

FOOD AND DRUG ADMINISTRATION

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

WITH REPRESENTATION FROM THE REPRODUCTIVE HEALTH  
DRUGS AND ANTI-INFECTIVE DRUGS ADVISORY COMMITTEES

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MEETING

+ + + + +

Friday, September 11, 1998

+ + + + +

The meeting was held in the Versailles 111  
of the Holiday Inn at 8120 Wisconsin Avenue, Bethesda,  
Maryland, Doctor Eric P. Brass, Acting Chair,  
presiding.

ORIGINAL

PRESENT :NDAC MEMBERS:

ERIC P. BRASS, M. D., Ph. D, Acting Chair

GEORGE A. BLEWITT, M.D.

KATHLEEN HAMILTON

MARY A. KODA-KIMBLE, Pharm.D

PATRICIA A. McGRATH, Ph.D.

RHDAC MEMBERS:

BONNIE J. DATTEL, M.D.

VIVIAN LEWIS, M.D.

DEBORAH L. NARRIGAN, MSN, CNM

AIDAC MEMBERS:

ROSELYN RICE, M.D.

DAVID SOPER, M.D.

OTHERS PRESENT:

RALPH B. D'AGOSTINO, Ph.D.

ROBERT DeLAP

EDWIN E. GILLIAM, MSN, Ph.D., CFNP

MARK GOLDBERGER

SOLOMON SOBEL, M.D., FDA

CAGE S. JOHNSON, M.D.

BRAD LEISSA, M.D.

RICHARD A. NEILL, M.D.

HARI CHERYL SACHS, M.D., FAAP

BETH L. SLINGLUFF, ANP

RHONDA STOVER, R.Ph.

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Charge to the Committee, **LINDA** M. