17:11 310:13

dry 33:14 35:10 96:17,20 109:15 147:11 154:16,20 157:15 158:8 177:13 194:19 204:6 212:2 273:4 305:12

due 27:9 48:4 62:17 71:16 147:21,22 152:4 153:17 154:2,3,19 177:10,13 193:22 194:4,7 296:5

Duke 10:9

duration 56:1 106:17 117:10 132:12 135:15 136:2,7 145:5 146:9 150:10 238:17

Durham-Humphrey 164:6 189:7

during 12:2 14:11 36:1 61:11 62:8,16,19 66:6,17 80:14 88:10 109:5,6,11 111:2 143:22 149:15,18 151:1 187:12 190:17 198:2 202:15 283:18

DVD 260:18 261:16 262:13

dysfunction 99:12 211:16 293:9

dysfunctions 280:14

dysuria 64:15 80:14 138:4 140:17 148:14,18,20

E

eager 204:18

earlier 22:14 26:18 42:12 118:14 122:4,18 124:15 133:10 172:2 181:4 194:11 215:16 216:3 218:12 249:16 255:14 272:20 279:21 288:5 291:3

early 41:22 60:17 81:7 92:19 166:2 169:8 242:1 254:3

ease 204:19

easier 74:16 100:5 130:21 132:8

easily 95:22 307:21

easy 39:12 215:12 258:11

economic 200:2,8

Ed 23:20 218:18 264:22

Ed's 267:17

educate 72:8 77:17

educates 260:5

educating 71:7

education 8:2 10:5 25:12 27:21 30:14 69:8,11 72:21 73:15 76:3 84:12 86:13 193:2 200:15 201:9 211:2 214:6 264:1 268:2 279:22

280:18

educational 69:3,16 70:9 71:3,14,22 72:11,18 73:3 74:9 84:1 197:8 225:11 245:9 248:13 252:12 259:8 261:17

educator 18:3

educators 196:4

Edwin 6:18 8:9

effect 50:20 64:21 68:6 99:16 108:9 110:3 177:14 225:17 235:6 241:8,11 251:22 273:1,13 283:1 284:22 285:3 307:11,15

effective 26:1 27:19 29:4 31:10 64:3 68:22 70:16 77:15 79:6 86:8,11,17 106:7 164:19 195:4 200:8,22 208:21 209:13 213:17 239:11 257:20 288:21

effectively 163:9 257:5

effectiveness 306:22

effects 24:18 33:14,21 36:9 75:18,21 91:4 93:17 94:16 109:15,19 111:1,7 154:12,14 155:3,21 156:3 157:13 158:5,8 159:13 175:17,18 177:4,11,21 194:18 207:1 208:9 209:8 212:2 213:6 223:2,22 224:14,21,22 227:10,20 237:20 250:7 277:11 290:18 299:15

efficacious 197:16 223:7

efficacy 8:14 31:16 32:1 36:5 78:14,15 83:9,11 85:13,15 86:1,2 103:18 106:15 107:5 108:11,13 110:7 160:20 161:9,11 179:1,2,3 183:6,17,19,20 184:1 211:22 223:7,10

efficiency 19:2

effort 27:10 46:1

efforts 69:3 72:17 74:8 197:9

eight 59:6 149:15,16 157:2

Eight-nine 55:13

Eighty-five 55:1

Eighty-nine 56:14

either 40:10 43:15 45:11,14 47:10 52:15 71:17 73:7 82:17 83:8 86:11,14 134:12 135:20 136:2 138:4 140:20 144:21 145:22 146:6,18 150:2,20,21 178:20 187:19 238:20 240:12 253:5 255:17 268:19 285:7 286:5 290:6,8

elderly 91:5 116:5 122:3 127:6,7 130:8 168:6,10,20,21 169:17 170:20 182:14,16 185:11 223:18,20 227:19 228:4,5 241:8,15 244:17 249:1,12 250:5 271:15 277:11 278:22 279:9 302:3 303:7 304:9 307:3,12

electronic 254:10 274:18

element 43:17 50:5 73:15 76:6 82:5 119:14 217:3

elements 41:21 73:8 84:5 85:9 113:15 119:1 129:3 218:3

eligibility 51:4 87:17 88:3 161:17 207:8

eligible 44:6 58:13 87:20 88:13 89:13 141:2

eliminating 257:8

Elizabeth 10:2 196:18

Elkadry 7:18 30:9 63:10,13,14 69:9 85:22 86:5

else 103:5 165:4 178:21 186:2 187:22 223:15 234:9 238:1,20 240:16 260:2 274:11 278:9 279:5 296:13

elsewhere 253:20

Eman 7:18 30:9 63:14

embarrassed 26:21 194:11

embarrassment 70:20 198:20 266:14 269:19,22 270:15

embellish 167:4

emerge 265:18

emerges 267:3

emerging 267:2

Emory 2:19

emotional 24:15

emphasize 126:14 130:13 131:2 294:11,19

employed 198:22 311:8

employees 12:13,14 13:4,5

employers 13:14

employment 13:18

empower 73:8

empowered 71:9
empties 120:4
empty 25:7 58:6 88:8 120:1 131:22 152:6,22
emptying 140:9 149:4 152:13 153:5 186:22 187:2,6
encounter 252:20
encountered 252:19 253:19
encourage 14:18 196:12 200:17 259:17 264:5
encouraged 68:13
encourages 15:16 23:2,10 191:7,15
end-of-study 137:9,13,15
endorse 200:19
endpoint 32:1,9,13 52:14,20 54:9,18,20 55:7,14 56:6,7,9 57:6 63:9 76:18 91:19 101:11,20 106:19 107:21 110:4 125:19 135:12,19,22 142:2,9,11,13 143:1 144:5,20 145:12 146:4,15,16 158:13 181:19 218:2 251:16,21 271:22 272:4
endpoints 41:17 52:4 55:11 56:14 57:9 93:9,10 107:2,7 134:7 135:9,18 136:4 141:22 142:2,16,21 158:15 238:6 251:17 272:2 282:10
energy 24:17
enforce 263:17
engage 195:21 223:11
engaging 194:21
enhance 38:11 132:14
enhanced 49:13 72:17 124:15
enhancements 112:13
enjoy 196:7
enjoyed 16:15
enormous 163:5 199:19 204:2 284:22
enrich 20:6
enriched 181:22
enroll 82:10
enrolled 138:10 173:5 219:1
enrolling 218:20
enrollment 51:15 61:10 62:8,18 82:4 137:1 138:13 149:17 150:6 160:14 217:19
ensure 14:18 22:21 72:22 96:3 191:3
enter 181:9
entered 254:12 274:21
entering 187:1
enters 309:11
entire 41:15 150:18
entirely 178:6,7 208:10
entitled 200:2
entity 205:10
enuresis 230:9,16,20 231:3
environment 184:12 185:5
envision 230:4
epidemiological 242:2
episode 32:7 108:2,7 199:15
episodes 32:3 106:21 107:1,11,12,13,15,22 108:1,6,14 150:19
equal 143:6
Equally 68:17
equate 140:11 152:12
equity 23:8
equivalent 145:18 242:14
erectile 293:9
Erick 1:20 311:2,13
erroneous 301:6
error 40:16 76:13
erythema 35:9 109:14 157:6
esophagitis 111:6
esophagus 298:5,15
especially 25:8 30:2 75:12 92:2 131:11 166:14,22 185:14 224:10 234:7 237:19 253:20 285:20 289:13 293:18
essence 164:8
essential 85:12 305:10,13
essentially 126:5 173:22 215:20 251:3,22
establish 70:2 113:14 206:7
established 71:2 115:1 142:7 143:6 183:19 193:17 214:2
estimate 40:22 41:5 114:14 117:18 120:8 122:15 215:19
estimated 24:11 193:19,20 200:5
estimates 40:16 114:17 118:12 122:2
et 117:7 251:18 299:18
ethics 12:17 13:2 19:18

evaluate 37:12 41:11 43:17 74:5 136:12 137:12 143:21 156:5,18

evaluated 44:4 135:9 138:11 146:14 176:4

evaluating 137:4

evaluation 1:6 5:8,12,16 6:14,15 8:19 17:12 68:3 111:20 133:20 137:4 150:17 211:14 227:14

evaluators 52:10 81:17 141:17 149:10

event 18:9 35:4 147:1,13,18,21 154:3,7 178:3 182:22 224:7 296:14,21

events 35:7,9,17 109:7,8,11 147:7,16,20 148:1 153:21 154:2,5,15,18,20,22 155:6,9,12,14,17,22 156:2,10,11 157:2,13 177:3,6,17,20 198:15 208:19 212:4 224:5

eventual 244:10

eventually 80:22

everybody 98:8 190:21 219:16 260:10 289:17 310:6

everyone 16:4 64:1 181:1 204:5 254:17 275:3

everything 119:10 130:2 164:21 177:7 274:11 309:17

evidence 33:18 36:3 66:5 250:5 259:12 279:1 304:10,17 307:6

evidence-based 69:11

exacerbated 205:22

exacerbation 111:5

exact 54:4 87:14,15 114:2 117:13

exactly 37:19 76:15 80:4 94:12,16 105:2 168:7 181:9 217:4

exam 45:5,6 188:20 202:15 228:12

examination 217:2

examine 29:18 64:7 67:12 84:22 217:11,12

examined 33:8 53:7 76:6,20 173:10

example 33:4 39:12,16 42:3 44:11,14 47:6 53:13,14 54:1,11 58:1 59:4 88:5 158:8 160:22 175:16 191:12 240:7 268:21 295:11 297:21,22 307:13

exceeded 43:7

excellent 203:4

except 62:5 180:16 269:14 305:19

exception 12:11 61:17 65:22 189:8 235:19 304:2

excessive 60:16 121:12 122:10 149:3 180:10

exciting 196:9

exclude 15:13 206:17

excluded 51:8 62:18 82:13,15,22 89:6 137:18 138:7,12,14 139:8,10,13,17 148:17,21 149:12 152:3 162:3 220:18

excluding 206:9

exclusion 15:14 137:16 138:16 187:16 188:19 235:5

exclusionary 81:9 140:1

exclusions 82:3,8

excuse 204:10

executed 72:7

Executive 2:5 9:17 192:22

exercise 195:16 196:8 209:17

exercises 202:18,19 203:2,9,13,16 211:20 257:18

exhibited 54:10 55:4 59:3

exhibiting 294:22

exhilarating 204:11

exist 69:16 77:2 213:13 214:8

existed 44:9 70:16

existing 25:17

exists 59:14 70:13 189:9 303:7

expand 68:13 291:21

expanded 72:17

expect 110:3 166:22

expectation 252:8

expectations 49:4 212:21

expected 30:11 48:16 77:5 109:19

expecting 79:10

expense 193:8

expenses 23:6 191:14 201:13

expensive 222:17 245:15

experience 14:4 64:13,17 65:8,13

96:17 105:7 134:17 201:17 207:1 268:5 269:18 307:2

experienced 70:5 109:6 212:10 218:9

experiences 204:1 289:22

experiencing 122:10 167:10

expert 13:16 167:18 208:15 265:16 306:3 308:6

expertise 16:21 19:21 221:6 308:16

experts 30:19,21 40:10 76:21 265:14

expire 16:7

explain 30:10 194:14 201:18 258:11 279:2 281:7 304:2

explained 84:14 149:6 152:18 202:20

explicit 310:8

explicitly 262:6

exploratory 144:13

explore 45:21

expose 208:9 209:13

exposed 108:22 208:11

exposure 18:10 109:1

express 11:8 77:22 261:19

expressed 232:9 261:18 294:4

expressing 166:19

extend 273:15

extended 34:5,13 273:3

extensive 69:4,17 72:19

extensively 33:17 77:10

extent 175:17,22 244:12

external 40:10

extra 87:10 90:16

extreme 34:16 60:16 121:12 123:1,4 130:4

extremely 257:19 307:8

F

FAAN 3:7

face 178:18,21 236:16

FACP 2:9 3:3 6:3

fact 43:8 53:22 64:1 66:5 68:2 83:4,19 88:9,13 93:5 94:1 99:15 119:15 152:19 157:12 162:18 163:16 166:10 184:13,22 189:22 194:5 206:8 217:21 232:21 237:16 240:11,21 242:6 249:13 251:7 257:2 266:15 269:2 279:19 283:5 284:12 298:13 304:17 305:10

factor 66:1 166:5 179:6 222:18 270:15 300:14

factors 44:9 54:14 104:14 132:21 133:3,6 140:15,16 149:2,6 151:13,15 153:12

facts 29:5 37:21 38:8 43:10 44:17 50:15 51:21 54:6 59:18 71:14 77:9 90:5 166:20 196:3

factual 267:8

fail 289:4

failed 79:3 101:13 143:2,12 144:7 289:1,8,12

failure 41:5

fair 11:6 79:16 151:14 192:6 250:5 291:22

fairly 144:3 152:16 213:17 219:6 250:6

faith 233:5

fall 100:4 128:7

falls 100:2 155:2,20 180:21 224:6

familiar 181:1 298:1

families 197:5

family 3:10 17:21 58:2 60:15 121:11 149:2 165:11 180:4 194:20 195:18 199:4,7 216:18 226:9 246:10 288:5

Farber 2:9 19:11,13,21 20:10,11 83:6,7,16 85:12 86:22 160:16,17 161:15 162:4 166:18 187:13 188:12,18 189:16,18 208:14 220:11,12 239:22 240:1 252:10,11 256:14,15 269:5,6 270:22 271:6,8,10 273:19 276:14 277:16,17 282:15 284:3,4 286:3 291:10,11 294:16,17 302:8,9,20

Farber's 88:17 270:5

far-reaching 197:19

fatigue 42:2

favor 248:4

favorable 75:18

FDA 1:5,14 2:6 5:5,9,13,16,20

6:11,15 8:13,20 9:6,12 11:19,20 12:22 13:3 15:12,16 16:1,5 17:2 18:12 19:8 20:9 21:10 22:2,5,22 23:2,10 31:14 37:18,22 38:1,12 56:10 57:18 58:18 75:15 82:8 87:1 88:18 89:3 94:7,13 97:9 101:9 103:14,17 115:10 142:15 143:8 159:18 160:7,10 161:8 162:12,15,22 163:21 165:18,21 175:14 178:16,22 191:5,7,15,21 206:1,5 215:21 217:5 218:16 229:3 235:1,14 263:11 264:7 272:8 288:5 295:8 301:19 308:22

FDA-AERS 156:7

FDA's 14:22 85:10 144:11

fear 199:15 244:3

feature 51:5 85:6

featured 72:6

federal 2:2 6:8 11:13 12:10,13,15,17 13:2,5

feedback 37:18 38:1

feel 68:20 69:21 71:9 86:4 102:15 151:9,20 159:7 179:16 194:10 195:17 203:8 214:2 221:11,13 247:19 248:12

feeling 58:6 88:8 152:5 204:11 211:21 222:12

feels 232:1

fees 23:6

Fellowship 7:20 63:16 266:3

felt 92:21 142:7 143:9 152:17,20 155:19 202:11 204:2 278:18

female 49:7 63:4,16 109:2 130:6 171:11,17 172:6 194:21 210:21 266:3,4 267:14

females 21:3 70:5 109:3

fetus 66:5 213:1

fever 64:14 65:6 138:3 148:14,17 149:14 236:12

few-week 67:6

field 99:11 208:15

fielded 70:3 166:12

fifty-two 251:11

fighter 221:4

figure 46:5 171:14 296:19 304:6,8 305:8,9,13

filling 80:2,5

final 38:11 44:10 52:6 63:1 81:5 243:22

finally 29:12 41:2 49:17 66:9 67:12 71:10 73:15 127:6 132:2 133:8 134:16 140:2 144:19 146:4 153:11 159:1 176:3 202:14,21 203:20 229:2,8 238:22 250:21 286:19

financial 13:5,8,11 14:14 15:13,17 23:4,12,13 191:10,12,17,19 199:19 205:8,10 311:9

finding 206:7

findings 30:3 128:20 129:6,11,12 141:11 156:22 180:15

fine 87:1 117:2,9 160:18 161:11 268:22 287:18 294:11

firm 15:18 23:5

firmly 254:13 274:22

firms 15:11

first 21:22 28:11 29:3 31:8 33:21 37:9,21 44:1 48:1 55:2,11 61:2,9 67:15 71:13 79:8 83:17 84:8 85:16 90:21 91:6 92:1,5,18 93:7 96:15 97:2 104:3 105:17 110:7,9 115:18 117:15 121:17 123:18 126:16 127:7 128:4 132:10 133:2 134:1 160:19 163:2 166:16 167:1,11 169:2 179:9,11 183:4 192:20 201:3,10 204:16 212:8 215:13 222:14 225:4 227:12 233:19 246:8,13 249:19 252:11 257:2,21 261:5 275:18 277:21 290:16 294:22 302:9,13,19

first-line 209:21 221:20 302:13

firstly 224:18 279:3

first-pass 250:14

fit 164:15

five 54:7 56:5 106:1 112:15 147:12,18 149:22 150:19 151:3 275:15

fix 253:6,9

flank 62:1 65:6 140:18 148:15

flap 264:18

flaps 265:2

flash 254:12

274:20
flashing 254:11 274:20
floor 63:21 99:12 194:4 211:19
flu 97:21
fluid 105:15 211:19 258:10
fluids 25:8
focus 19:1 38:19 50:8 113:6 168:5 294:8
focused 44:20 47:19 84:5 112:18
focuses 40:17
focusing 115:15
folks 299:19
follow-up 44:8,13 49:1 58:10 62:19 102:13 154:21 174:11
Food 1:5 12:7 17:7 22:18 191:1
foot 62:17
force 163:6 164:20 229:4
forego 195:15
foregoing 311:3
foremost 31:9
forever 231:10
forget 98:1
forgive 134:5
forgot 160:6
form 24:1 73:3 134:9 153:22 252:9 256:18,22 260:15 302:4
formal 22:18 307:10,12
formally 307:14
formed 250:9
forms 34:17 148:8 153:6 186:20 187:10 257:4 279:16
formularies 299:17
formulation 34:3 251:5 271:18 272:1 280:10
formulations 34:5 35:1
Fort 4:20,21
forth 282:1 305:3
Forty-one 88:6
forum 11:7,17 266:7
forward 11:11 19:6 22:5 77:19 94:12 245:6 264:9 280:11,16 281:4
foul-smelling 64:15 123:10 138:5 148:15
Foundation 10:3 196:20,22 197:7,10,13 200:19
foundational 113:12
foundations 197:11
Fourth 227:19
fraction 75:20
fractures 148:1
frame 182:15
freedom 196:7
free-flowing 39:19
frequencies 213:22
frequency 24:7 26:8 27:15 32:8,13 39:13 60:1 65:11 66:10,21 68:1 71:7 74:1 106:13 107:2,14 108:4,15 116:16 153:1 194:2 211:12 228:9,13 239:9
frequent 41:17 44:21 49:5 121:11 125:2 205:12 241:15
frequently 35:17 121:18 124:17,22 130:18 140:8,10 147:3,5,9 154:16,19 206:15
Friday 1:12
friend 90:19 91:14
friends 195:18 198:8 204:8
front 28:13 38:7 46:1,5,18 48:5 63:4 171:15 219:18 278:13,22 310:9
frontal 161:5,21 240:8
frontline 72:22
frustrated 194:12
Frustration 194:16
FTC 264:14 304:22
full 24:16 53:20 190:9 265:12
fully 39:10 40:2 57:6 143:21 186:18 193:8 229:2 294:4
function 94:4 203:16 227:20 250:4,22 271:15
functioning 252:5
fundamental 71:13
funded 193:8
funds 201:15
funny 230:5
Furthermore 66:7 67:22

G

GA 2:20
gain 69:20
gained 70:7
Galva 5:3
gamut 141:3 180:3
Ganley 5:7 184:13 218:18 262:19 263:6,16 271:14 297:21 299:21 300:18
gap 124:6
gaps 69:16 112:10

114:21 129:21
garnered 47:14
Gary 249:11,17
Gassman 5:18
gastric 110:18 111:5 116:1 119:21 120:3,16 128:9 213:8 306:15
gathering 22:20
gear 116:12
gel 105:22 251:5,9 252:1
Gellad 2:12 18:18,19 88:15,16 101:7,8 102:13 103:3 160:5,6 165:2,3 167:3,21 185:9,10 222:4,5 234:22 235:1 245:20,21 246:5 264:16 275:20 281:6,7 285:10,11 292:6,7 295:7 297:3 299:10 305:15,16 307:17 308:6 309:15
Gelnique 251:6
general 2:19 15:5 38:17 44:18 46:16 47:15,18 48:9,18,22 61:4,6 62:14 75:8 122:5,19 124:5 128:19 129:11,16 130:7 168:19 170:21 175:5 182:2 230:3 272:2 302:6 309:6,11
generalizability 80:19
generally 105:10 127:9 135:5,16 183:20 184:11 189:11 206:16 212:1,5 217:15 234:2 236:2 237:5,19 251:13 253:4 286:13 300:13
generation 128:5
generations 194:11
generic 279:10 290:17
gentle 11:9
Geriatric 228:4
gestalt 221:7
gets 186:11 298:7
getting 237:16 260:16 270:14 281:17
GI 111:6
given 51:15 68:22 78:14 93:12 97:13 125:14 138:17 161:9,11 171:5 184:8 219:2,12 230:19 251:12 252:7 272:15 282:9 305:10 307:13
gives 178:5 190:8 272:13
giving 193:16 247:20
glaucoma 43:1 83:2 110:19 128:3,5 137:22 213:8
globally 197:8
gloss 133:5
goal 11:6
goals 28:9 71:2 72:11 73:21 74:10 108:9 192:5
God 303:1
godsend 203:11
golf 198:8
gone 97:21 152:9 244:11 286:14
goodwill 305:3
go-round 16:11
gotten 97:21
government 11:14 12:13 13:4
grab 97:3
Graduate 2:14
grant 13:4 193:11
granted 220:18
granting 196:10
grants 193:14 197:11
graphics 46:1 48:5 72:1
grapple 280:22 296:17 300:12
grappling 244:15
gravid 213:4
gravis 111:11
great 1:15 74:18 90:10 166:1 191:21 208:3 233:15 246:1 257:14 259:3 260:13 268:21 297:22
greater 29:18 62:13,14 67:2 77:5 196:10 209:3
greatest 42:20 48:19
greatly 69:4
green 34:19
gross 67:19
ground 192:19 230:7
grounds 242:2
group 32:12 47:4,7 76:15 78:6 81:1,5 107:22 108:1 216:8 249:21 271:19
grouped 115:21 177:19
grouping 154:13 155:15 178:2
groupings 177:3 178:4
groups 31:21 32:4,8 118:10 199:12 202:4 212:6
growing 66:11 75:9 97:13
guardian 303:16
guess 22:9 98:9 101:20 143:22

165:7,9,14 175:12 222:5,12 223:18 235:2,13 237:4 244:4 247:7 284:4 292:7 293:4 294:17 295:7,13 297:7,19 298:7 299:14 309:19

guidance 28:2 256:17 304:5

guide 27:22 50:2 51:22 70:8 73:2 114:8

guided 202:21

guideline 105:4

guidelines 67:5 228:2 303:12 305:1

guides 29:10 50:4,11 59:19 216:14

guilty 166:10 195:17

gut 33:17

guys 177:22

gyne 99:21

Gynecology 266:2

H

habits 188:21 195:3

half 115:10 141:19 292:19

hallmark 66:18

Hampshire 1:16

hand 11:16 214:17 243:7 253:12 309:9

handed 92:19

handle 175:12,17,21 224:15

hands 171:10 225:19

Hanno 4:8 78:22 79:1,15,19 80:12 178:14,15 183:5 207:14 232:7,8 257:12,13 276:1,5,8,18,20 288:18,19 290:14

happen 113:10 170:12 217:6 285:17 289:20 308:14

happened 58:15 102:16

happens 100:2 181:15 216:15 237:19 292:10 299:14

happy 167:21 275:18

hard 22:7 97:4 130:15 164:14 225:8 279:4 296:6 305:8 307:11

hardly 289:5

harm 45:13

harmful 25:8

Harriet 42:4,8

Harvard 7:19 63:18

haven't 124:8 128:6 229:14 232:18 256:11 265:10 267:9 287:7 294:8

having 21:8 64:5 68:14 71:11 81:1 84:11 86:14 106:18 149:13 160:14 164:12 180:7 182:21 187:21 189:3 190:5,6 194:1 202:6 203:10 205:14 207:10,11 208:5 217:22 238:10 241:4,19 246:13,16 248:5,7,10 253:8 255:6 257:16 258:18 285:21 298:8 301:6

Head 7:4,10 16:13 31:5

headache 236:11,13 237:2

headaches 236:8

heading 180:21

head-to-head 273:7,10

health 2:14,15,19 3:5,9 10:7 16:12 17:22 18:1 19:1,20 26:17 28:1 30:15 33:7 41:14 43:20 48:12 53:11 64:18 65:16 68:19 69:5,15 70:18 71:6,12 72:9,16 73:1 74:3 75:7 77:13,17 96:4 151:1 182:7 189:5 195:20 196:4,6,10 197:5 200:18 205:4,11 206:18 208:5 209:18 227:5 228:20 248:11 253:2 287:14 303:15,17 305:12

Healthcare 2:16

health-related 33:8

healthy 196:8

hear 22:1 101:15 179:18 186:9,13 198:7 235:14 237:11,22 255:6,15 256:1,5 292:1 295:7,14

heard 21:1 32:17 65:20 93:20 98:10 104:17 106:10 112:6 162:19 225:4 265:10 267:9 270:15

hearing 9:16 19:7 22:3 97:9 167:14 190:14,20 191:4,8,22 192:5 214:12 289:22

heartburn 296:10

heavily 279:7

heeded 66:14

heft 143:10

held 11:5

Heller 10:5 201:8

Hello 210:13

help 27:21 43:17 48:7 60:6 71:19

72:3 74:4,17 76:20 77:17 125:2 133:5 163:8 168:11,22 169:15 172:4 179:16 182:22 192:1 196:3 197:4,22 199:10 200:12 201:3 206:18 209:5 210:2 237:18 253:18 255:12 260:3 262:19 289:10 303:17 304:12

helped 30:5 47:20 70:8 204:4 227:18 297:1

helpful 18:11 77:8 133:13 214:5 237:10 258:12 278:5

helping 25:19 224:12 237:6 248:9 282:4

helps 165:17

hematuria 62:1 67:16,19 83:1 138:1,4 139:18 140:18 148:15,18 152:3 228:9

hemorrhagic 268:22

Hemwall 6:18 8:9 23:16,19,20 31:3,6 32:18 74:12,13 79:8,18 80:4 81:11 83:16 85:20 86:5,19 87:5,20 89:19 91:6 92:12 93:18 95:3 97:7 98:10,16 100:20 101:17 165:16 167:17 169:3,18,21 170:6,8,15,22 171:4 172:3,8,15 178:2 180:20 188:1 189:22 215:9,11 218:22 249:3,10 250:8 265:3,11 266:8 270:4,9 271:5,7,9,12 272:16 290:10,12 306:9,11

hereby 311:3 312:3

herself 208:9

HHNK 291:17

Hi 17:17,18 18:18 163:3 205:3 265:21

hide 267:7

high 84:17,20 92:3 175:20 195:14 217:2 268:2 278:19

higher 41:19 47:12,13 51:9 80:13 105:8 115:2 120:6 127:20 144:16 168:9 173:15 184:15 222:22 272:13 273:6

highest 210:22

highlight 304:16

highlighted 28:18 37:20 60:2,7 132:18

highlighting 46:9 120:11

highly 65:12 69:1 211:3

hikes 199:4

hip 26:13

Hispanic 96:5

history 51:19 57:21 58:2 60:14 121:11 149:3 165:10 180:4 186:22 188:21 216:19 226:9 246:10,15 309:18

hitting 41:4

HIV-positive 147:14

Hoel 249:11,17 273:17

hold 201:22

holder 156:18

holders 156:7

holder's 156:10

holistic 41:3

home 25:14,15 89:11 91:10,11,16 137:2 139:4 142:1 185:21 199:1,11 219:9 306:7

homeless 260:21

homes 249:13

honest 223:8

honoraria 23:7

hope 163:8 185:6 197:4 204:21 264:11 297:1 308:22

hopefully 186:4

hoping 279:22

Hopkins 4:5

hospital 4:21 7:21 63:17 304:4

hours 34:7 64:19 116:17 117:6 119:6

house 25:5

household 185:22 186:1,2

Howard 208:1

Howards 4:12 90:12,13 92:6 93:15 162:14,15 163:12 164:22 227:1,3 233:6 239:5,6 260:8,9 261:1,2,11 276:16 277:8,9 284:19,20

huge 118:4 229:20

human 65:16 203:17

hundred 52:8 54:7 251:11

hundreds 69:19 207:20

hunger 60:16 121:12 123:2,4 130:4 149:3 180:11

hurdles 299:3,5

husband 198:9

Hutchinson 258:5

276:11
Hutchinson-Colas 4:16 248:17,18 258:6 276:11
hydrocephalus 161:5,20
hypersensitivity 110:20 111:9 153:22
hypertension 195:13

I

i.e 160:21
IA 5:3
ibuprofen 295:20
icon 49:7,8
idea 114:20 148:21 182:20 189:12 226:9 238:10 245:14 259:3 260:13 293:7
ideal 289:17
identical 119:17
identification 115:18 116:7 119:3 129:22
identified 52:21 53:19 54:8,19 76:12 109:20 159:11 307:3 308:19
identifies 86:15
identify 28:11 57:21 168:11
idiopathic 150:12 151:6,9
ignore 298:10
ignored 65:2 286:6
II 38:6 46:21 47:3 48:1,4
III 5:16,19 8:19
IIQ 33:5
I'll 17:5 30:16 79:8 87:13 89:20 98:9 110:11 112:10 114:14 116:6 121:16 133:20 134:3,7,16 139:13 163:2 165:3 167:22 169:11 172:9,21 179:9 183:4,5 185:18 189:6 220:9 222:5 235:15 241:12 254:6 280:5 293:15 306:6
illiterate 95:17
illness 295:10
illnesses 198:18 220:20,22 295:12
I'm 17:3 22:15 23:20 36:22 40:21 50:7 63:14 68:12 78:7 80:19 81:20,22 82:4 85:20,22 87:5 90:15 92:6 94:21 95:20 99:8,9 103:21,22 111:12,18,20 112:2,4,20 115:5,15 117:2 118:7,10 119:19 120:11 127:1,17 130:13 133:18,19 165:5,7,9,12 166:10 167:21 169:5,10,14 171:9 174:8 175:12,17,20,21 176:3 182:13 183:3 192:21,22 193:7,15 201:8,9,17 204:9 205:3 218:13,17 222:12,19 223:19 224:8 227:1,19 230:5 231:8 232:16 233:15,16 234:12 235:16,22 238:15 240:11,18 243:3 245:2,7,17 246:10,17 248:21 249:10 250:2 255:4 258:12 260:19 264:19 265:21,22 275:18 278:10,17 281:10 283:3 284:20 285:4,6,7,12,15 286:12 287:5 288:1,9,14,19 289:22 290:7 295:15 303:1,10,12,18 304:1,2 307:14 308:1,6
images 136:19
imagine 100:22
immediate 34:5,16 60:15 165:11 271:21 272:6 273:2
immediately 67:18 203:3 253:7
immediate-release 34:9 251:8 271:18 272:1
impact 24:4,13 32:18 33:4,6 67:7 69:22 74:6 136:5 197:19 199:19 200:8 231:19,21 237:1 250:4 269:17
impacted 201:19
impacts 211:10
impairment 273:16
implications 232:3
implicator 146:12
imply 266:14
importance 91:17 133:9 179:20 191:22 209:11 221:10
important 23:1 26:16 33:15 40:19 46:15 48:12 58:14 66:15 67:16 68:17 71:5,16 76:2 77:11 83:17 84:10 87:21 94:8 96:14,22 97:6 98:17 102:3 112:7 124:20 127:19 133:11 153:19 166:15 167:13 171:5 179:6 183:9 190:1 191:6 208:5 209:17 213:13 233:12

252:13,16 259:5,21 268:16 279:9 289:14

importantly 55:4 77:4 126:12

impossible 235:5

impression 241:13 247:7

impressions 225:16

improper 294:1

improve 28:22 55:13,15 56:12,19,21,22 63:2 66:10,20 68:19 73:12 74:17 86:16 91:21 222:10 280:19 283:18 285:8 297:6,14,18 299:12 305:6,7

improved 28:3 32:14 48:3 56:17 59:11 75:16 77:10 110:5 154:21 158:19 280:13 285:14 301:16

improvement 32:21 33:10 55:17 76:2 107:10,12,18 135:20 144:6,15 145:21 160:22 238:10,14,16,19

imputed 13:12 15:12

inappropriate 87:11 98:11 100:18 217:20

inappropriately 174:8,9 179:17 215:7

incapacitating 199:16

incentive 90:16 93:12

incidence 36:8 227:10 250:6

inclined 244:7

include 13:15 14:4 21:13 40:22 59:17 71:3 83:19 87:22 111:7 191:13 199:20 211:11,14 262:15

included 42:15 44:19 45:5 66:14 76:15 81:6 84:14 87:3 94:10 136:8,16 137:5 140:17 147:18 149:2,6 156:10 164:2 180:7 229:12 251:11 299:6 301:12

includes 73:4 211:18

including 13:12 14:6 21:14 23:3,7 24:13 31:21 46:15,21 69:18 72:21 73:21 137:9 156:6 195:2 208:17

inclusion 304:18

incomplete 140:9 149:4 152:6,13 153:4 186:22 187:2,5

incontinence 24:6 26:8 32:3,7 33:4,6 43:1 45:17 47:18 105:11 106:12,18,21,22 107:9,22 108:14 116:19 128:17 141:5 147:11 174:2 193:21 194:4 197:2,4,18 199:18 200:16 205:13 211:13 212:14,16 228:19 234:4 248:12 268:17 269:1 294:21

incontinent 199:15

incorporated 123:1

incorporates 37:17

incorporating 37:22

incorrect 39:8 40:8 44:7,10 59:3 119:15 144:20 146:5 159:5

incorrectly 84:22 136:1 143:15 146:6,9

increase 24:10 27:22 32:10 59:13 67:14 108:16 182:21 222:13,22 224:4 299:7

increased 32:11 60:16 121:12 146:18

increases 24:9 211:5 222:19 300:3,4

increasing 71:3 108:10 198:1 241:18

incredibly 205:16 259:5

incremental 28:6 98:19

incur 85:3

incurred 209:3

IND 82:11

Indeed 228:11

independent 84:11 197:12 208:15 286:20

in-depth 69:20

indicate 106:7 138:13 144:2 220:19

indicated 49:6 118:8 119:12 126:14 138:9 150:11 160:20 173:6,8 174:14 212:15

indicates 53:18 146:11 149:9 258:9

indicating 58:21 61:8 145:14 158:19

indication 26:5 92:2 106:11 141:11,17

indicative 47:6 92:17 273:15

indicator 161:1
indirect 200:6
indisputable 68:6
individual 39:22 73:10 254:21 275:7
individuals 11:8,9 48:14 92:7 199:9 217:2 221:4 229:7 243:19 244:18
individual's 13:7 23:1 191:6
industry 12:11 14:22 15:3,4,5,8 22:15 193:10 197:12
ineligibilities 57:20 58:16,17 88:20 134:4,8,10 139:22 140:6,7 141:3 148:12 180:3 220:6
ineligibility 58:20 140:11 152:15 159:3 179:14 180:8 274:7
ineligible 51:8 58:22 88:6 141:9,17 178:19
infarction 296:14
infection 4:10 53:15 59:17 65:10 104:18 138:3 235:19,20
infections 81:4 148:6 151:4 211:15 212:3
Inflammation 4:10
influence 225:7
influenced 81:2
inform 28:15 71:15
information 12:16 21:12 22:20 25:12 43:20 49:12 53:4,20 56:13 64:16 68:18 69:17 75:7 81:12 82:1 83:21 84:4 86:13 87:10,12 91:2 96:16 104:5 114:16 162:9 164:20 167:13 186:4 190:8 191:12 213:19 242:13 252:7 255:8,11,17 256:2,7 258:8,16,19,20 261:15 262:1,7,10 264:20 267:8 277:22 301:12 305:13 306:19 308:5
information-gathering 191:3
informative 27:20
informed 55:4 82:7,17 139:11 208:8 210:3 280:15 303:3,15 304:13
informing 71:6
informs 60:13
infrequently 158:9
ingredient 25:20 75:19
ingredients 138:6
inherent 248:1
inherently 101:4
initial 38:3 42:12,17 43:4,10 44:16,18 45:20 49:1 51:12 53:4 54:19 82:9 105:13 123:18 172:20
initially 41:15 44:7 53:19 54:7 64:10 160:13
initiation 67:5
initiatives 72:10,13 73:3
Injury 20:2
innovative 197:16
input 97:8
inquired 136:22
insert 242:15 255:19 258:16 279:13 301:21 302:10
inside 256:2
insidious 244:13 269:14 294:20
insight 92:14
insights 19:22 70:6 116:11 192:1
insignificant 233:10 283:3
instance 82:7 268:20
instances 192:3
instead 220:21 283:4 284:16 308:2
institution 266:2
instructed 134:12,14
instructing 64:16
instructions 31:22 97:17 149:1
instructor 63:18
instruments 33:2
insurance 205:9 300:5
intake 105:15 258:10
integrated 73:4
intended 51:21 83:22 224:21 308:21
intensity 301:9
intent 264:9
interact 233:14
interaction 209:18 233:11 248:11 307:18,20 308:5
interactions 186:12 223:1 242:7 307:9 308:16
interactive 72:19 73:6
interest 6:6 12:5,6,15,18 13:2,8 14:16 15:13 46:2 58:18 179:1 210:15 252:22 311:10
interested 94:13 97:9 140:7 242:10 255:15,22 312:8

interesting 20:16 22:6 92:12 173:1 237:21 306:11
interests 13:15 14:15 19:1 23:7,8
interfere 64:12
interject 267:22 306:9
intermediary 208:5 209:15 229:20
internal 40:10 295:15 296:18
internally 236:20 242:8
International 104:9
internist 202:14
internists 237:12
interpret 98:15
interpretation 136:6
interpreting 171:22 278:17
interrupt 161:7
interruption 11:9
interstitial 4:10 79:21
interval 40:18 55:8 114:11
intervals 73:18
intervention 259:12 286:17
interventions 105:14
interview 52:7 87:8 136:12 137:10,15 138:15 140:4 142:13 144:9 146:3 217:16
interviewed 51:19 52:2 181:12 238:8
interviews 52:13 69:20 137:5,6 154:21
intimacy 198:18
intimate 196:8 199:6
intravenously 164:13
introduce 78:5
introduced 22:13 93:5
introduction 6:2,17 11:2 23:18 31:6 32:17
introductory 6:11 16:1,5 20:14
investigator 39:12
investigators 92:21 137:7
investments 13:15
invitations 198:15
invite 15:21 31:1 36:16 192:20
invited 14:22 30:18 265:14
involve 15:10
involved 51:11 126:1,3,10 136:22 164:12 237:20
involvement 15:14
involves 13:19 188:20
involving 118:21
IRB 82:11
irrespective 225:1 309:7
irritation 43:2 100:7,8 147:10 157:7
isn't 163:13 167:14 194:20 236:6 253:14
isolated 148:19
isolation 198:16
Israel 63:17
issue 14:21 15:18 23:6,13 48:12 83:12 101:11 121:7 123:6 125:22 185:12 191:18 215:3 222:7 224:19 225:3 226:8 229:5 240:19 244:4 246:9 247:5 248:1,2 269:11 279:9,10,19 280:4 281:13 285:20 288:16 290:5 293:15 295:17 297:4,17 299:22 300:6,9 302:2 307:17 309:1,6
issued 14:17
issues 11:7 18:10 78:15 109:18,20 112:5,7 115:14,16 145:6 160:14 192:2 207:9 226:13 245:3 253:22 256:20 269:19 279:14 300:12 310:2
itchy 43:2
item 282:8 283:8,16 294:7 300:22 301:11
items 110:1 132:13 134:18 177:14 179:15
iteration 152:9
iterative 37:17 74:8
it's 22:14 24:5 40:3,18 66:15 79:9 80:13 84:9 87:7 89:17 92:10,16 94:4,22 96:17,21,22 97:5,6,12 98:5,13,19 99:5 100:5,13 101:3 102:17 105:1,5,10 111:3 113:6 118:3,4 120:10 130:14,20,21 131:10 132:7,8 133:13 139:19 155:14 156:21 164:5 165:20 166:14 167:12 170:6,8 171:2,17 178:2,10 179:4 180:20 183:9 187:15 190:1 194:14 204:11 205:4 206:13 208:7,9 209:4,6 211:7,8 215:12 226:10 228:9,12

229:18 230:10,12 231:6,11 232:12,13,20 233:7,9 234:15 235:7 238:12 239:13,14 243:9,21 246:2 247:18 249:20,21 250:19 252:4,15 253:20 254:3 257:19 258:11 259:3,4,14,18 260:12 261:10 262:22 263:13 266:18,21 267:18 269:18,21,22 277:5 278:16 279:1,9 283:11 286:11 288:16,21 289:7,9 292:8,11,12 293:4,5 295:20 296:1,6,22 297:13,14,17 298:2,20 299:11,12 300:2 303:7 304:3 305:1 306:11 307:8,10,20,21 308:6,13,16

IV 5:8,12 6:15 9:6,12

I've 49:12 99:11,14 100:13 105:2,19 115:21 124:2 142:15 149:6 166:10 201:19 247:3 251:1 252:19 253:19,20 287:6 291:12 304:3 309:17

J

January 17:20

JD 10:5

Jersey 4:18

Johns 4:5

Johnson 4:19

Jolla 2:10

Journal 200:1

Juana 4:16 276:11

judge 37:12 45:7 171:21

judged 45:16

judging 260:1

judgment 113:20 172:1

juggling 195:12

Julie 5:15

July 70:4

June 20:1

justification 165:14

K

Kate 10:6 205:3

Kegel 209:16

Kegels 195:3

Kegle 202:19

key 30:3 37:11 38:9 46:9 47:2,5,9 49:20 69:13 73:19 84:5 107:1,6,9,20 112:5 245:10 279:6

keynote 79:22

keys 279:21

kidding 165:5

kidney 43:1 141:4 206:13 246:15,16

kids 99:22

Kimberly-Clark 193:15

kinds 161:22 256:4 269:15

King's 33:7

kit 18:8 19:5

knowable 299:12

knowledge 16:20 200:11

knowledgeable 133:4

known 58:3 110:19 125:12 184:17 185:4 191:11 197:7

Koff 4:20 78:5,7 188:17 247:15,16 276:15

Koff's 188:14

Kristie 8:3 30:13 69:10 74:13 95:4

L

La 2:10

lab 206:7

label 7:7 9:2 14:6 21:10,14 28:10 29:5,9,10,12 30:4 36:17,18 37:1,4,9,11,15,16,20 38:1,2,5,6,14,19 39:4 41:8,13,16,20,22 42:3,8,13,14,16 43:4,10,11,12 44:7,17,18 45:2,4 46:7,13,14,20,22 47:1,2,3,5,8 48:14 49:13,15,17,21 50:1,3,11,15 51:4,8,21,22 52:16,22 54:6,15 58:4 59:19,21,22 60:3,8,13 61:2,13,14 62:3,12 63:7 64:16 66:14 71:14,21,22 76:8,11,16 77:9 79:3 80:1,6,11 84:15,16 85:8 88:21 89:1,22 90:4,17,21 91:7,11,13,15,18 92:10 93:13 94:2,7,9 95:17 96:10 97:1 102:1,17 110:18,22 111:14,15,21 112:4,15,16 113:3,4,5,7,13,15 115:8,20 116:21 117:16 118:3,14,20 119:12,15 120:13,18 121:3,20 122:13,17 123:3,18 124:1 125:3,15 128:6,11

130:2,16,20,22 131:4,7,16,20 132:6,22 133:9 134:4,8,10,22 135:13 137:21 138:11 139:22 140:5,10 141:2,3,9,17 148:12 149:1,10 150:9 152:8,10,15 158:1 159:2,6 162:8,9,20 163:13,17 164:2,16 165:6,8,12,15 166:15 167:13 173:7,9 174:4 176:10,11,13,14 178:19,20 179:14,15 180:2,7 181:3,7,9 186:10 187:18,19 189:3 190:4 206:4 207:3 208:3 215:16 216:4,7,13,17,18 217:1,3,5,7,22 218:21 219:7,8,9,13 220:18 221:14 225:18 229:5 235:21 236:1 242:9 245:22 246:8 247:8 261:6 263:9 279:19 281:15,16 282:3,5,10,12,16 285:8 286:4,6,8,10 289:1 301:14,16,18 302:12,21 306:6 308:6,15

labeled 110:12 157:11 159:15 186:3,15 300:10

labeling 27:21 29:2 30:5,8 35:5 50:5,12 112:11,13 123:4 126:13 129:2 130:9 132:9 134:18 157:19 163:8 196:3 212:7,20 213:9 214:5 216:2,13 226:1 237:1 261:4 262:10,12,16,20, 21 263:2,5 277:15 280:18 283:19 299:6 301:18 302:5 303:20 305:6 309:10

labels 48:13 92:3 95:15,17,21 163:6 166:9,11,14,21 225:13,15 229:4 242:6 273:11

label's 63:2

laboratory 4:4 104:12

labs 66:17

lack 29:12 50:20 200:11 307:15

LaGro 10:2 196:18

laid 146:20

language 95:20 96:3 189:9 236:2 258:17

large 29:6 65:19 76:15,16 125:13 180:5 194:3 246:2 290:21

largely 26:20 48:4 197:17 241:8 243:21

larger 77:3

largest 117:21 210:20

laser 130:14

last 19:11 35:13 59:2 67:9 139:12 142:22 209:10 234:3 252:18 274:14 310:3

lasted 150:10

lasting 26:8

late 65:18

later 31:15 85:11 102:14 115:17 157:19 167:21

latest 67:4

Latino 95:15,16 234:7 260:20

Latinos 234:15

laughing 212:16

Laughter 219:15 246:4

launch 72:18 156:12 157:9

laundry 199:22

law 163:21 229:5

laws 12:15,18 13:2 164:4

layered 29:18 76:6

layers 29:2

LCS 115:8 122:4,18 123:13 124:15 127:8,9,15 130:17

lead 24:17 206:19

Leader 6:18 7:14 8:4

leaders 208:16

leading 38:11 198:16

leaflet 242:13 256:2 262:7,10 279:12 299:6

leak 194:3,7 202:7

leakage 198:1

leaking 25:7 116:19 119:6 203:22 204:8 212:16

leaning 171:13

leap 233:5

learn 184:16

learned 84:16 181:12 202:1 209:15 229:19

least 19:12 21:3 26:9 35:6 79:17 87:10 116:15 117:6,20 124:1 132:14,18 135:14 142:10,14 143:3 145:1 146:22 167:7 176:5 183:16 185:1 190:5,6 207:11 208:21 243:14 247:13 258:9 270:12 281:3

286:5,10 290:9 306:5,21

leave 25:5,14 167:22 199:3 219:17

led 44:3 125:17 174:11,12 261:13

legal 262:15

legitimate 300:13

lend 212:9

Leonard 22:11 163:3 258:6

Leonard-Segal 5:11 6:12 15:21 16:2 17:17,19 18:16,18 19:11 20:13 163:3 164:4 167:3 183:3 185:17 189:6 235:15 238:18 242:4 255:4,20,22 262:9,17 263:12 264:12,22 296:4 298:8 300:15

Leonard-Segal's 257:13

less 52:19 107:15,22 108:1,6,7 121:2 140:20,21 143:6 145:10 150:3 194:10 195:6 227:7 247:8 250:15 292:7 293:4

lesson 295:17

let's 33:11 34:3 35:2 41:8 47:22 59:21 66:13 93:16 181:14 281:1,2

lettering 136:18

level 49:19 84:17 93:22 120:6 128:22 136:10 226:3,4 268:2 283:21

levels 24:17 34:1,4,15,20 36:7 41:21 75:19 94:15 119:18 273:4,5

Licata 8:3 30:13 69:4,9,10 95:4,5 96:1,7,9

life 18:2 24:4,10,13 27:12 28:4 32:19,21 33:3,9 36:6 64:13 74:15,17 76:2 156:18 161:1 197:20 201:19 205:17 211:10 229:1

lifestyle 70:12 73:13 105:14 209:12

lifestyles 73:10

lift 100:3

lifted 204:3

likelihood 30:12 150:11 210:2

likely 40:19 92:9 98:6 176:1 180:17 194:6,10 195:12,15,17 207:17 241:10

Likewise 23:10 27:4 191:15

Lilly 193:14

limit 136:20 145:18 158:14 159:21 185:20 208:19 242:2 248:19,20 249:20 277:15,19 298:2 308:3

limitation 241:16

limitations 24:14 98:14 130:1 245:1 252:3

limited 12:18 259:18

limiting 54:14 105:15

limits 78:2 212:18

Linda 10:5 201:8

line 80:10 105:17 144:12 224:6 288:22

lines 242:17

lingering 216:5

linking 67:9

liquids 96:20

list 78:21 85:9 140:6,14 229:13 233:7 240:3 300:18 305:17,18,21 306:12

listed 105:19 130:12 131:6 147:17 236:1 240:2

listen 198:6 295:15

listened 192:7

listing 130:18

lit 173:14,16 208:14,19

literacy 48:12 81:19 114:18,19 115:8 118:6,7,10 120:8 122:2,16 124:5,7,9 126:19 127:4,5 129:5,7,16,18 130:7 146:13 168:18,19 169:19,22 170:12,14,16

literal 281:8 285:11

literate 48:14 170:20 172:21 175:6

literates 122:21

literature 35:4,20 67:8 69:18 86:7 153:17 272:22

little 21:8 25:11 75:7 78:2 91:1 98:2,14 103:4 116:10 120:19 122:14 123:22 130:14 133:1 134:18 136:14 148:10 166:6 167:4 178:1 218:7,9 233:18 235:10,14 238:13 245:17 250:3 256:3 257:21 287:6,16 290:13 304:3

live 221:16 287:9,17 305:11

lived 202:5

liver 20:2 33:18 127:12 128:14 206:13

lives 24:19 27:10 64:5 68:6,8,10 70:1 198:3 268:1

living 24:12

LL 115:7

LLC 3:16 15:7

lobe 161:5,21 240:8

local 35:8

locate 202:2

located 25:3

locked 254:18 275:4

lodging 191:14

long 25:18 55:19 79:14 110:2 117:16 144:21 188:20 189:10 198:11 199:13 201:20 203:18,19 218:5 224:13 231:15 237:15 238:4 246:11 267:3 286:14 292:1

longer 55:21 56:11 76:22 136:2 167:8 214:13 218:4,10 237:3 238:13 308:11

long-term 65:17 151:4 227:6 239:12 293:19

Lorna 3:15 15:2,7 22:15

lose 202:11

loss 61:22 62:5 73:13 140:17 149:7 193:22 195:3 197:9 255:10

losses 200:7

lost 173:22 199:17

lot 81:12 96:18 98:10 112:1 116:22 117:1,4 123:13 126:2 130:21 142:3 151:16 155:12 159:3 166:21 180:2,9 183:10,13 187:4 190:1,8 213:2 226:13 230:4 233:4 238:9,14 240:17 242:6 246:1,18,19 248:4 249:3 253:2 265:7 268:6 277:6 280:11 289:7 290:21 291:3,18 292:19 293:8 295:12 296:8 297:11,12 305:5,9

lotion 100:10

lots 136:12,19 177:19 296:6

love 179:18 186:8,13

loved 198:16 288:16

low 30:12 34:20 36:8 48:13 81:18 84:20 94:4,14,15 99:15 114:18 115:8 120:8 122:16,21 124:9 127:3 128:15 129:5,7,16,18 168:18,19 169:19,22 170:12,14,16,19 171:3 172:21 173:16 175:6 212:1 223:8,10 249:14 250:6,19 295:4

lower 34:20 35:11 40:18,20,22 42:22 47:13,16 60:9 75:19 93:22 114:11,15 115:4,7 118:15,17 119:18,19 120:13 121:1,2 122:4,15 123:15 126:19 127:13,15 128:12,16 129:2,6 145:16 215:19 227:10 250:8,10 268:11 273:13

lowered 200:8

lowering 198:19

lowest 128:4,17 129:8

low-literate 43:7 44:19 48:15,17,21 49:3 72:3

LTC 4:20

lucid 90:14

luck 286:22

lumps 133:2

lunch 9:15 12:3 22:3 188:15 189:15 190:13,19 198:8 204:8

lunchtime 190:18

M

M.D 17:9

MA 7:9,22

mad 288:14

mail 258:1

main 37:20 230:22 270:13 277:10 281:17

mainly 84:16

mainstay 25:18 75:13

maintain 226:3

maintained 52:2 110:8

maintenance 151:2

major 109:18 115:11 134:7 135:9,18 141:22 142:2,21 158:14 302:4 308:19

majority 29:6 47:4 55:22 59:10 66:7 67:21 76:10,17 79:11 82:14 85:4 177:12 188:12 189:19 197:21 268:7 292:12

makeup 81:15

male 160:11 171:11 172:5

males 137:17 172:6

man 288:15

manage 26:20 42:1 63:22 64:11 69:22 70:11 75:2 253:2 268:4

managed 26:16 290:15 291:7

management 2:5,14 27:20 43:18 50:5 73:13 75:3 76:7 105:13 259:13 280:19 301:7

managing 74:20 195:10 201:3 216:13

mandate 263:2

manner 18:11 255:2 275:10

manufacturer 264:5

manufacturers 205:9

mapping 25:2

March 19:13

Marcus 3:3 6:3 16:10 17:9

marginal 232:11,14

marginally 216:17

markedly 33:22

market 92:11 100:17 156:12 157:9 289:6 293:18 303:13 306:1,2

marketing 231:9 301:15

marketplace 182:1 185:19 200:21

marriages 199:2

Martinez 3:7 275:21

Maryland 1:16 311:14

mask 237:14

masked 240:5,9

masking 295:10,17 298:4

mass 51:11 173:2

matched 154:5

material 91:3 206:11 261:17 262:2 272:14 295:8

materials 301:13

MATRIX 156:19

matter 30:19 64:19 244:10 260:21 269:2 279:8 286:7

matters 14:11,12

maximize 214:6

may 13:15 15:18 16:7 17:13 18:5 20:3 23:5 26:10 27:13,14 28:17 30:17 41:18,19 50:17 51:6,7 58:3,15,21 66:22 74:1 76:3 79:1 81:2 85:10 95:3 96:17,18 97:2 100:6 105:18 110:1 114:1 116:13 120:16,18 125:2 128:7 132:15 134:4 150:22 152:17 154:12 155:21 158:4,19 159:5 163:19 166:1,6 176:8,17 184:16,17 191:10,13 196:17 198:19,22 199:2,5 200:10 201:7 205:2 208:19 210:12 215:1 216:16 219:5 224:4 226:5 227:22 230:11,21 234:4 243:12 246:5 254:15 258:12 270:17 275:2 276:3 279:5,18 294:20 296:2 298:4 299:6,7,18 307:11

maybe 86:19 87:1 90:17 94:22 95:8 97:3 102:14 118:9 175:22 180:21 225:10 235:16 237:3 238:11,12,20,21 242:8 255:7 262:18 266:11 277:19 280:21 297:8 298:13

Mayo 208:16

MBA 4:3,16 8:3 9:17

McNair 1:20 311:2,13

McNellis 8:16 103:17,21,22 157:22 160:20 162:2,7

MD 2:9,12,18 3:3 4:3,6,8,12,16,20 5:7,11,15,18 6:3,12 7:3,18 8:16 9:10 10:8

meal 120:4

mean 21:3 64:8 114:3 117:1,2 118:3 121:9 127:2 128:15 177:18 180:3 189:19 224:5 236:19 246:2 247:2,17,18 248:1 266:14 271:2,4 276:21 283:2 286:7,11 292:16 294:18 295:20 299:13,14 308:2

meaning 226:7 230:11 256:8 307:15

meaningful 32:20 226:1

means 29:11 41:4 52:12 66:4 141:7 199:12 231:12 233:1 267:14

meant 84:21 118:15 126:9 135:5 140:11 149:4 152:7 153:14

measurable 70:2

measure 33:2 37:10 74:6 119:13 213:21

measured 55:14 73:16 114:19 117:10,13

118:19 250:13
measures 73:19 137:4 156:19
measuring 93:11 252:4
mechanisms 299:7
med 18:8 19:5
media 11:18,21 51:11 72:16 173:3 260:16
median 55:16 57:1,3,12,16 81:18 107:10
medical 3:5 4:19 7:4,19 8:17 9:11 16:14 19:14,18 29:9,13 31:5 42:20 45:5 47:12,13,16 48:19 50:19 51:9,19 56:3,6 57:20 59:20 63:17,19 67:18 68:15 71:4 81:9,21 82:22 103:22 112:5,7 113:18 115:2,4,11,17 119:7 120:6 127:20 128:13,18 133:19 134:11,14 139:13,17 150:7,17 159:8 188:21 205:9 206:16 208:16 226:7 228:21
medically 53:9 165:13 226:1
medication 19:3 24:21 29:4 31:10,11 65:7 66:4 76:7 134:12 195:5 208:6,7 235:13 244:6 247:1 253:6,14,18 257:16,21 258:2 282:4 285:19 286:9,10,15
medications 99:14 195:13 247:20 253:5,15 280:13 295:21 296:10 299:19 308:20
medicine 2:9,13,18,19,20 3:5 4:5,14,18 10:10 16:12,16,20 18:21,22 19:15,16 63:16 210:21 234:6 266:3,4 280:12 292:10 302:1 307:22
medicines 98:20 185:14 241:11 308:12
meds 307:20
Medtronic 193:15
meet 51:3 108:9 125:19 140:19 141:13,15 148:16 163:22 198:8 205:19 207:7 248:8 283:5
meeting 1:7 2:1 3:1 4:1 5:1 11:4,6,12,17,21 12:2,8,20 13:9 14:11 15:2,4 17:1 18:5,7 19:4 20:4 22:22 23:9 103:12 184:20 190:17 191:5,15 201:13 214:12,13,22 233:20 254:10 274:19 279:15 310:10,12
meetings 16:19 115:12 202:4,6 203:7 204:7
meets 260:5
Megan 121:18,19
Melissa 124:21 125:1
mellitus 151:12
member 3:13 6:9 15:22 186:1,2 193:11 288:6 301:10
members 2:8 4:2 11:15,18 12:11,12,22 13:1,10 14:15,16,19 15:9,10 16:6 21:18 103:11 162:16 185:22 190:16 192:13 205:7 210:20 275:17 310:7
membership-based 205:5
memberships 197:11
memory 251:14,17
men 21:5 45:21 46:2,3,18 48:2,5 49:2 87:3 89:18,21 90:2 104:19,21 105:6,9 116:5 127:1,3 129:19 136:20,22 172:17 174:3,4,6,7,12,21,22 176:11 193:19 194:6 211:4 227:13 278:18 280:14 282:16,19
meningitis 236:10
menopause 24:11
men's 172:17
mental 227:20 277:11 307:10
mentality 98:4
mentation 91:4
mention 21:2 44:22 81:8 106:6 109:22 110:11,22 127:12 294:18
mentioned 26:18 31:6 42:12 100:21 109:12 110:12,17 111:3 114:10 121:4 127:14 129:4,13 131:19 176:8 216:3 222:15 234:16 235:2 246:8 250:8 271:16 278:21 288:4 301:5 306:6
mentioning 27:3
Merck 6:19 7:5,11,15 8:6 20:20 22:1 23:17,21 31:5

36:22 112:1 114:10 193:10 201:14,15 248:21 252:11 281:11 287:19 302:17 305:4

Merck's 167:8

message 61:5 68:15 213:15

messages 37:11 38:9 39:4 41:18 43:9,12,14 46:7,9,11 47:2,5,9,12,13,16 48:19 49:15,20 61:15 62:5 77:12 94:8

met 47:10 55:8 63:9 76:18 91:21 145:17 150:1 158:13 248:15 282:10

metabolism 33:22 250:14

metabolite 75:20 250:9

metabolites 33:19

metabolized 33:17

method 146:18 267:20

methodology 87:7 113:21

methods 136:14 208:21 301:22

metrics 114:9

metropolitan 50:22

microhematuria 247:22

microphone 192:12

middle 58:22 142:21

mild 35:18 65:2 153:8 193:12 194:1 307:9

military 78:8

milligram 34:10 106:14

milligrams 20:19

million 24:11 75:8 156:14 193:20

millions 68:21 200:22 233:8 291:21

mimic 251:8

mind 28:9 82:5 87:22 144:12 155:10 180:8 220:6 232:19 233:18 239:19 245:8 253:11 264:4 274:8 290:9

mine 228:7

Minh 2:3 6:7 12:4 15:20 21:2 220:9

minimal 28:8 45:13 56:6 64:21 68:5 289:7

minimize 40:17

minimized 252:8

minimum 132:12

minor 13:13 38:10 46:8 63:3 136:5

minority 234:14

minute 121:16 139:12 161:8 163:20 189:15 234:3 306:9

minutes 21:2 103:9,13 163:1 192:11,12 203:10 283:11,12,13 296:15

misconceptions 266:12

misdiagnosis 75:3 206:20 233:6 244:2

misheard 176:9,17

Mishra 7:3 29:22 31:1,3,4 36:20 93:21

misplaced 251:17

missed 47:10 79:1 125:1,6,7 126:9 228:19 240:7 296:21

missing 195:17 277:12 292:8 293:4 294:1

mission 193:2

mistakenly 64:20

misunderstood 85:21

misuse 52:19 55:6 69:1 98:10,21,22 99:2,7 100:15,18 101:18 135:8,10 141:22 142:1,9,14,20 143:4,18,22 144:15 145:7,16 146:14,17 158:14 159:4 205:21 207:5 238:6

misused 98:19,20 144:10,18 145:2 146:19

misuser 52:21 53:8 102:22

misusers 52:21 53:20,22 54:8

misuses 55:22

mitigated 56:9 142:3 174:1 181:13

mitigating 44:9

mitigation 40:4,6 53:8,13 54:9,15 55:3,11 56:7 87:13 129:14 142:4,6 143:1,18 145:3 158:15

mitigations 125:21,22 126:10

mix 224:7,8

mixes 148:17

mix-up 240:20

mL 34:8,13

MLIS 10:2

modalities 200:11

modality 200:20

moderate 35:18 193:12 194:1

modification 31:22 83:17,20,22 85:14 86:2,7 221:18 257:18

modifications

38:10 42:14 46:10 171:15 211:19
modified 43:11 46:6,20 49:8 73:17
modify 261:10
Moffitt 5:3 96:12,13 97:11 223:16,17 276:9 287:2,3
moieties 94:1
Molecular 4:13
Mom 234:18
moment 139:14 196:8 243:2 245:17
money 195:7
monitor 142:18 155:12
monitored 177:3,15
month 150:10 292:18 300:5
monthly 193:6
months 26:9 60:4 70:6 116:15 117:6,20 118:16 119:4 121:18 132:12 140:21 150:4,14 154:9 185:2 190:2,5 195:6 207:11 225:5 267:18
morning 16:4,5 23:20 31:4,15 36:21 50:7 63:14 77:19 103:21 104:2 111:21 112:6 113:1 114:10,15 133:18 272:20 300:17
morph 262:22
mortifying 202:13
mostly 109:2 159:14 194:7
mother 121:19
motivation 196:5 225:10
Mount 7:21 63:16
mouth 33:14 35:10 96:17,20 109:15 147:11 154:16,20 157:15 158:8 177:13 194:19 212:2 270:18 273:4
move 106:9 108:19 141:21 145:12 156:4 245:6 280:16 281:4
movie 196:7
Moving 151:12
MPA 9:4 10:6
MPH 2:12 4:8
MSD 13:20 14:12
Muller 9:17 192:21,22
multicentered 134:22
multidisciplinary 69:15
multifaceted 72:14
multiple 55:10 100:1,12 195:12 200:10 230:6 231:18 279:18
multiply 233:8
multistage 37:17
muscle 154:4
muscles 194:5
mutual 94:10
mutually 95:11
myasthenia 111:11
myocardial 296:13
myriad 19:17
myself 166:10 223:20 246:3
myth 211:8 304:7

N

NAFC 193:1,11
name/place 251:15
namely 33:19 108:13
Nancy 9:17 192:21
nanogram 34:8
nanograms 34:12
narrow-angle 83:2 110:19 137:22 213:8
narrow-waisted 126:21 176:16
national 9:18 10:7 72:8 192:22 193:12 200:5 205:4
natural 85:1 253:14 279:3
naturalistic 113:11 135:6,8 148:22 181:15
nature 114:2 266:19
NDA 1:9 8:15 14:13 20:20 121:10 130:20 131:21 133:12 156:6,10,17
NDA21-351 103:20
NDAC 1:7 6:4,8,9 15:22 16:6,10,19 17:20 18:19 19:3,13,22 20:6 310:14
nearest 51:14
nearly 26:2 35:14 38:9 47:10 74:14 207:6 272:10
necessarily 84:15 93:12 102:4,15 124:8 139:20 206:22 208:4 239:10 248:8 263:16 267:5 292:9 293:11 296:3 309:16
necessary 39:9 41:20 43:11 59:20 74:9 151:20 252:16
negative 67:7 85:4 203:22 251:21
negatively 211:9
negotiations 142:16
Neil 2:9 276:14
neither 66:20 122:22 152:3 311:7 312:7
nervousness 273:6

net 173:4
Network 10:7 205:4
Neumann 7:9 30:3 36:16,20,21 172:9,13,18 174:18 175:2 215:15
neurogenic 268:13,16 269:12
neurogenically 268:17
neurologic 161:3,19,21 268:11 294:19 295:1
Neurology 4:4
Newman 99:3,8 100:21 268:6
news 112:8 128:19
nice 104:17 243:16
nicotine 73:14 255:9
night's 24:16
nine 56:2
Ninety 154:20
Ninety-four 56:5
Ninety-six 56:1 63:8
Ninety-two 61:6
NJ 4:19
NL 115:7
nobody 180:12 202:19
nocturia 24:7 211:13
noise 182:16
nominally 87:11
non 15:2 29:13 124:3
nonclinical 250:12
Noncompliant 195:5
nondrug 49:10
none 29:9 109:7 138:19 150:4 153:8 154:21 156:2
non-employee 23:3
nonetheless 273:11 305:21
non-OAB 50:10 59:2 60:22 76:22 124:10
non-pharmaceutical 209:11,19
Nonprescription 1:7 2:8 3:13 5:12 6:13 12:8 17:11 111:19 133:20 310:13
nonprofit 193:1 197:1 210:19
nonserious 157:10 159:14
non-significant 32:15
nonsurgical 99:13
nonusers 140:3
nonverifiable 139:3
Non-Voting 2:2 3:13 5:5
nor 66:20 104:12 311:8 312:7,8
norm 24:22
Norma 3:7 17:17,19 275:21
normal 27:1 43:6 44:19 68:16 70:21 71:5 114:17,18 115:7 120:8 122:16,21 124:5,7 127:4 129:5,6 130:7 161:4,19 172:20 173:14 198:9 203:17 211:8 219:4 246:5 270:14 307:8
normally 93:1,2,13
Notary 311:1,13
note 104:10 157:11
noted 15:15 46:17 109:16 122:10 143:4 212:4
nothing 70:21 153:6 253:13 254:1 275:13
notice 155:6
noticed 42:6 124:21 125:1
notion 255:7 263:22
November 1:12
nuances 112:4
numerical 272:3
numerically 108:5 271:22
nurse 18:3 99:10 138:16 202:16,21 286:20 288:11
nurses 288:11
nursing 3:10 18:1 249:13
NY 3:6

O

OAB 7:17 24:2,9,12,22 25:19,21,22 26:6,7,16 27:5,16 28:3,16 29:9,14,21 31:11,17 32:18,20 36:15 37:2 38:17 39:18 44:22 45:7 51:12 52:18 53:2,14 54:4,21 55:12,17 56:17 57:2,7,10 59:11,15,16 60:4,6 61:1 63:12 64:9,11 65:13 66:1,7 68:6,14,20 69:5,21 70:5,11,20 71:4,9 73:9,22 74:7,14 75:2,7,9,11,13 83:10 86:14,15 104:8,10,12,16,21 105:1,20 115:8,18 116:7 124:3,4,8,9 125:14 129:22 130:6 135:20 138:3 139:21 140:19,20 141:13,18 144:6

145:21 150:1,3,9,12 151:4,6,9 152:18 153:18 157:15 158:18 159:9 161:6 166:3 188:8 193:13,17,19 194:12,21 195:9,19 196:13 198:2,4,14,17,19,22 199:5,9,19,20 200:4,10,15 201:2,9 206:20,22 208:6,10 209:4,5 210:4 211:3,11 212:8 213:3 216:20 218:8,9 219:2 266:13 270:11

Oak 1:14,15

object 251:18

objective 40:6 108:13 113:4 116:13 121:8 123:7 124:16 310:7

objectively 213:21

objectives 28:10 113:14,16 118:5 119:22 123:3 127:18 128:12,20 136:15

observant 258:10

observation 215:1 307:15

Obstetrics 266:1

Obstetrics/ Gynecology 4:17

obtained 46:14

obvious 53:21 298:3

obviously 86:1,20 90:17,18 98:17 115:22 141:7 150:15 178:10 186:8 229:20 240:10 252:2 273:6

occasions 195:18

occur 50:17 75:1 190:9 198:2 294:20

occurred 154:8 156:12 239:15

occurring 226:20

occurs 221:3,5

ODE 5:8,12,16,19 6:15 8:19 9:6,12

offer 243:2

offering 201:1 287:8

offers 243:8 287:21

office 2:5 5:7,8,15 6:14 8:19 67:1 75:1 199:11 202:17 241:2 288:13

officer 2:2 6:8 8:17 103:22 133:19 311:2

offices 72:17

of-study 140:4

oftentimes 290:17

oh 21:7 131:13 223:16 306:10

oil 100:4

okay 21:8,11 42:8 78:22 79:15 81:11 83:16 87:5,15 89:2,21 91:6 93:18 95:14 96:8 97:7,11 103:3,8,16 119:8 123:11,16 127:21 128:14,16 160:5 162:10,21 167:2 169:18,21 170:10 174:22 176:19 182:13 183:3 189:14 203:19 227:22 235:15 248:21 249:10 254:9 263:18 269:3 270:9 274:14,17 275:16 276:5 278:18 282:6 283:10 287:4,5 298:20

old 61:5 97:18 176:11 305:11

older 25:9 47:3 50:22 97:15 158:3 168:15,18 202:1 223:18 224:11 234:17 245:14 249:21 251:1 252:5 270:14

oncologist 265:19

OND 5:8,12,16,19 6:15 8:20 9:6,12

one-by-one 116:6

one-on-one 69:19

ones 95:2,9 127:19 128:3,16 134:7 143:14 147:16 180:9 188:5 242:8

one-third 170:8 195:8

ongoing 28:7 51:6 74:7 266:17

online 72:16 73:6 96:9 230:21 231:2 248:8

onset 26:11 53:2 55:1 64:14 83:15 102:22 213:10

on-treatment 110:7

open 9:16 11:6,17 22:3 99:22 134:21 167:14 190:14,20 191:4,8,22 192:5,6 196:9 197:2 214:12 215:1 218:13 264:18 266:7

opened 265:7

open-ended 39:14 44:2 53:6 217:19

open-label 41:9 50:21 178:11

opinion 222:10

opinions 11:5 192:4

opportunities 84:8 199:6

opportunity 25:6 45:21 58:14 67:2 77:17 92:9 101:9 174:1 201:12 210:17 219:12

243:11 244:21 280:17

opposed 99:6 165:12 187:21 264:19

opted 282:17

optimal 30:5

option 26:2 27:18 68:13,22 74:18 77:16 86:17 225:7 227:18 243:8,9 287:22

optional 243:9

options 25:12 70:16 71:8 72:22 73:6 74:2 194:15,17 211:16 214:8 243:8,13 248:7,10,14 280:16

oral 33:16 34:5,13,17,21 35:1 75:22 94:1 106:1 111:8 191:9 227:11 272:10,11,13 280:12 290:17 306:16

order 6:2 11:2 39:7 40:1,17 42:1 45:7,10 46:11 57:5 59:12 69:16,20 70:2 78:20 104:13 148:16 160:3 190:22 198:5 203:16 220:10 221:10 283:20

organ 193:4

organization 197:1 205:5 210:19,21

organizations 69:7,14 72:6,7,12,14 94:21 95:1,7,9 209:20

original 93:21 131:19

originally 132:4 166:2 284:14

orlistat 255:10 256:3

OTC 1:10 7:17 14:10 18:10 21:1 26:5 27:17,18 28:10 29:1,4,5 30:2,11 31:7 36:13,18 37:8,16 39:5 49:8 51:15,21 54:5 59:12 63:12 64:7 66:14 68:13,14 73:12 74:17 75:11,22 76:8 77:5,9,14 92:1 93:3,20 94:17 98:22 100:22 110:15 128:5 135:6 179:7,13 183:9 184:12,15 185:3 186:15 189:9,13 201:2 206:1,4 207:5,18 209:2 210:7,9 216:2 224:4 232:14 236:4 237:1,6 242:6,15 255:8,11 256:1 259:8 264:7 286:14 287:21 291:3 298:9,21 299:2 300:2 301:15 304:21

others 17:6 38:18 106:8 199:5 204:10 219:6 235:16 242:20 279:8 294:3

otherwise 190:10 192:15 216:17 244:11 281:12

ought 224:22

ourselves 22:14 184:12 193:9 249:6 304:12

outcome 23:8 52:18 244:6,11 251:19 312:8

outcomes 67:7 68:20 73:12 227:6 243:22

outings 199:4

outline 112:2 134:1

outpatient 235:6

outside 30:21 76:20 198:22

outweigh 222:21 233:17

outweighs 13:7 214:3

over-18 166:13

overactive 14:3 21:1,2 24:2,3 28:12 31:10 42:5 63:21 67:11 72:9 79:20 83:18 99:17 104:3 105:7,13 106:11 115:9 116:14 117:17 173:3 187:14,21 188:19 189:4 193:13 197:18 200:2 201:18,19 204:19 206:8 211:3 220:14 221:15 223:9 230:2,3,6,18 233:1 235:3,11 240:22 241:1 244:20 247:1,4,10,20 257:3,10 264:3 265:17 267:14 268:13,14 269:12,13 291:13,15 292:22 293:2,3 294:21 303:6

overall 33:9 35:21 42:16 72:10 73:12,21 81:15 82:1 87:2 128:15 142:8 147:2,19 150:18 156:9 170:13 177:5,6 178:4 247:7 250:10,16 253:5 306:22

overcoming 293:12

overconservative 166:7

overdosing 212:19

overlap 155:21

overly 288:19

oversight 304:21

overstate 239:6

over-the 20:7,21 162:7 163:21 164:7 179:1 205:18 225:14 229:18 242:18

269:9 293:13

over-the-counter 1:10 13:22 14:2 20:17 21:21 64:5 90:19 99:21 106:5,15 162:17 163:5,7,15 164:5 171:12 183:11,12,18,21 185:14,19,20 196:14 204:20 207:19 210:1,18 220:3 221:16 222:9 223:3,14 225:17 226:19 228:17 229:17 230:13,15 231:13 232:11 233:13,16 235:17 240:13,15 248:2,15 253:8 264:13 265:1 274:5 279:13 281:20 293:11 295:9 296:10 297:5,16 299:15,20 307:21 308:20 309:3

overuse 100:1

overused 259:6

overview 7:2 8:14 31:2 103:18 112:3

overworked 194:20

oxybutynin 13:22 14:5,10 20:18 21:20 25:20 33:12,16,17,19,22 34:4,9,14 36:7 75:13 83:3,11,14 85:15 86:2 105:21,22 111:9 127:22 138:6 152:4 157:14 180:19 208:17 214:1 220:3 227:9,15 240:6,9 250:13 251:6,7,9 252:1,14 269:9 272:10,11 273:2 274:4 283:18 284:13 290:17 305:18 306:13 307:19

Oxytrol 1:9 7:2,17 9:2,8 14:1 20:18,21,22 21:21 24:1 25:19,20,22 26:5 27:18 28:4 29:1,3,16,20 30:1,11 31:2,7,9,10,14,16 32:4,8,12 33:3,13 34:18 35:1,8,22 36:13 37:1,8 39:17 43:19 46:3,6 48:3 50:1,14 51:5,15,20 52:3,15 53:15,16 54:12 56:5,11,22 57:3,12,15 58:11,13 59:13,18,22 60:5,18 63:11,12 64:5,12,20 66:3,9,11 67:14 68:18 69:12 74:16 75:11,14,22 77:15 84:11 94:2 97:12 99:14 104:6 106:10 107:7,11,15,21 108:12 109:9 110:2,5,12,17 111:3,15 133:16 134:17,21 135:17 142:1 160:21 196:14,21 201:18 203:3,12,16,18 204:4,6,14 205:18 206:5,15 207:17 209:2 211:21 213:15 248:20,21 249:2,20 250:6 251:7 289:5 290:20,22 307:22

Oxytrol's 36:9 109:20 111:21 210:18

Oxytrol-treated 306:20

P

p.m 190:19 283:14 310:12

P450 242:17

PA 2:17 4:11

package 28:19 38:5,8 44:17 46:1,20 49:9 51:16 60:3 83:8 242:15 255:19 256:3 257:1 258:8,16 262:2,8,20 263:1,4,9,13 279:12 280:18 301:14,18

packaging 28:14 51:20 63:3 255:8 282:18

packet 258:20

pads 202:10 203:4,5,21 204:2

page 6:1 7:1 8:1 9:1 10:1 58:19 272:8,15

paid 193:9 201:14

pain 60:9,10 61:22 62:1,17 64:14,17 65:6 79:21,22 80:2,5,6,14 123:9 140:18 147:12,19 148:15 211:16 213:10 295:20,21

Pam 276:9

Pamela 5:3

panel 28:13 38:7 46:5,18 48:5 54:9 63:4 96:15 151:11 162:16 174:5 190:16 214:12,21 215:2 217:6 306:3

panels 40:9

panel's 157:17

pants 202:12

par 204:5

paradigm 43:18 189:13 236:5

parentheses 306:15

Parker 2:18 89:15,16 90:3,8,10 168:4,5 169:5,20

170:3,7,10,18 171:1,5 172:4,11,19 174:17,20 182:10,13 183:5 229:10,11 259:1,2 263:20,21 270:21 276:13 278:10,11 302:22 303:1

Parkers 304:4

partial 1:10 13:21 21:5

partially 20:21

participant 15:12 42:9 44:5 192:7

participants 5:5 12:20 15:13,16 23:3 41:9 57:20 61:14 62:4 125:14 220:5 274:6

participate 215:2 216:22

participated 16:18 18:4 20:1 52:13

participating 15:2 51:14 199:12

participation 19:3 198:15

particle 286:18

particular 13:7 14:11 15:6 80:4,10 82:5 95:7 101:4 153:21 155:13 183:14 220:16,19 221:8 225:2 226:14 227:21 234:15 239:13 251:1,19 253:11 271:20 279:11 292:8 296:2 309:1,8,11

particularly 77:22 120:10 126:19 157:15 231:17 280:9 302:3

parties 311:8

partner 199:7

partners 23:21 305:9

partway 92:22

party 312:7

pass 12:4 33:22

past 16:19 65:16 66:8 70:6 100:12 119:4 121:17

patch 21:21 25:20 26:4,12,13 30:1 53:2 54:4,22 55:19,21 56:2 72:3 74:16 75:14,16 86:3 97:19,20 98:1 100:12 102:22 105:21 106:14 142:10,15 143:3 145:2,8 154:10 203:3,9 212:18 218:4,5 252:14 271:17 272:14 284:13,16 289:5 290:20,22

patches 56:1 99:20 100:1,21 145:4

patents 13:17

paternalism 164:21

pathognomonic 104:11

patient 5:3 19:19 92:10 96:14 99:4 184:6,8 194:21 195:21 211:1 213:16 214:6 217:13 221:8 228:13 242:15 244:4 255:19 257:21 261:14 262:7 268:21 278:1,3 279:12,18 284:5 290:17 293:9 300:1 302:14

patient-centered 259:6

patient-doctor 19:18

patient-physician 252:21

patients 16:17 27:5 28:5 31:17,21 35:7 65:2 68:7 80:1 81:9 91:5 97:1 100:12 111:6,10 161:17 162:6,18,19 176:5 178:18 185:13 186:19 188:22 193:7 195:5,12 200:14 208:1 212:11 213:20 225:16 227:4,7 232:17,21 233:2,5,9 244:2 249:12,13 252:12,20 253:1,2,4,17 256:19 257:2,20 258:13,16 268:1,6,7 269:17,20 277:1,3,7 280:6 281:13,15 284:9,13 286:5 292:13 305:19 306:20 307:1,4

patient's 244:6

Patients 162:2 195:8

patient-treatment 35:15

patterns 145:7 278:21 304:10

pay 82:19 160:9,10 291:4 300:1,5

payers 300:20

paying 259:18

payment 191:13

pays 299:22

peak 34:12

peaks 34:11,16,19

Pediatric 18:6 20:4

pee 203:8,10

peeing 202:12

pelvic 45:6 63:16,20 99:12 193:4 194:4 211:19 266:3,4

Pennsylvania 4:9 99:9

people 17:10 52:8 82:6,9 83:13 84:14,21 85:7,18 88:2 89:4 90:1,18 92:1 97:1,15 98:3,4

114:3 118:2,22 120:16 124:5,12,13 126:6,8 129:3 144:21 151:19 163:6,8,16 164:19,20 167:9 168:13,14 169:15 170:20 176:9 177:9 179:14,16 180:7,11 181:6,8,14,22 182:4,18 184:22 185:15 188:3,18 189:4 193:5 197:4,9 202:4 206:12,16 208:2 215:22 216:16,22 217:6 218:8,10,19 220:9 222:16 223:11 224:10 225:14 227:8 229:4 230:7,11,17 231:2,19 233:9,12 234:13 237:15,17 238:5,7,8,9,11,14,16,18 241:20 246:19 247:3,20 248:6 259:17 260:3,13,18 264:18 285:1,2 286:14 288:5 289:4,8,10 290:21 292:16,21 298:10 300:11 301:8 302:3 307:12 308:8

per 34:8,12 44:6 51:8 94:10 106:14 107:11,12,13,15,22 108:1,2,6,7 128:18 137:21 141:2,9 158:2 179:3 187:8 200:4

percent 26:19 35:6 41:5 43:7 46:17 47:15,17 48:3,4,10,17 49:15,17,19 52:19 55:2,3,5,7,9,13,21 56:2,5,14,17,18 61:4,6,14 62:4,6,13,14 63:8 67:17 70:15 76:18 80:12 85:17 87:2,19 88:2,7,19,21 89:2,12 95:16 101:12,14 102:18 105:6,7 109:3 115:2,3 117:12,19 118:2 120:14 121:3,15,22 122:3,6,15 123:11,15,16 125:4 127:16,22 128:1,3 129:1,18,20 136:11 137:12,14,19 140:12,22 141:7,12,14,16 143:4,7,17 144:10,17 145:2,4,15,18 146:2,7,18,19,22 147:8,10,12,20 149:10 150:8 154:20 157:8,9,10 158:14,17,20,22 159:1 165:13 170:12,14 173:14,15 174:7,8,9,13,15,21 178:18 179:14 181:5 185:1 193:18 194:17,21 207:7,18,20 211:6 232:19,21 238:15 271:2,5,6,8,10 272:11 278:17 281:13,15 282:22 283:4,5 286:5 298:18 306:20

percentage 48:2 65:18 81:19 83:12 117:21 137:19 180:6 187:19 282:19 284:8

percentages 40:14

perception 229:16

perfect 296:22

perfectly 227:22 268:21

performance 272:12

performed 35:19 48:16,22 49:4 93:10 251:15

perfunctory 219:6

perhaps 105:6 125:9 126:12,19 132:17 175:14 176:9 187:13 235:20 244:21 280:18

period 29:16 62:19 137:8 156:13 236:3,14 240:6 267:3

periods 108:22 125:1,6,7

peripheral 208:18

permanent 162:16

permit 196:12

permitted 51:4 181:8

persist 66:22 236:3

persistent 290:4

persists 236:13

person 91:12 186:5

personal 15:12 24:14 113:8 190:15 199:20 269:17

personally 68:12 201:19 224:5

perspective 9:9 30:10,20 39:2 63:11 64:8 99:5,6 133:17,22 167:7,19 237:8,11,13 272:16 290:13

pertained 52:3 148:12

pertaining 117:10,12

pertinent 143:13,14 144:1 157:18

Pfizer 193:14
ph 167:18
pharmaceutical 15:8 201:16
Pharmaceuticals 23:22 249:18
pharmacies 51:1
pharmacist 196:1 224:11 246:22 286:21 308:9,11
pharmacokinetic 75:18
pharmacologic 27:19 70:16 72:22 73:5 86:17 211:20 231:18
pharmacological 71:8
pharmacology 3:4 4:13 16:12,13,21 33:11 34:2
pharmacotherapy 105:20 259:15
pharmacy 51:9,14 52:5,10 72:20 92:18 93:14 135:1
PharmD 2:3 6:7
PharmDs 196:2
phase 31:17 33:1,5,7 35:3,6 36:2,4 52:1 82:14 95:10 106:16 108:20,21 109:11 110:4 136:8 139:8 144:1 154:9 156:2 162:3 217:15 250:17
PhD 3:7,15 6:18 7:3 8:9 9:17
phenomena 268:12
Phil 276:1
Philadelphia 4:11
Philip 4:8
phone 52:2,7
photos 136:19
phrase 132:14
physical 24:14 195:15 202:15 206:6
physically 68:10 287:13
physician 2:16 7:21 16:17 18:22 45:4,12,15,16 54:11 173:9,13 184:8 187:21 188:11 189:21 190:3 213:10 221:15,17 224:12 233:1 244:9,12,19 252:17,21 257:5 261:5 266:17 269:8,20 271:1,4 278:1 282:5 284:6,10 302:14
physicians 27:4 81:1 221:5 244:21 292:21
physician's 67:1 241:2
physiologic 83:10 221:19 256:16
picked 95:6 230:16 283:4
picking 282:21
picture 126:18 129:9 309:12
piece 97:4 186:17 252:12
pieces 210:3
pilots 221:4
pin 105:2
pink 46:4 136:17 171:12 246:2 278:16
Pittsburgh 2:15,16,17 18:21 19:1
pivotal 42:16 43:12 46:22 47:8 48:14 50:9 112:16,18 113:22 114:22 116:8 122:7 123:8,9 124:14 127:8,9 129:18 130:16 131:4 133:10
placebo 31:21 32:4,9,12,14 36:1 75:15 83:20 107:8,12,16 108:1,7,15,18 110:6 208:18 212:6 250:20 251:9 252:2 271:17 272:6 284:22 285:3
placebo-controlled 31:20 106:17 178:10 251:4
placement 131:3
places 306:12
placing 27:13
plan 53:6 69:13 196:6
plans 30:13 70:9 162:7,8
plaque 17:3 18:14 19:9 20:10
plaques 17:4
plasma 34:4,7,9,17 36:7
play 198:8 258:14
player 260:18
please 12:1 16:9 42:20 78:6,17 93:17 163:11 188:15 192:8 196:17 201:7 205:2 210:12 215:11 220:4 254:13 274:5,21 282:12 283:20 294:12 301:13,16 302:8
pleased 16:22 20:5
plus 127:8 138:14 149:14
pneumonia 147:15
podium 31:2 111:13
point 40:16,22 41:5 55:1,20 56:1,5 63:8 71:17 84:2 88:6 101:15 104:20 114:5,16 117:20 118:10,11 119:10 120:7 122:2,6,15,20,22 123:22 125:6,21

126:11,13 128:4 129:15 136:9 137:3,11,17 139:6,15 141:16 143:5,20 145:3 147:2,12 148:3,6 149:22 150:8 152:14 153:2,11,15 157:1,4 158:16 159:4 166:18 179:21 188:22 199:3 203:12,20 215:19 222:1 233:11,17 250:2 257:14 258:7 263:21 267:17 268:8 293:22 294:5 306:18

pointed 143:16 144:9 151:22 152:8 155:4 157:22 228:22

pointing 118:7

points 48:18 113:19 114:8 120:7,22 128:21 136:12 137:12 233:6 238:16

Poison 156:8

Policy 2:14

polydipsia 66:19,20

polypharmacy 307:5

polyuria 66:19,20

pooled 35:4

poor 181:10 217:9

populated 158:12 177:2

population 18:4 28:12 46:16 47:15,18 48:9,15,18,19,22 61:4,7 62:14,15 75:10 80:22 81:16 87:19 95:16 96:5 97:13 99:4 109:2 121:1,3 122:5,19 123:14 124:5,8,9 127:14 128:20 129:11,17 130:7,8 135:2 158:3 165:14 168:13,19 169:1 170:4,21 171:2,6 175:5 179:5 180:6 182:3,4 183:14,19,21 232:3 234:7,14 249:14 252:6,18 253:13,19 260:14,20 267:15 271:3 309:2

populations 38:17,18 126:20 127:7 179:4 245:13

portion 38:8 165:6 194:3

posit 303:3

positive 36:5 61:10 62:12 163:15

positives 243:7

possibility 151:7 155:5

possible 41:10 43:5 47:7 58:1,19 59:4 62:2,20 78:18 96:3 101:16 139:18 140:15 141:6 148:13 149:8,11,18 150:5 180:9 197:14 204:21 296:8 305:11,12

possibly 57:22 84:21 85:21 105:16 157:21 217:20 296:7

post 142:22 143:17 145:2 268:19

post-hoc 144:13

postmarketed 178:9

postmarketing 14:4 21:13 35:3,13,22 36:10 100:17 134:17 153:20 155:13 156:5,15,17,20 159:12 177:8

postmenopausal 194:5

post-mitigation 44:15 144:10,18 146:8

post-OTC 72:18

post-void 227:16

potential 13:5,8,11 42:1 50:16 52:20,21 53:8,20 54:8,13 56:3,8 60:13 67:1 71:6 76:10,22 77:4 93:20 96:16 111:7 129:11 140:16 205:21 207:1,5 210:18 214:2,3 222:20 245:7 268:10 277:11 294:13 296:20

potentially 51:9 75:4 171:13 207:11 213:1 280:17 296:12

potentials 76:12

powered 143:21

PPI 298:2

practical 92:7

practice 25:4 37:16 41:18 63:20 65:1 68:3 99:17,19 277:6

practiced 203:8

practicing 63:15 99:11 286:20 303:8

practitioner 99:11 202:17,21

precautions 110:22

precede 268:18

preceded 65:8

precious 195:18

precisely 190:14

preclude 23:15 191:20 243:8,13

precluded 109:20

predefined 55:6

pre-defined 39:15

predict 135:6 225:8

predominantly 170:5

preemptive 25:4

Preexisting 53:9
preferred 155:11 177:16
pregnancies 202:9
pregnancy 45:6 49:13 59:17 60:6 61:2,6,10 65:11,14 66:2,6,11 104:18 110:12 124:13,14,15,18 125:12 126:16 129:14 161:18 194:8 202:19 213:2
pregnant 44:11,14 48:8 49:3,7 61:7,11 65:13,21 83:4,5 116:3,4,5 124:11,12 125:9,13 126:22 129:8 137:21 171:14 174:14
pre-launch 72:15 95:10
premise 287:3
pre-mitigation 142:22
prenatal 65:18 66:12
preparation 227:22
prepare 195:22
prepared 312:4
prescribe 99:14 227:15 269:8 308:8
prescribed 79:4 195:6 289:2
prescribers 260:7
prescribing 19:2 278:21 304:10 306:19
prescription 1:10 13:22 20:7,17,21 21:4 23:22 24:20 25:22 31:11,19 35:5 71:18 74:21 94:2 98:13,20 99:1 104:6 106:4 110:14 134:17 158:1 175:13 179:2 184:5,7 194:13 205:22 209:9 210:9 226:2,18 233:13 242:14 246:22 264:14 299:16,19 300:2 308:13 309:4
presence 197:12
present 31:14 47:21 60:20 65:5 77:6 98:12 100:19 104:5 159:9 209:3 225:12 226:22 228:12 240:5,8 272:21 285:22 295:12
presentation 15:22 23:2,11,14 29:17,22 38:4 50:8 74:11 81:8 85:11 93:21 101:19 111:12 115:16 169:9 191:7 243:16 266:12
presentations 6:16 8:13 21:12 22:2 23:17 90:14 91:3 103:15,17 143:17 155:5 192:16
presented 17:9 35:5 41:10 49:12 69:4 92:9 97:12 101:19 118:22 168:8 184:21 185:3 301:13 309:22
presenter 78:19
presenters 23:4 78:1 159:20 310:6
presenting 67:10,16 114:14,16
presents 228:8
President 210:14 249:18
prespecified 40:9 52:3
pre-specified 39:11 282:9
press 254:13,15 274:21 275:2
pressure 161:4,19
presumably 215:6
pretty 120:5,22 127:3,21 128:15 136:21 176:14 177:7,18 232:1 280:8
prevailing 71:1
prevalence 24:9 105:2,8 168:9,17 211:5 241:18
prevalent 211:4 253:21
prevent 228:21
preventative 19:19
preventing 71:11 298:15
previous 119:15 120:12 151:13 176:22 209:15
previously 57:7,10,11,14,15 ,17 129:4 137:2 139:9 149:6 188:3,6,8 218:8
price 160:13,14
Prilosec 295:11,13,17,22 297:21 298:1 299:15
primarily 288:11
primary 13:18 32:1 52:14,20 54:8,17,19 55:7 56:7,9 63:9 76:18 81:1,21 95:12 101:11 106:19 107:6 108:13 110:4 113:14 125:19 134:6,8 135:12 142:1,9 143:1 145:12 146:15 148:11 158:13 174:5 218:1 244:21 251:16,21 271:22
principal 15:6
print 90:5 255:18 256:8
prior 16:18 70:7 134:14 184:6 186:22 227:13

285:18

priori 47:11 113:17 142:7 143:5 144:4 145:17

priority 229:20

privately 193:5

PRN 231:8,12

proactively 27:5

probabilistic 221:9

probably 88:6 90:21 95:12 159:15 164:15 165:14 166:11 167:8 172:16 184:15 212:18,20 221:5 228:16 229:18 233:9 242:18 248:21 256:21 258:18 277:3 290:14

probe 126:1,3

problem 25:1 70:13 105:1 175:22 197:19 202:15 224:20 232:20 234:18,19 241:17 252:8 283:2,3 288:6,7,9 290:3 292:9 298:20 302:1 308:19 309:11

problematic 206:19 280:7

problems 27:6 176:1 183:13 193:3 195:16 205:13 229:7 234:9 242:3 291:19 292:1

procedures 137:1

proceed 22:9 87:4 214:20

proceeded 150:13

proceeding 311:3,4,7,9,10

proceedings 11:19 138:13

process 22:20 37:17 40:3,6,9 53:7 55:11 56:7 74:8 96:22 191:2,22 234:5

processed 142:5

product 8:4 14:21 20:17 21:4,5 28:5 29:7 30:8 34:14 37:13,14 39:5 41:12,13 42:9,18 43:3,22 44:12 45:2,8,15 46:2 47:20 48:6,7 51:17 52:11 56:19 58:16 60:8 61:8 64:12 75:11 76:22 77:8 79:11 82:19 84:6,9,22 85:2,8 86:3,15 87:4,19,20 89:11 90:19 91:8,10,12,14,16 ,20 92:1 93:3,19,21 94:14 96:16 99:4 104:7,19 106:3,5 117:17 119:8,9 121:20 122:12 124:20 125:2,16 126:21 133:12 136:1 138:6 144:11 145:2 164:7,9,11,12,13 166:6,15 167:6 172:7 173:5,20 174:7,10 175:1 178:8 179:12 182:1,5 183:18,22 184:2,10,21 185:1,2,20 186:4,6 188:5 189:3 191:11 200:20 204:14,20 209:2 210:9 212:21 216:1,9,22 217:8 218:6,9 219:2,3 220:13 221:16 230:10 236:21 237:14,18 238:11 239:4 242:8,16 249:13 251:8,9 252:1 255:11 257:11 261:15 264:6,17 266:10 267:5 273:11,14 279:11 282:17,19 283:22 285:14 289:3 293:17 298:6,9 302:19 304:21 306:2,19 307:5 309:8

productive 11:12

productivity 24:19 200:7

products 15:11 25:11 70:13 71:18 75:6 99:21 101:3 106:2,3,4,7 145:5 163:5,7,9 164:18 166:10,14,22 185:21 186:3 189:11 199:21 235:17,19 236:1,11 242:17 255:10 264:13,15 265:1 291:6 295:9 299:16

product's 51:22

Products 5:19 8:18 104:1

professional 28:2 53:11 69:7,13 77:13 95:9 197:22 210:21 225:20

professionally 68:11

professionals 26:18 30:15 72:9 197:5

Professor 2:9,12,13,18 3:4,8 4:3,8,12,16 16:11 17:21 18:20 19:14 99:10 266:1

profile 28:4 30:1 34:9,13,18 35:1,16,22 36:1,9 75:18 76:8 178:8 250:17 273:1,14 280:8

profound 243:2

program 4:11 7:14 10:6 27:21 29:1 30:14 36:18 37:5,20 39:1

40:5 53:19 63:16 69:12 71:3,14 72:11,21 73:4,8,16 74:6 84:1,10 111:3 225:11 266:3

programmatically 54:16

programs 2:5 72:8,15 84:12 200:13

progress 240:10 305:5

progresses 64:9

progressing 66:16

progression 53:10 65:4

project 165:21

projections 226:19

projects 197:8

prolapse 193:4

prolonged 136:2 162:1 240:6 279:4

prominent 109:13 247:12

prominently 261:4

promised 182:11

promote 189:12 197:16 200:15

promotes 210:22

prompt 64:18 65:15 150:7

prompts 67:18 68:3

prone 25:9

proper 18:8 37:2 181:6 186:5 280:4,18 293:5

properly 179:4 184:1 186:5 280:16 293:1

proportion 52:14 129:20 143:9,19 244:18

proportions 142:9,19 211:5

proposal 26:15

proposed 14:1,2 21:1 49:8 112:11 130:20 131:7,16 132:6,22 137:21 165:8 206:4 283:19 301:14

proposing 26:6

proposition 196:2

Prospective 51:13

prostate 104:22

protecting 239:3

protective 199:21

protocol 82:9

prototype 37:21 242:19

proven 75:10 76:7 196:13

provide 19:22 27:18 28:19 30:9,11,20 37:1 39:1 52:6 74:18 75:6 76:1,2 81:15,22 87:1 116:10 163:7 167:19 186:3 188:1 190:4 197:5 200:15 258:8 299:4

provided 12:20 58:14 91:3 101:10 192:1 193:11 213:19 255:11 258:15 300:18

provider 64:19 70:18 74:3 77:14 189:5 200:18 206:18 209:18 210:2 212:10 248:11

providers 69:15 71:12 72:16 73:1

provides 15:7 77:15 185:6 193:2 249:14 270:12

providing 67:2 71:5 164:18 184:2 197:3

pruritus 35:9 109:14 157:7

psychometric 251:14 252:4

psychosocial 33:6 199:22

public 2:15,18 3:5 9:16 12:21 14:20 16:12 22:3,19 25:3 71:5 72:19 190:14,20 191:2,4,8,22 192:5 199:15 210:21 214:12,19,22 215:1 222:15 229:16 230:3 303:15,16 304:12 311:1,13

publications 200:14

publicity 253:16

published 67:8 200:1

pullouts 265:2

purchase 51:16,18 52:11 84:9,11 87:18 89:4 90:18 92:20 93:3 134:3 138:18,21 139:7,11,16 140:5,13 141:1,8,13 149:12 151:17 159:2 160:12 207:12 215:7 216:22 219:3 281:14

purchased 139:4 186:1 206:15 265:6

purchaser 96:16 256:7 301:21

purchases 302:18

purchasing 93:2 160:8

pure 82:10

purpose 39:2 62:9 135:7 161:12 163:4

purposeful 245:12

purposes 13:14

pursue 238:21 280:15

purview 263:11 264:7

pushing 213:4

putting 94:12 102:4 130:1 167:13 255:8

293:10,13 297:5 306:1 308:3

puzzled 199:3

pyelo 65:5

pyelonephritis 65:5 138:2

Q

quagmire 186:11

qualified 138:16

qualify 44:15 280:6

quality 19:2 24:4 27:12 28:4 32:19,21 33:2,8,9 36:6 64:4,13 74:17 76:1 156:18 161:1 211:1,10 229:1

quantitative 69:19

question 42:10 43:22 44:6,8,13 78:17 79:19 82:12 85:16,21 86:6,20 87:6,14,16 88:7,16 89:19 90:3,22 91:1 92:4,12 93:4,17 94:20 95:3,6,14 98:9,17 116:12 117:3,10,12,15,22 118:13,18,20 119:4,12,16 120:13 121:17 122:9,17 123:10 124:21 125:6 126:5 129:13,14 161:2,10,13,14,15 162:15 163:10 165:4,5,10 169:2 171:6,8 176:10 178:16,17 182:11 185:10 186:18 188:17 189:2 216:15 218:19 219:21 222:7,9,20 229:9 230:14 232:15 235:1 241:12,21 248:19 249:9,11,19 254:5,7 260:9 261:10 262:3 270:5 272:19 275:12 281:8,18 282:8 285:12 286:17 294:6 297:2 300:3 305:22

questioning 78:3

Questionnaire 33:4,8

questions 8:10 9:13 10:12,15 30:17,20 39:9,11,14 41:16 43:21 44:2,4 57:21 58:10,21 77:20 78:10,12,20 79:2,7 80:18 81:13 83:7 85:12 87:17 90:15 96:13 103:6 113:16 116:11 117:9 118:1 121:14 123:1,8,13 157:18 159:18,22 160:2,17 165:4,17 168:2 176:20 178:16 183:4 192:14,18 214:11,14,20 218:14 220:9 223:13 232:2,5 249:4 254:3 255:2,14 265:8,13 269:6 270:2 275:11 276:7 278:6,8 282:7 283:14 300:13

queue 198:11

quick 248:19

quickly 102:9 103:2 131:11 145:12 215:16

quit 195:5

quite 11:5 39:19 99:4 100:21 105:5 158:10 163:14 165:16 216:6 217:7 239:18 247:5 294:20

quote 269:12

quote/unquote 140:10 180:2 187:4 268:12

quoted 163:20

R

R&D 6:18

race 146:13

Rachel 122:9,12

racial 81:18

Raffaelli 9:10 133:16,18,19 176:22 178:6 179:9 186:7 238:2

raise 86:16 192:18 230:14 231:4 300:12

raised 208:14 226:13 228:6 267:13 268:10

Raj 29:22 31:4

Rajesh 7:3

ran 52:1

random 92:10

randomized 272:9

range 40:16,20 49:5,17 105:5 181:8 207:9 211:11

ranged 108:22 129:17 207:9

ranging 48:16 123:14

rapid 64:14

rare 65:5 212:5 239:14 247:17,18 277:13

rarely 65:7

rash 128:2

rashes 157:7

rate 52:19 55:6 98:10 101:2,18 143:4,22 144:15 145:17 158:14 238:6

rates 35:12 92:3 98:12 99:7 105:8,9 135:10 142:20 146:14 212:1 250:19

rather 80:3 152:11 181:14 201:4 209:5 247:2

258:18 279:20
ratio 34:21
rationale 114:4
rats 250:12
raw 87:21
reach 64:11 72:15
reaching 72:14
reaction 128:1
reactions 35:8 109:13 110:20 147:4 148:5 154:6 157:6 159:13 175:19 177:10
readability 38:11 63:2
readily 27:2 204:20 298:21
reading 45:1 91:13,18 163:12 164:1,16 166:21 173:7 206:3 225:13 295:8
real 68:15 98:13 166:17 176:2 205:13,14 216:16 222:6,7,11 224:19 226:16 227:21 233:7 270:12 289:19,22 297:4 307:17
realistic 285:16
realistically 300:6
reality 68:4 94:14
realize 227:9 282:17
realizing 298:12
real-life 41:11
really 39:10 40:1 74:17 79:22 82:16 88:5 89:7 98:16 99:5 100:11,15 102:9 112:16 115:19 117:2 119:1,13,20 122:8 126:9 127:13 128:6,18 129:17 130:3 131:6 132:16 133:4 135:10 137:19 146:12,16 157:10 165:11 166:19 171:5 180:3,15 181:18 188:19 194:15 202:11 203:15 204:14 210:7 212:13,15 216:19 217:10,22 218:13 222:9 232:15 234:6,9,10,19 235:7 237:15 241:1 246:18 247:11 248:1 253:18 257:5 259:8,19,20 260:4 264:3 278:11,12 281:17 286:1,16 287:17 288:22 300:7 303:22 304:6 305:8
realm 151:7 179:13
reason 23:2 34:21 43:13 84:2,6 95:12 100:10 139:4 148:4 152:21 165:20 191:7 194:7 246:12 254:22 269:21 270:13 275:9 281:18 282:2 286:13 297:15 299:5
reasonable 74:15 110:3 114:3 142:8 150:14 181:17 212:20,21
reasoning 221:9
reasons 49:5 81:10 82:6,15,16,22 83:1 89:7 102:11 139:13,17 140:1 151:2,19 207:9 222:14 229:6 266:18 297:11,12 308:7
reassurance 252:6
recall 170:4 174:4 184:19
recap 30:16
received 31:22 201:15
receives 197:10
receiving 65:18
recent 112:19 158:1 166:12 272:22
recently 105:5 193:10
receptor 106:3
recess 283:12
recognition 17:9 66:1
recognize 16:6 17:3 18:14 19:9 20:10 27:2 50:16 59:9 63:6 65:21 151:8 183:10 211:9
recognized 11:11 54:1 59:7 61:18 102:6 150:6,21 160:4 192:9 268:14
recognizes 290:15
recommend 133:8 210:8 225:1 261:9
recommendation 187:9 261:16 264:11 302:17 303:4,5
recommendations 132:10 162:11 242:11 261:14
recommended 91:13 202:16 203:1 209:20 214:5
recommends 90:19
reconcile 88:18 101:9
reconstructive 210:22
record 11:10 15:15 78:19 163:4 220:9 254:20,22 275:6,8 311:7
recorded 99:1 311:4

recruited 44:20 92:15 122:8
recruitment 51:11 136:15,16,20
red/itchy 128:2
redesign 46:1,19 174:12
redesigned 38:7
redid 305:17
redirected 74:8
reduce 25:7,16
reduced 28:3 34:1 160:15 311:5
reduces 34:15
reducing 71:10
reduction 32:7 108:13,15
refer 40:15 42:20 115:7 135:16 231:2
reference 184:18 272:14
referred 38:3 40:4 102:1
referring 89:9
refers 263:10
refined 74:9
refinements 46:8 63:1
reflect 113:17 121:5 170:19,20 171:1 264:8
reflects 156:21
reflux 111:6
refractory 68:1 213:14 269:1
refrain 11:20 12:2
regain 196:7
regard 46:6 67:5 76:19 81:1,14 218:14 243:18 244:17
regarding 61:20 76:3 91:4 161:15 183:17 214:8 248:19 268:10 283:21
regardless 125:8 252:13 260:13
regards 95:15
regimen 223:4
regress 65:3
regular 12:13 13:5 73:18 195:15 202:15
regularly 203:9,19
regulated 15:4
regulations 12:15 300:17,19 304:22
regulatory 205:6
Reidenberg 3:3 6:3 11:3 15:20 16:3,8,10,15,18 17:3,9,14,15 22:9,11,17 23:19 77:21 78:9,11 80:16 83:6 88:14 89:14 90:11 93:16 94:18 96:11 98:8 100:16 101:6 103:4,8,16 159:19 160:1,16 161:7 162:10,21 163:19 165:1 167:2 168:1 175:8 176:19 178:13 182:9 184:4 185:9 188:14 189:14 190:12,21 196:16 201:6 205:1 210:11 214:10,16 215:12 218:15 219:11,16 222:3 223:15 224:16 229:10 232:6 233:21 234:21 239:5,17 241:6 242:4,21 245:19 247:14 248:16 249:8 252:10 254:1,9 255:5,16,21 256:6 257:12 258:5,22 260:8,11 261:1,8,12 262:13 263:8,18 265:9 267:6 269:3 270:2,7,20 271:13 272:7 273:18,21 274:2,14,17 275:16,19 276:3,6,17 277:8,16 278:4 279:2 281:5,21 282:6 283:7,10,16 284:17 285:5,10 286:12 288:3,18 289:15 290:10 291:9 292:5 293:20 295:5 300:16,22 301:3 302:16,22 305:15 306:8,10,17 307:7 308:18 310:1,5
reinforces 284:12
reiterate 278:11
relate 73:20 230:8 231:16 295:3
related 13:9 14:12 35:17 43:1,5 49:16 59:1 89:5 109:8 141:22 154:10,13 155:6 156:3 183:13 223:14 227:20 277:10 279:10 311:8
relates 37:6 50:10 60:21
relating 57:9
relations 72:20
relationship 15:17 191:10 199:6 266:17
relationships 23:5,12,14 24:15 191:18,19
relative 34:21 250:7
relatively 128:15 136:5 150:22
relaxant 154:4
release 34:5,6,14,16 271:22 272:6 273:2,3
relevance 226:16 279:18
relevant 73:17 112:20 226:14 231:17 239:19

254:6
relief 76:1 204:3 236:5 239:8
relieve 25:19
remain 21:4 195:8 198:5 204:6
remained 38:9 43:9
remaining 76:21
remains 304:19
remarks 6:11 16:1,5 20:14 112:17
remember 40:19 60:18 67:16 190:1 201:20 235:21
remind 15:9 103:10 214:22
reminded 12:1 300:16
reminder 11:9 300:16
remote 21:9
removing 72:3 97:18 197:3
Rep 22:16
repeat 41:20 161:14 163:11
repeated 298:6
repeatedly 279:15
repeats 270:11
rephrase 86:19
replacement 73:14 255:10
Replogle 7:13 30:6 38:20 50:3,7,8 63:13 82:4,12 84:14 87:6,13,15 89:2,20,21 90:7,9 92:13,16 101:18 102:21 160:13 188:7
report 55:21 105:8 148:8 153:6 176:5 186:20 187:4,9 195:9 200:17
reported 1:20 14:15 35:6,11,17 52:22 56:2 57:2 61:11 62:20 88:10 89:1 111:8 135:14,20,22 137:22 138:1,15 139:19 140:8,10,13,15 141:5,18 143:2,11,13 144:15 145:21 146:22 147:4,6,8,9,14 148:2,13,19,20 149:8,11,16,17 150:2,5,9 151:4,15 152:5,15,17 153:12 154:15,16 155:20 156:11 157:3,8,12 158:9,18 177:11 180:4 212:5 215:20 238:14,16 250:19 307:2
reporting 1:20 147:2,20 148:9 153:22
reports 147:18 148:7 153:3,16 155:18 157:9
represent 15:5 29:15 77:2 296:12,13
representation 129:16
representative 3:8 5:3 12:11 15:1,3 96:14 156:22 182:3 296:8
represented 169:1,17
representing 23:21 193:7
represents 37:21 54:18 210:20
reproductive 4:17 5:19 8:18 66:8 104:1
request 215:2 261:18 262:14
require 28:17 247:6 262:7,11,21 268:3
required 246:17 263:17 299:2
requirement 205:22
requires 206:1 208:7 259:11 294:2
research 1:6 7:10 9:3 17:12 19:1 69:18,19 70:8 73:19 74:4 100:17 111:16,22 112:2,7,9,10,12, 19,20 130:11 132:11 176:16 193:11 194:9,20 195:11 206:12 211:2 249:18
researcher 16:16
residents 303:9 304:4
residual 227:16
resignation 70:20
resolution 65:10
resolved 54:14 153:9 154:21 284:1
resonance 120:16
resources 73:1
respect 14:22 103:11 107:6,8,9,14 108:4,11 163:21 192:8 224:18 225:3,13 226:14 262:13 267:9
respectively 32:5
respects 243:10
respond 65:6,9 68:7 81:12 87:6,14 89:20 92:13 165:16 181:18 195:21 249:9,11 286:3 289:13
responded 44:5 58:3,21 88:7
respondents 129:19 195:9
responding 40:15
responds 39:14
response 29:12

41:6 44:12,14 45:12 52:9 103:7 163:2 173:13 174:1 245:21 254:8 272:19 273:20 274:1,13,16 283:9 301:2 307:3 310:4

responses 39:11,15,19,20 40:8 44:8 45:3,13 117:22

responsible 36:22 75:21

rest 29:17 46:7

restate 86:20 174:20

restrict 25:8 198:14

restricting 198:5

restrictions 303:22

restroom 25:3 204:10

result 28:2 41:16,17 49:8 69:1 112:12 130:11 174:13,14 176:12,15 198:19 206:7,20,21

resulting 29:19 33:22

results 14:5 21:14 30:6 42:17,21,22 45:22 47:7 49:11,22 54:17 62:11 70:10 74:4 80:20 91:17 107:5,19 108:5 112:21 116:12 119:19 136:6 173:8 176:13 203:4 213:2 215:18 217:18

resume 103:9,12 190:13,18 283:12

retail 51:1 193:16 196:1,12 208:2

retaining 195:1

retention 58:5,8 88:4,10 110:18 111:4,5 116:1 119:21 120:1,3,16,21 121:6 128:9 131:12,15,17 132:1 140:12 149:5 152:7,11,12 153:3 176:3 180:12 186:19 187:4,7,11,12 193:3 213:8

retest 43:11 46:19

retested 43:15 46:21

retinopathy 227:7

retired 288:11

retraining 86:8 105:16 211:19

return 52:5 203:14 219:14 298:13

returned 52:13 219:19 310:8

reveals 194:9

revenues 193:9 197:10

review 21:13 30:3,6,13 31:13 35:3,19 36:17 38:19,21 58:11 59:3 69:11 115:5 135:4 136:10 153:16 172:9 186:20 187:9 208:14,20 215:14 262:11 272:22 304:19

reviewed 40:1 44:8 53:21 63:1 106:6 142:6 148:8 259:16

Reviewer 9:11

reviewing 30:1 59:5 115:11

reviews 69:18

revised 63:4 121:4 126:14

revisit 183:20

rid 204:2

rigorously 130:3

risk 27:13 28:6 29:15 40:17 41:19 56:3,6,8 59:13 64:8 66:5 68:22 77:3,4 98:19 102:5,12 111:4,5 113:18 116:2 120:6 121:7 122:8 127:20 128:13 132:20 133:3,6 140:15,16 149:2,5 151:12,15 153:12 166:4 182:21 209:3,7 213:1 223:11 228:20 233:5 298:10

risk/benefit 232:5

risking 199:13

risks 50:16 51:10 68:4 77:6 81:9 208:7 209:14 212:19 214:3 222:21,22 223:5 232:14 233:17 293:13 299:18

risky 306:3

RN 3:7

Robert 4:19

Roger 265:16,21

Rogers 3:7 17:17,18,19 18:2,4,15 94:19,20 95:14 96:6,8 233:22 234:1 260:11,12 275:21 281:22 282:1 285:5,6 286:4 288:3,4

role 15:4 227:5 259:15 260:2

room 1:15 181:1 254:20 275:7,17

ROSTER 2:1 3:1 4:1 5:1

routine 59:8 66:17 151:1

routinely 27:4

routines 198:5

royalties 13:17

rule 285:19

ruled 104:14

rules 40:8,11 192:19 261:2

ruling 211:14 235:12

run 134:4 201:22 205:14 224:14 243:6 266:2 308:11

running 185:18

Ruth 2:18 276:13 304:3

Rx 184:17,22 185:5 290:22 291:4 305:1 306:19

Rx-to-OTC 6:19 7:14 8:5 21:6 196:20

Ryan 9:10 10:6 133:18 205:3

S

safe 14:9 21:20 26:1 27:19 29:4,18 31:7,9 94:14 164:19 186:15 193:16 196:12 200:9,21 224:9,13 229:22 239:4 249:14 277:5 286:11

safeguard 50:5,13

safeguards 29:3 31:8 37:2 66:14 216:13

safely 63:11 163:9 164:9 186:5 210:6

safer 101:4 106:8 229:18

safety 8:14 19:2 28:4 31:14 33:12 35:2,14,16,21,22 36:1,9,11 47:2 49:20 50:16 75:17 76:7 103:18 108:19 109:3,17,18,19 111:2 128:6 134:8 146:21 148:11 153:19 156:5,6,15 159:10 175:11,13 177:8,17 178:8 180:1 212:1 214:2 220:7 229:20 230:19 231:4,16,22 238:4 243:17 245:4 250:1,17 274:8 280:8 281:4 294:9,12 301:4 306:22 309:18,21

sale 84:2

sample 52:6

samples 96:6 234:12

San 2:10 3:9,10 18:1 19:15 252:17

saw 53:16 54:2 84:20 89:22 90:20 172:10 218:7 219:10 234:17 256:11

scale 125:13

scan 289:21

scary 179:12

scenario 41:16 42:4 47:21 113:15 118:21,22 119:11,14,17

scenarios 41:10 42:22

schizoaffective 155:18

School 2:13,14,20 4:5,14,19 7:19 10:10 18:1,21 63:19

Schwartz 167:18

science 3:9 4:4 9:5 18:1 111:19

Sciences 4:17

scientific 35:20 96:19

score 33:5 41:7 46:18 49:15 118:15 272:1

scored 48:18 127:4,13 128:15,21

scores 40:15 43:6,8,13 45:18 46:14 47:14,17 48:16 49:17,19 62:12 73:20 84:19,20 114:13,19 122:20 216:4 272:3

scoring 42:11

scouring 130:22

screen 27:5 53:4 54:19 55:3 188:20 247:21 254:19 275:5,6

screened 13:11 89:21 137:20

screening 51:13 136:15 137:18

script 92:22

scripts 137:6

se 128:18 179:3

second 29:5 43:17 48:8 58:12 79:19 83:12 85:17 86:20 91:1 92:4 93:8,17 97:11 98:6 126:1 129:15 132:5 158:6 161:2,12,14,15 178:22 179:10 182:12 189:2,6 227:14 250:11 269:11 290:20

secondary 32:9,12 55:10 56:13 107:1,7 134:7 135:18,19,22 136:4 142:2,11,13 144:5,20 146:4,15,16 251:16,21 272:2,4

secondly 115:21 234:12 241:9

section 12:19 13:3,14 130:2,12 131:13,14 132:3,15,17 133:6,10 266:4

seeing 91:20 133:9 190:3 225:3,5,7 230:21 241:21 251:21 266:10,13,17 269:7 284:10

seek 28:1 29:13 59:20 65:15

67:18 134:14 200:12 209:5 210:2 225:19 269:20 285:9

seeking 25:1 62:16 197:22 199:10 200:12 206:1 228:21 308:4

seem 81:6 180:17 246:12 270:17

seemed 136:20 150:13 151:19 239:2

seemingly 217:20

seems 27:16 74:15 90:18 151:7 152:20 179:12 226:12 243:18 278:19,22 279:3 297:15

seen 35:7 47:14,16 58:12 64:3 75:22 76:5 79:13 109:11,13 111:2,9 124:2 128:6 178:7,8,11 216:12 237:17 244:19 249:1 253:20 273:16 284:6 291:12,14 292:22 309:17

sees 78:20 188:18 220:10 268:6 293:10

Segal 22:12 163:4

Segal's 258:7

seldom 184:6

select 48:2 169:16 243:19 245:13 274:4,10

selected 92:8 95:2 178:19

selecting 95:13 215:7

selection 87:8 171:19,21 172:2,19 176:11 181:11 215:6 217:16 219:5 248:4 280:4

self 27:19 43:17 50:4 54:13 74:19 75:2 76:6 87:7 119:2 153:8 169:16 171:18,20 172:1,18 176:10 178:18 181:10 189:7 215:5 216:12 217:15 219:4 248:3 274:3 298:14 300:9

self-administer 164:14

self-blame 198:20

self-care 236:16

self-choice 89:7

self-diagnose 206:3 220:14 241:3 277:3,7 278:3

self-diagnosed 196:13

self-diagnosis 119:2 189:12 212:9 248:3 267:9 277:4 301:6

self-esteem 198:19 202:11

self-exclude 218:21

self-help 199:12

self-limiting 199:1

self-manage 50:15 209:4,5

self-management 24:21 27:9 28:7 29:2 31:8 37:2 50:12 259:11 264:1

self-managing 28:16 59:14 70:15 77:7 79:14 86:12 225:6

self-recognition 45:19

self-recognize 266:22

self-reported 70:5

self-select 37:4 76:11 172:6 179:4 182:20 206:3 216:7 220:2 232:18 280:5

self-selected 174:7,9,22

self-selecting 215:5

self-selection 7:8 9:3 14:7 21:15 29:7 30:4 36:17,19 37:11 38:2,15,20 42:13 43:16,21 44:6,16 45:18,20,21 46:16,18 47:1,22 48:10,21 49:1,2,22 50:2 51:2 57:19 58:9 76:9 84:18,19 87:11 89:17 92:17 111:16,22 112:4,22 113:3,6 125:13 126:16 129:8,19 168:11,13 169:10,13 171:11,21 172:1,5,20 173:12,19 175:3 181:3,6,11 182:7 215:17 216:5,14 217:10,11,12 278:12,18 281:9,10

self-treat 80:3

self-treatment 227:4 236:16

send 257:16 263:2,17

sending 258:1

sends 68:14

sense 16:22 165:7 204:2

sensitive 222:11

sensitivity 93:6

sent 37:22 202:15

sentence 130:18 133:2

separate 115:22 132:20 172:15 217:15 281:19

separated 132:6

separately 211:17

sepsis 291:16

series 41:10 291:6

serious 60:11 61:20 62:2 75:4 109:7,8 124:18 131:10 141:7 147:13,16,18,22 148:6 150:20 151:3 153:8 154:3,7,17 155:8,17 156:1 157:10 159:8 177:6 180:9 206:10,17,21 207:15 228:10 229:7 239:13 241:13 264:20 295:10,12,18 296:9,20 301:8

serve 17:1 74:5

served 16:10 17:20 18:19 19:13

service 4:20 17:2,8,10 18:2,13 19:4,8 20:9

services 13:7 15:8 65:16 96:1

session 14:17 190:22 191:4

setting 7:17 30:11 31:7 37:8 39:5 40:11,12 54:5 63:12 66:11,19 135:6,8 148:22 181:15 184:6,22 185:3 186:16 207:5 208:2 210:7 220:4 228:17 235:6 274:5

settings 98:20 100:22 203:9

seven 52:8 59:6 153:3 156:1

Seventy-eight 55:20 154:1

Seventy-three 154:6

several 30:18 42:15 43:21 44:1 46:9 47:17 69:6 72:7 119:6 151:17 176:5 205:16 211:17 222:14 227:12 229:12 240:4

severe 138:2 269:1

severely 228:14

severity 35:18 53:10 139:21 198:1

sexes 105:10

sexual 198:17 280:11,14

shame 70:20 198:20 204:17 248:5,9,12 266:14

share 59:16 60:22 76:3 267:12 289:6

shelf 265:6 308:10

she's 86:3 288:8,11

shift 74:2

shifts 73:21

shoppers 196:2

short 29:16 267:4

shot 97:21

shoulders 204:4

showed 56:20 76:16 107:5 146:16 159:5 181:3 188:2,3 215:18 217:18 234:13

showing 34:15 63:11 226:2

shown 34:8,18 58:18 76:9 110:5 166:12 232:17,18 256:19 270:19 277:7

shows 34:6 81:15 147:7 206:12 272:17 276:21 299:4

sidebaring 184:14

sides 243:3,5 245:3 253:22

sign 82:7,17 124:17 131:9

signals 35:16 111:2 128:7 159:11 180:2

significance 146:17

significant 32:6,18 64:22 67:20 96:18 104:20 107:14,17,18,21 108:3,8,17 127:10 145:6 147:1 152:16 179:22 180:1 205:20 207:4 208:18 211:5 236:22 251:20 252:8 269:18 271:16,21 272:5 283:1

significantly 32:11,14 42:1 66:9 107:8 110:5 129:2 211:9 212:19 227:10 297:14

signs 46:12 60:17 65:14 66:18 194:19

silently 64:2

silhouette 63:4 126:15 176:17

silly 204:12

Silver 1:16

similar 26:11 28:17 32:15 40:7 73:12 93:10 98:22 104:16,21 105:9 107:19 108:5 119:16,17 122:19,20 158:4 161:6,18 175:19 185:3 188:17 193:13 250:20 269:1 284:5 294:14 295:13,22 298:4

similarly 65:11 86:8

Simon 10:3 196:20,22 200:19

simple 95:19 96:3 175:21 267:1

simpler 74:16

simply 26:22 70:21 78:5,21 92:19 201:4

simulation 34:10

simultaneous 56:2

136:3 146:7,10
single-arm 134:22
single-dose 34:10
sit 184:19 196:7 203:7 204:7
site 35:8 45:1 52:10 89:22 90:1 92:18 109:12 147:4,10 148:5 157:5,6 159:12 177:10 218:22
sites 51:1,9 135:1
sitting 204:9 303:13
situ 228:7,15 233:7 237:10 239:7,10 244:3 247:17 277:12
situation 27:10 91:11 113:8 221:2,7 291:1,7 298:17
situational 221:3
situations 41:11 59:19 94:6 180:21 202:3,10 213:14 273:15 289:20
six 38:14 55:1 63:8 112:15 266:18 275:15
sixteen 108:20
size 168:6,12,16
skin 35:17 43:2 97:20 100:3,4,7 109:18 111:9 154:6,8 175:19 199:21
skin-related 154:2
sleep 24:16 68:9 198:17
sleepiness 157:21 186:10
slender 126:15
slide 72:6 81:15 104:8,15 105:3 107:4 109:10 142:19 151:14 154:11 165:9 170:15 215:11 216:10 251:2
slides 210:16 249:16
slightly 26:12 173:15
slowly 66:16 120:4
small 76:12,21 102:16 137:19 208:18 233:2,7 272:8 276:22 291:19 309:17,18
smaller 26:12 203:5 216:6 255:18
smart 268:1
smooth 34:19
sneezing 212:17
soaring 195:20
so-called 226:20
social 9:5 24:14 111:18 260:16 307:8
socially 68:11
society 104:10 151:16 210:15 228:5
solution 195:20 204:18 293:12
solutions 25:10 197:16 205:14 209:11,19
somebody 125:7 133:4 162:21 180:4 187:13 223:15 226:10 253:9 263:2 290:3 302:18 303:11
someday 303:12
somehow 92:8 132:18 133:7 164:12
someone 64:1,19 94:22 130:21 185:5 186:2 296:12 305:20 308:12
somewhat 107:4,19 290:1,3
somewhere 115:1 258:9
somnolence 111:8 154:17 158:2 212:3 250:18 273:5
sooner 67:2
sorry 85:20 154:11 174:8 255:4 278:10
sort 89:5 92:16 100:17 114:8 115:13 118:2 119:1,11 120:18 133:2,5 139:12 143:22 144:11 145:20 152:8,11 153:5 154:13 161:16 166:18 177:5,14,19,20,22 180:11 181:22 182:15 186:12 187:5 217:19 221:6 224:17 253:15 255:19 299:8
sorted 242:9 290:7
sorts 94:5
sought 81:3 150:7,17 194:14 197:15
sounds 178:21 204:12 217:9
sources 156:6
Southern 253:21
space 259:17
span 180:3
Spanish 72:1 95:19,21 96:2,10 258:18
spanned 141:2
spans 19:16
speak 11:10,19 111:20 115:6 151:20 178:1 192:9 235:22 252:17 271:1,2,3 275:13
speaker 160:11 191:8 192:14,20 196:17 201:7 205:2 209:15 210:12
speakers 192:11,15 222:15
speaking 23:15 191:20

special 10:5 12:13 13:4 201:9
specialist's 199:10
specialize 96:4
specific 14:12 38:18,22 78:18 111:2 119:14 178:3 183:7 192:14 206:6 215:2 240:2 242:12 257:7 266:6 267:8,11 278:6 306:2 309:7
specifically 38:14 161:8 165:6 168:6,10 172:9 182:17 235:21 267:14 268:12 279:16 306:6
specified 40:13 53:5
spend 21:22 127:1 259:18
spent 18:2 159:3
SPF36 161:1
spill 24:18
spirit 11:13
spite 162:19 282:1
split 117:8 121:13 124:3
spoke 151:18 152:19 187:1 199:2 202:14
spoken 211:12 270:10
sponsor 6:16 23:7,17 78:12 90:13 112:14 113:21 114:22 115:3 118:8 121:8 123:6 126:3 127:20 130:10 135:10 136:21 138:9 142:3,17 143:4,6,8 144:9 145:17 151:22 155:10 158:13 160:7 175:15 177:2,18 191:11 197:13 201:14 206:1,11 207:16 210:5 228:22 238:4 243:15 245:10
sponsored 193:14
sponsors 152:8
sponsor's 23:3 112:11 142:8 143:16 155:4 191:13 207:6 209:1
spouse 199:7
spouses 13:13
spread 118:6,9,11 120:8,9 122:2,16,20
spreads 118:7
Spring 1:16
squirming 202:7 204:7
SSRIs 231:19
Stacey 4:20 78:7 276:15
Staff 2:15 18:22
Stage 38:2,6,8 46:13,21 47:3 48:1,3,4 49:10
stages 37:20 236:21
staggering 200:7
stake 205:10
Stan 167:17
stand 132:15,21
standard 178:2 184:14 236:4
standing 14:19
standpoint 230:19 231:4,22 232:3
stands 310:11
staring 288:10
start 15:22 16:4 41:8 91:8 103:18 169:12 202:7 219:20 221:18 232:2 235:15 254:11 265:16 274:20 307:4
started 42:5 89:12 202:9,18 203:3,14 227:8 265:18
starting 204:6 285:18
starts 100:3
state 78:17 131:8 251:13 254:21,22 275:8,9,17 311:14
stated 44:11 121:8,9 123:2 139:1,9 206:5 282:5
statement 6:6 12:5,6 22:18 80:5 93:8 94:9 191:9,16,20 209:7
statements 14:20 260:10
states 17:11 60:3 164:7 200:3 209:1 211:4
stating 144:17 278:5
statistical 53:5 108:9
statistically 32:6 107:7,13,16,17,21 108:3,8,17 127:10
statistics 105:3 298:17
status 12:16 41:14 50:19 74:18 110:15 206:1 307:10
stay 25:14 196:8 288:20 290:19
stayed 39:18 46:7 135:21 145:22
staying 78:1 159:21
steady 75:19 251:13
step 77:10 87:13 201:3 204:16
step-by-step 72:2
Stephen 7:9
steps 219:4 308:10
Steve 30:3 36:16,21 172:9
stick 171:14 196:5
sticking 235:9

310:7
sticks 232:19
stigma 197:3 199:15,18 293:7,8,12
stigmatized 194:10
stomach 120:3
stones 43:2 246:15,17
stop 28:20 29:11 37:15 50:18 52:15,17 53:1,18 55:15,17 56:21 57:1,3 63:7 64:16 91:20 100:8 101:13,14,22 102:2,4 127:22 128:1 131:13,18,21 143:3,12,15 144:2,7 187:8 194:18 198:10 217:21 218:6 226:10 236:4,14 237:18 238:19 243:20 285:9
stopped 55:12 56:18 76:17 102:19 145:14 149:19 203:21 218:11 281:16
stopping 57:9 158:20 203:12 283:22
stops 164:21
store 25:10 91:13 265:6
straight 116:20
strain 199:2
straining 199:7
strategies 64:11 70:14 73:5 75:3 142:4,6 158:15 195:1 196:5
strengthening 157:21
stress 43:1 45:17 47:18 128:17 141:5 174:2 194:3 212:11,14,16 228:19
stricter 149:13
strive 48:13
stroke 147:18 148:1 268:20,22
strong 41:21 43:5,8,13 45:18 46:14,17 47:7 49:11 72:20 116:18 183:11 261:13,16 264:10
strongest 42:18
strongly 11:5 29:19 227:3 261:9 262:14 279:11 301:20
struggle 24:22 27:3 198:21 209:22 280:4
struggling 205:19
Stuart 4:12 276:16
stuck 281:11
studied 38:1 55:12,18 77:10 211:22 252:21 307:14
studies 7:8 14:6,7 18:7 21:14,15 30:4 31:20 32:6,9 36:4,18,19,22 37:3,9,10,12 38:2,3,6,15,16,20 39:2,3,5 41:7,9,15 42:2,13,15,16 43:16 46:21 47:1 48:1 49:11,16 61:21 63:1 76:9 83:19 84:17,18 93:9 100:17 105:8,9 111:14 112:15,21 113:1,9,12 118:21 119:16 120:10 123:5 124:1 126:2 129:16 135:2,5,11 137:3 153:17 168:8,14,21 169:9,10,14,17 172:2,19 178:9 181:2,4 182:17 185:12 187:18 193:13 207:4 215:15,17 216:5 225:14,22 226:14,15 230:14 231:1 249:12 250:17 265:4,5 280:5,22 284:21 285:1 286:8 291:18 292:22 306:21 309:16,17,18,21
studying 184:13 246:11
stuff 256:21 270:17
subanalyses 218:3
subgroup 144:13 146:13
subgroups 146:14
subject 12:14 30:19 39:22 42:2 44:5 45:7,16 52:22 62:17 103:12 138:8,14 147:14 152:2 154:9 186:21 187:1,3,7 190:17 258:15
subjective 114:3 160:21
subjects 39:16 40:14 41:5 44:19,20 45:2,14 47:19 48:21 51:8,13,19 52:4,15 54:11,18,20 55:15,16,18,22 56:4 57:2,9,14 58:1 59:1 61:10 62:7,20 63:9 82:15 90:16 93:10,11 101:12,21 102:6,7 108:21 109:6 134:13 135:12,22 137:21 138:7,11,19,21 139:3,7,16,21 140:3,12,15,19 141:1,4,5,8,12 143:17 144:1,8,10 145:1,7 146:1,3,19 147:3,5

148:8,13,18,22 149:8 150:9,13,17 151:5,8,14,16,22 152:5,9,10 153:4 154:1,18 155:8 158:21 160:8 175:4,5 186:20 187:5,11 215:5,6 251:11 272:10 283:17

subject's 40:2 45:11

Subjects 51:20,21 52:1,6 148:16

submission 121:9,10 130:20 131:21 133:13 156:22 206:6

submitted 13:20 20:20 38:12 112:14 137:7 206:11 210:17

suboptimal 27:9 129:17

subsequent 42:15

subsequently 121:4 139:8

subset 76:21 216:6

subsets 169:19,22

substantial 24:4,10 47:4

success 40:13 41:4 74:5 114:7,9 118:19

successful 52:18 107:20 136:21

succumbed 147:15

sudden 195:4

213:10 292:15

suffer 68:20 75:8 118:16

sufferer 32:19,21 197:20

sufferers 38:17 124:3,4,8,9,10

suffering 116:13 204:19

sufficient 281:1

sufficiently 251:10

suggest 91:12 190:15 250:5 256:6 257:1

suggesting 255:17

suggestion 79:10 97:8

suggests 33:9 79:15 243:10

suit 73:9

suited 30:2 75:12

summarize 46:13 128:19 210:16 293:21 301:3

summary 8:8 14:4 36:3 49:10 74:12 112:8,9 214:1

Sunshine 11:14

superficially 279:20

supplementary 255:19 262:2

supplemented 69:17

supply 196:4

support 8:2 13:20 14:9 21:17,19 29:20 30:14 69:8,12 73:4,6,16 84:12 193:16 220:1 274:3 281:9 300:19

supported 104:6 106:16 108:20 152:19 193:4 205:7

supporting 36:12 151:5

supportive 300:18

supports 259:12 304:17

supposed 126:22 169:14 276:2 281:14 296:1 302:1 303:10

Supposing 283:10

suppositions 249:4

sure 80:19 81:20 84:4 93:7 95:5 164:4 167:2 222:19 223:16 230:5 233:15,16 234:12 235:22 239:3 246:10,17 258:12 265:12 270:7 272:20 276:8 283:4 290:8 295:15 306:10 309:14

surface 232:1

surgery 4:9 99:10 210:22 287:11

surmise 139:20

surrounding 197:3 199:18

surveillance 36:10

survey 117:22 166:12 193:12 195:9 270:4,19

surveyed 270:10

surveys 266:16

susceptible 241:9

suspect 278:4

switch 1:10 6:19 7:14 8:5 13:21 20:8,17,21 21:6,17 26:15 36:14 106:15 110:14 196:21

switching 210:8

swung 277:14,18

symptom 32:20 33:10 43:9 52:16,22 53:3,10,17 54:21 55:1 60:1 62:5 67:17 76:1 79:22 80:13 97:2 101:21 102:1 104:10,11 117:10 132:12 140:19 141:13 150:2 178:4 198:1 206:6 235:7 236:6 296:5,7 306:14

symptomatic 65:9

symptoms 25:19 26:1,7,11 27:2,11,15 28:3,17,21 29:8,12,14 32:18 36:14 39:18 42:4 43:5 44:21 46:12,16 47:6,20,21 48:7 51:7,12 54:2,13 55:12,18

56:4,8,12,17 57:3 59:4,7,11,16 60:4,11,22 61:15,16,18,21 62:2,8,20 63:6 64:12,14,17 65:8,13 66:10,20,22 67:10,22 70:6 71:15 76:3,4 83:3 91:21 101:13 104:16,21 106:12 116:15 117:13,16 123:9,20 124:7 125:8,14 130:5 131:2,5,9,12 132:2,5,21 133:3,7 134:11 135:13,21 138:1,4 139:18,22 140:13,16,20,21 143:2,11,13,14 144:2,6 145:13,22 148:13,19 149:7,9,11,14,17,18 150:3,5,6,9,15,16,21 151:4 152:17,18,21 158:18 159:9 161:6 162:1 165:12 166:2 167:11 173:3 180:9,10 181:18 187:15 190:5,6 194:2,12 195:11,19 196:13 198:14 200:18 205:20 206:9,12,14 207:10 209:22 210:4 211:11 212:8 213:2,20 220:16 221:19 235:18,22 236:2,3 237:14 238:10 239:8 241:4 244:5,8,13,22 246:14,16 247:11 253:9 257:3 268:11 269:13,15 283:17,22 284:11,15 285:22 288:13 292:14,17,18 294:14 295:1,13 296:1,5,11 298:12,13,19

syncope 155:19

syndrome 79:21 187:14,16 220:15,17 221:15 253:11 257:10 294:22

syndromes 220:20

synergistically 73:11

synthesize 243:4

syrup 106:1

system 2:17 14:1,5,10 19:1 20:18 21:20 24:1 29:3 34:18 75:12 108:12 135:16 156:7 203:20 220:3 254:10 273:3 274:4,18

systemic 34:22 99:16 272:13

Systems 17:22

T

table 6:1 7:1 8:1 9:1 10:1 78:5 142:20 146:11 149:9 156:20 204:9 219:18 237:12 310:9

tables 40:21

tablets 106:1

tabulated 39:22

tackle 183:4

tactics 25:2

taking 71:1 158:4 179:5 207:21,22 224:3,8 227:8 231:11,20 233:9 237:15,19 241:10 246:22 247:5 257:21 259:10 279:19 287:13 308:9,12,13

talk 20:16 52:17 53:1,18 60:13 61:9 82:4 102:8 103:2,11 112:11 114:18 125:4 134:16 139:13 166:5 175:11 188:20 209:9 247:11 250:3 265:19 266:19 291:13,14 297:15 300:16

talked 54:11 88:1,2 89:5 95:8 116:8 126:18 132:11 149:13 158:21 171:19 172:2 184:5 207:6 226:8 265:8 267:21 273:17 287:7 295:16

talking 53:11 102:15 134:18 159:3 165:3 167:5 169:3 212:11 240:21 242:7 260:20 279:16,17 291:2 293:18 307:5

tangible 68:10

target 28:11 41:4 76:18 113:17,20 114:12 115:1 117:11,14,19 121:14 171:1,6

targeted 27:21 38:18 42:15 46:19,22 47:3,22 49:12 51:12 61:3 136:17 278:16

targeting 183:20

targets 40:13 47:11

task 214:17

tasks 272:11

tax-supported 303:16

TDS 135:14,15 136:3 154:10 283:19

TDSs 144:22 156:14

teacher 16:16

teaching 77:16

teaching/ speaking/

writing 13:17
team 22:1
technical 21:9
techniques 256:16,17 302:11,12,15
telephone 51:13 260:15
temporary 4:2 12:12,22 13:10 14:16,19 15:9
tends 100:4
tension 203:7,14
tent 176:12
tent-like 126:17
term 16:19 169:6 230:2,10 259:5 267:13 292:1
terminating 226:5
terming 223:18
terms 16:7 82:3 85:15 107:20 115:5 155:11 160:19 161:3 177:16 178:3,4 234:15 236:5,22 253:5,8,9 269:11 295:2 296:15 299:16 300:20
terrible 178:21 236:7
terribly 243:2
test 41:15 45:6 50:14 91:9,15 104:12 117:4 251:15
tested 47:2,6 61:7,10 75:11 94:9 116:13 118:5,13 119:22 124:16 130:3 272:11
testify 201:11
testimony 13:16
testing 41:20,22 129:22 137:9 307:10
tests 251:14,18
Texas 3:9 17:22
text 43:9,13 71:22 96:10
thank 15:19,20 16:2 17:13,15 18:15,16 20:11 21:8 22:6,10,11,17 23:19 31:3 36:20 63:13 69:8,9 74:13 77:18,21 78:9 79:1 80:17 81:11 82:12 83:7,16 86:5,6 88:14 89:14 90:11,13 91:6 93:15,16 94:18,20 96:11 101:6 103:3,13 111:15 159:19,20 164:22 165:1 167:16 175:8,10 178:13,15 179:8 182:9 185:8 190:12 192:10 196:15,16 201:5,6,10 204:21 205:1 210:10,11 214:9,10 215:12 218:15 219:11 222:3 224:16 229:12 232:6,8 233:21 234:21 242:21 245:19 247:14 248:16 258:22 261:11 263:18 269:3 270:20 273:18 276:17 281:5,21 283:7 284:17 289:16 290:12 291:9 292:5 293:20 295:5 310:5,11
Thanks 111:17 160:17
that's 37:18 38:12 40:6 79:18 80:9 85:6 87:2,21 88:21 89:5 90:21 91:17 92:12 94:12,16 97:7,8 98:16 99:7 100:20 112:22 117:2 125:5 126:11 127:11 128:18 129:3 130:2 135:16 137:2 146:20 151:6,15 152:22 162:12 166:9 170:15 171:2,4,5 172:3 173:6,22 181:21 182:7 184:3 189:10,22 207:5,15,16,17 208:4 211:7 212:14 217:1,5,17 219:10 225:8 228:1 231:13 232:15 234:4 235:5,9 239:18 241:2 244:14 245:11,14 247:22 249:5,21 250:9 252:13 253:19 255:20 257:18 258:2,17 259:5,20 262:12 264:14 268:10 271:12 281:17 282:5 285:15,17,21 286:1,9 287:18 288:15 289:14,18 291:7 295:14 297:10,19 299:8,22 300:4 302:13 303:19 304:18 305:6 306:5 307:19
the-counter 222:2 225:7
thee 178:18
themes 302:5
themselves 15:14 27:13 84:7 102:5 126:4 164:11 185:16 189:1 196:11 203:13 204:10 212:9 218:21 227:8 253:18 287:19 293:2
theoretical 77:1
therapeutic 34:14 264:2
therapies 24:21 209:12 213:7 238:21 268:8
therapy 68:7 105:19 195:2 208:21,22 211:20 227:18 267:22 290:4

thereafter 311:5
therefore 32:19 66:11 114:13 192:8 280:1
they'll 225:17,18 238:21 286:22
they're 26:21 99:22 101:1 113:5 114:2,6,8 116:4 124:12,13 134:9 160:11 165:18 166:16 190:10,11 195:10,17 212:5 217:4 224:3,7 236:10 238:19 241:9 246:13,16 257:22 265:14 267:20 268:2 280:14,15 281:12 284:15 287:7,14,15 289:9
they've 246:1 253:10 286:15 305:5
third 50:4,12 65:19 126:3 170:10 182:11 226:11 227:17 250:16 290:20
third-party 300:20
thirds 170:9 193:22
thirst 60:16 121:12 122:10 149:3 180:11
Thirteen 147:21
thirty-one 52:8
thoughts 167:14 183:1 226:22 229:13 230:1 233:18 235:2 243:7 245:18
thousand 52:8
thousands 207:20
threshold 114:20 117:11,14,19 118:19 120:22 121:14 122:1 143:5 145:17,19 237:7 282:22 295:4
thresholds 113:17,20 114:2,7,12 115:1 128:21
throughout 38:4 301:5
throwing 195:7
thus 11:9 194:1
tier 290:20,21
ties 119:2
timeframe 26:9 56:15 67:4
tiredness 60:17 121:13 123:1,4 130:4 149:4
tireless 197:8
title 134:20
today 19:7 20:6,15 21:13 22:8 26:17 29:17 30:19 38:4,13,19 40:22 42:6 56:11 57:19 63:1 64:10 68:12 69:16 70:15 76:5 94:11 97:10 98:17 99:3 109:12 110:2 112:3 121:5 125:20 133:21 162:19 167:15 192:5 197:12 201:11 207:2 219:17,21 229:2 243:15 249:5 265:8 301:13 310:3
today's 11:4,6 12:8,20 13:9,19 17:1 195:20
toilet 25:2
toileting 195:2
tolerability 34:22 75:17 109:18 208:19
tolerated 28:5
toll 198:3
tomorrow's 195:20 196:9
tool 27:20
tools 73:7
topic 11:16 12:2 197:2 239:19 260:10 310:7
topics 11:3 19:18 56:10 57:18 134:8 148:11 153:19 192:4
torn 240:11
total 33:5 101:12 109:7 139:1 140:22 142:10,14 145:13,15 146:2,5,6,8 149:15 158:16 170:7
totality 29:19 60:20 73:7 220:1 252:7 274:2
totally 90:15 264:19
Totman 3:15 15:2,6,7 22:13,15 306:8,18 308:2
Totman's 15:4
touch 127:17
touched 294:18
tough 305:8
toward 38:18
towards 74:7 136:17
track 213:20
tract 53:15 59:17 81:3 104:18 138:3 148:6 151:3 162:1 211:14 212:3 268:12
trade 14:1
traditional 114:6
training 206:16 221:6 256:21 266:3 279:17
TRANSCRIBER 312:1
transcript 311:6 312:4
transdermal 14:1,5,10 20:18 21:20 24:1 26:4 29:3 33:12,16,21 34:3,6,18 36:6 75:11 105:21,22 108:12 135:15 214:1 220:3 227:9 273:3

274:4 307:19
translate 95:19 96:2
translated 95:21
translates 193:19
translation 96:1
translations 96:5
transparency 14:18 22:21 191:4
transparent 22:20 191:2
travel 23:6 30:22 191:13 193:8 196:7 198:14 201:13
treat 20:22 25:21 54:4 63:20 64:20 93:1 208:6 235:10,18 236:2,6,11 257:3 292:9 293:5 295:21 296:10
treatable 71:4 73:22 86:16
treated 54:2 65:1 192:7 194:22 200:10 284:7 291:15
treating 26:10 42:5 210:4 231:1 235:7,13 296:1 298:15
treatment 24:2 25:2,17,22 26:6 27:17 31:21 32:2,20 33:3 36:14 56:5 62:17 64:3,22 66:21,22 67:5 68:2,8,14,22 71:8 73:6 74:2 75:14 77:16 83:10,18 86:9,14,17 99:13 104:4 105:17 106:11 194:14,16 200:20 201:2 206:20 209:14,21 211:16 221:20 222:10 223:10 228:11,21 231:3 238:22 247:10 248:14 251:12 257:4 277:21 294:2 296:5 297:6 302:13 303:6
treatments 68:18 74:22 200:9 213:13 222:8 223:12 240:19 247:9 251:5
treats 14:2 21:2
tremendous 64:4 198:3
trend 32:15 65:17
trends 35:21 36:11 159:10 178:11 180:1
trial 57:7 106:20,21 107:5,19,20 108:5,6,16 110:8,9 114:7 134:21,22 135:15 136:13 138:17 143:21 145:5 146:21 148:4,17,21 149:16,18 150:13,18 152:2 153:14,20 156:17,19 158:11 159:11 160:8 175:11,20,22 177:1 180:16 182:5 187:12 215:6 222:18 238:17 251:4 272:9
trials 31:17 32:1 33:1,5 35:3,6 36:2 40:7 75:16 106:17 107:1 108:14,18,20,21 109:5,6,11 110:4 155:14 162:3 212:6
tried 79:12 179:20 203:12 213:15 218:9 249:15 277:21 302:12
trivial 239:12
trouble 286:21
troughs 34:11,16,19
true 40:19 180:11 187:6 209:4,7 211:7 239:10 311:6
truly 27:17 176:4 260:5
trust 203:20 275:12
try 29:16 57:12 73:5 136:19 143:22 153:14 166:20 167:11 168:6 171:16 183:3 185:18 189:12 204:18 238:20 243:4 279:5 280:5 287:15 288:1 289:17 290:22 294:7 305:6,7
trying 60:5 114:20 117:17 152:12 165:7 167:5,8 171:9 175:12,17,21 190:3 214:6 218:17 235:16 273:12 279:4 286:16 295:9 300:7
tumor 236:9,10 237:5 240:8 244:14
tumors 161:5,22 269:2,14
turkey 203:21
turn 22:14 74:11 98:9 111:13 133:15 188:14 192:12 214:16
turned 256:10
Turning 43:16
TV 90:20
Twenty 75:8 271:6,8
Twenty-five 88:1
twice 195:12 212:18
two-thirds 170:3,11
TX 3:11
type 82:11 94:9,13 97:8 98:22 146:5 162:9 251:14

258:10 288:7

types 18:7 37:9 39:9,18 41:7 94:15 99:2 137:3 200:16 215:14 230:7 252:20 284:21

typewriting 311:5

typical 113:13 135:1,11 211:13 213:6

typically 66:17 114:12 116:17 118:1 120:9 228:8 308:13

U

U.S 17:7 65:15 75:9 156:21 196:22

U.S.C 12:19 13:3,14

Uh 288:10

Uh-huh 90:8

ultimate 309:20

ultimately 27:6 91:19 300:1

umbrella 177:20 178:5

unable 120:1 206:17

unacceptable 29:15 45:22 77:3

unanimity 302:6

unbranded 72:8,15

uncommon 228:8 239:7 240:4,12 241:14

uncontrolled 41:9 110:19

underlying 65:10 114:4 130:12,19 131:1 209:6

underneath 146:11

underrecognized 197:17,19

underreported 197:20

underscored 36:5

underserved 18:4 260:14

understand 23:1 26:16 34:2 37:4,6,11 39:4,10 40:2 46:3 57:5 76:10 80:21 81:5 95:5 97:2 113:5 115:19 119:1 145:8 150:14 168:7 169:15 171:10 172:5 181:7 191:6 202:22 216:7 221:12 227:21 229:2,4 246:19 260:7 264:7 267:16 293:8 299:10 303:17,20,21 307:4

understanding 41:13 43:5 69:20 97:16 121:2 206:4 305:2

understood 28:5 29:5 41:19 47:10,19 48:13 50:1 61:5,14 95:22 132:13 169:8 171:19 216:14 229:3

undertreated 197:21

underwear 202:8

undetected 283:3

undiagnosed 43:6 46:12,15 49:16 61:5,15

undue 167:11

unemployment 200:7

unexplained 61:22

Unfortunately 25:14 86:11

UNIDENTIFIED 160:11

unintended 30:12 68:4 224:22 308:22

unique 19:22 26:3 113:15

unit 199:8

United 17:10 200:3 211:4

University 2:10,15,20 3:9 4:5,9,13,18 10:9 17:22 18:21 19:15 99:9 265:22

unknown 244:14 280:20

unknowns 245:5 280:21

unless 246:13

Unlike 64:9

unlikely 65:12,22 66:12 67:13 69:1 79:5 150:12 154:10 206:17

unnecessarily 208:11

unproven 277:11

unpunished 180:22

unreadable 256:8

unrelated 155:19

unrestricted 193:9

unsure 254:14 275:1

untreated 199:20 208:12

unusual 36:11 120:10 228:12

unusually 129:7

unwanted 194:18

update 158:1

updated 38:5

upon 23:8 80:7 294:18

upper 40:20 55:8 145:16,18 158:13 241:16 242:2 249:20

upward 129:12

urge 24:6 26:8 106:12 116:18,20 147:11 193:21 203:10 210:7 212:12 241:16

urged 301:21

urgency 24:5 26:8 27:15 44:21

66:10 68:1 105:11 106:13 116:18 153:1 193:22 194:2 203:14 211:12,13 228:9,13 239:9

urges 195:4

urinalysis 45:6 137:9,13 150:22 227:16 228:16 285:21 289:21 293:3

urinary 4:10 24:5,6 27:15,22 32:10,13 39:13 53:15 58:5,7 59:17,22 60:22 66:21 68:19 71:7,15 75:7 77:17 81:3 88:4,10 104:18 105:11 106:12,18 107:2 108:4,10,15 110:18 111:4 116:1,15,17 119:21 120:1,21 121:6 131:12,15,17,22 138:2 140:11 148:6 149:5,7 151:3 152:7,11,12 153:1,3 162:1 180:12 186:19 187:7,11 194:2,4 198:1 205:13 211:12,14 212:3 234:3,9 268:11 286:21

urinate 96:21 116:16,18,20 119:5 121:18 122:11 124:17,22 130:17

urinating 60:9 80:7

urination 44:21 49:6 62:1 80:14 121:11 125:3 205:13

urine 42:7 52:6 60:10 64:15 83:1 123:10,11,17 138:4,5 148:15,20 188:20 193:22 194:3,7 213:11 247:21

Urogynecologic 210:14

urogynecologist 63:15

Urogynecology 10:9

Urologic 5:19 8:18 104:1 228:1

Urological 105:4 209:21

urologist 78:7 175:21 202:16 227:14,15 247:17,19 265:22 288:7

urologists 237:11 241:12 244:4

Urology 4:3,8,12,20 99:10 200:2 228:12 266:1,5

urosepsis 65:4,7 148:7

usage 70:4

useful 110:1 170:18 260:5

user 62:15 135:14 152:2 153:9 180:16

users 52:12 54:7,10 55:3,5,13 56:14,17,21,22 57:8 58:20 61:11 76:10 77:2 81:17 83:14 85:19 87:16 88:7 89:10 101:19 134:13 135:12,19 136:11 137:7,13 139:2,3 140:3 141:15 142:10,12,14 143:2,3,11,12 144:6,14,17,20 145:13,15,21 146:3,6,8,9,10,22 147:8,13,20 149:11,15,16,17 150:1,4,20 151:3,18 152:16,20 154:15 155:7,22 158:17 159:5 170:14 188:8 189:20 217:20 291:20,21

user's 39:7

usual 116:16 118:11 119:5 122:11 286:9

usually 27:7 40:14 67:18 68:1 197:22 198:3 290:20

uterus 213:4

UTI 43:6,9 46:16 47:7 54:2 59:5,7,9 60:7,11 61:15,17,18 64:9,14,21 65:4 83:3 102:6 116:2 123:6,13,19 124:6,18 130:6 131:2,7,9 133:10 139:18 140:16 141:6 147:6,10,17 148:1,9,14 149:9,11,13,15,18,21 150:1,5,6,12,16 151:6,8,10 159:9 161:18 180:9

UTI-like 65:8

utilizing 267:15

UTIs 54:3 59:6 61:16 65:9 150:18

V

VA 3:16 4:14,21 18:22

vacation 198:14

vaginal 189:11 213:12 235:19

vague 152:12

validated 33:1 70:10

validity 178:17

valuable 181:22

value 19:3 40:19 196:1

values 98:15
Vanderbilt 265:22
variability 40:12 41:2
varied 39:19,20
varies 301:10
variety 11:4 155:14 156:6 192:4 232:13 251:13 309:4
various 132:16 266:18 279:16 301:22 310:6
vast 16:21 19:17 79:11 85:4 177:18
verified 52:12 139:2 145:13 158:17
version 38:12 291:3
versus 41:3 47:12 57:16 85:15 93:8 96:10 114:18 129:5 162:18 163:16 172:5 232:14 264:20
VESIcare 289:8
vesicles 109:14
Veterans 2:16
via 44:20
Vice 249:17
video 72:2
view 166:18 255:21 281:18 294:5
viewed 26:16 220:6 274:7
viewpoint 222:6
views 11:8
vigor 261:20
violation 226:5,6,11
violations 225:22 226:20
viral 147:15
Virginia 4:13
virtual 302:6
Visco 10:8 210:13
vision 35:11 109:16 157:15,22 186:11
visit 27:4 51:15 110:7,9,10 184:9 193:5
visits 62:19 66:18 195:7
visual 212:3 251:17
vitally 252:13
voices 205:6
void 32:10 107:3,18 108:16
voided 213:21
voiding 25:5 188:21 211:15 213:11,21
volume 32:10 107:3,18 108:10,17 213:21
vote 219:21,22 254:2,5,7,11,13,14,15,16,17,18,19,22 255:7 256:9 261:3,6,21 262:4 270:3 273:22 274:9,19,21,22 275:1,2,3,4,5,8,13,15 277:14 281:7
voted 254:21 255:1 256:11 275:7,9,18,20,22 276:1,9 277:13,17 281:7 282:2
voting 2:8 4:2 12:12 13:1,10 14:19 15:3,10 254:10 274:18 275:14,17

W

wait 234:2 237:6
waited 70:18
waiting 197:21 198:2 257:22
waivers 13:4 14:16
Walid 2:12 18:19 275:20 295:6
walked 233:19
walks 198:9
wall 33:17
warned 94:3,5 162:6 218:1
warning 28:18 49:14 60:2,7 80:6,11 124:16 127:12 128:5 130:12 157:22 158:2 161:16 212:22 213:5 286:11
warnings 42:19 110:22 122:5,19 149:1 158:7 159:6 161:3 186:10 220:18
warns 29:9 59:22 60:8
wasn't 83:4 95:13 121:15 131:20 187:10 217:11 218:6 272:20 287:22 307:11
water 97:3
Watson 23:22 193:15 249:18 250:11,21 251:3
ways 253:3 309:4
weakened 194:4
wear 97:20 287:10 288:6
wearing 55:21 202:10
weave 303:21
Web 90:20
website 71:22 72:19 84:1 193:5 258:19
websites 200:15
week 107:11,12,13 110:9,10 136:11 138:15 142:13 144:9 146:2 238:8,9,14 251:12 257:22 288:20 292:17
weekly 32:3,7 106:21 212:18
weeks 28:22 32:2 52:1,4 56:12,18,22

135:21 137:5 142:12 144:8,14 146:1 181:16,17 226:10 238:7,11 239:11 279:6 282:4 283:19 285:9,14 287:4,12,13 288:2 290:2 292:10,11

weigh 162:17 279:7

weight 61:22 62:5 73:13 140:17 149:6 195:3,16 255:10

Weill 3:5 16:14

welcome 22:1 74:18 160:1 179:18 190:21 220:8 254:6 267:10 281:11 282:14 284:2 294:15

we'll 22:4 78:19 102:14 160:3 168:2 190:18 192:15 270:8 276:6 278:8 280:21 282:7 283:12

well-being 24:15

well-known 157:14

well-made 257:14

wellness 195:22

we're 20:15,16 21:8,18 26:6 79:10 88:22 97:9 98:17 103:4 114:20 143:13 157:20 165:16 167:14 183:21 190:3 193:4 207:17 215:19 220:21 223:1,2,6,18 232:10 233:1 236:17 240:12,14,21 241:14 242:3 244:15 248:3 255:22 258:12 263:22 267:6 273:12 278:5,6,7 279:15,17 285:1 288:10 290:5 298:21 299:2 300:7 306:1 309:9

wet 205:16

wetting 116:19

we've 22:13 64:10 74:13 76:20 104:16 106:10 116:8 121:4 124:7 125:12,20 127:14 129:7 165:22 182:17 199:9 210:16 211:11 216:12 225:4 226:8 236:11,19,20 237:4,17 242:5,7 249:5,15 250:12 255:5 262:4 266:16 270:11,17 280:10 292:22 304:7,13,15

whatever 97:14 139:4 225:18 253:7 256:11 259:7 260:15 263:4 264:3,11 269:21 279:12 289:9 299:5 304:5

whereas 106:21 107:11 108:1 147:5 199:16

Whereupon 310:12

wherever 202:2

whether 14:8 21:19 39:3,7 40:3 58:3 59:12 81:20 85:3 90:16 92:7 162:5 163:18 166:8 169:15 176:4 179:3,4,7 183:22 185:14 188:10 206:13 213:19 220:22 222:18 224:12,21 225:6 226:21 230:15,18 231:13,15,21 237:13 241:19,21 242:1,11,12,16 244:5 245:4,6,12 246:17 252:14 253:9,10 260:14 269:21,22 281:3,19 285:15 286:8,17 290:19 297:10 299:12 300:2,3 301:14 308:15,21 309:7,20

White 1:14,15

whoever 78:17 160:18

whole 96:22 130:1 181:8 232:13 240:19

whom 311:2

whose 16:6 193:1 199:10

wide 49:4 155:14 173:4

widespread 197:17

willing 80:8 165:16 167:20 204:18 260:6 292:14 303:1 307:14

willingness 74:2

window 150:14 239:2

wisdom 16:20

wish 226:16 254:15 256:13 259:2 275:1

wishes 254:4

witness 13:16

woman 27:6 39:13 44:11 46:5 126:15,21 171:12 173:20 176:12,16 199:5 201:9 292:4

woman's 24:13 74:15 196:6 198:11 205:17

women 1:9 9:2,8 14:2,3 20:18 21:3 24:8,9,12,22 25:4,9,10,14,16 26:7,17,19 27:2,10,13,16 28:1,3,6,12,15

29:8,13,16,21 30:7 46:6 47:2,4 48:8,10 49:3,14,18 50:22 51:3,6,12 52:11 53:14,16,17,21 54:1 55:12 57:6,11 58:5,13,15 59:4,6,10,19,22 60:4,8 61:3,5,7,18 63:6,20 64:6,10,13,18,20 65:13,18,20 66:4,7,22 67:14,18 68:15,20,21 69:12,21 70:11,14 71:6,7,11,15,19 72:8,15 73:5,8 74:19 75:1,8 76:15 77:4,6,13,15,17 79:3,11 80:13 82:13,21 84:5,7 85:2 86:12,18 87:2,3,22 88:5,10,13,19,21 89:6,8,9,10 92:18 93:7 99:17,20 100:7,14 101:22 102:3 105:7,8,12 111:15 116:3,4 124:11 125:14 126:22 129:8 133:17 136:17,18,19 142:1 172:16 173:5,10 174:14 187:19 189:19 190:1,7 193:12,18 194:5,6 196:10,14 197:21 198:4,22 200:11 201:2 204:15 205:6,14,19 206:2,19,21 207:7,18,21 208:8,10,11 209:4,8,13,22 210:2 211:4,7 212:22 220:12,21 221:11,17 222:11 225:4 230:8 234:1,14 240:13,16,17,22 241:3,19 246:2 248:5 266:9,13,15,16 267:7,18 268:1 269:6 270:10 271:1,2,3,8 278:16 279:5 286:19 291:13,14,19,20, 22 292:20 293:1,17 297:7,18,20 298:18

women's 10:7 24:19 59:11 64:4 68:6 74:6 205:4,11

wonder 215:8 231:12 241:16 281:3

wonderful 103:5

wondering 83:8 94:21 95:20 165:9,13

Wood 4:19

wording 129:13 131:3

word-of 270:18

wore 55:20

work 22:7 24:19 73:11 95:11 110:3 188:19 203:13 208:22 213:15 225:10 280:11 283:20 286:17 287:8,18 289:17 292:11 305:4,6

worked 54:6 202:3 287:4

worker 200:6

working 95:10 98:5 202:18 218:6 231:11 238:12 251:17 290:19

works 290:16

workup 45:5 190:9 285:18

world 98:13 176:2 216:16 226:16,18 256:1 259:8 270:19 289:17,22

worldwide 35:13 156:11 157:1

worried 227:19 285:4,7

worrisome 234:15 308:17

worry 227:17 244:1

worse 194:19 195:11 202:9 226:21 272:1

worsen 28:21

worsened 39:18 52:18 55:18 57:14 102:8 135:21 146:1 154:22 283:18

worsening 53:1,3 54:21,22 57:2 101:21 102:2 103:1 135:13 143:2,11 153:4 195:16

worth 94:12 126:18 231:6

worthwhile 79:10 80:15

wrestling 245:8

write 303:7

writing 162:5

written 191:9 210:16 261:10

wrong 126:7 178:20,21 229:18

Y

yeast 235:19

yellow 28:19 37:21 60:3,7

yet 42:6 96:7 176:21 206:11 223:2 256:11 303:1

York 3:6

you'll 17:6 97:3 142:18

young 199:1,5 201:21 241:15

younger 129:3

198:22 224:2
241:19 307:1,4

yours 80:7 183:4,5

yourself 78:6
116:19 205:16

you've 76:5 97:21
112:5 170:5,13
221:14 249:8
270:15 295:16

Z

zero 57:16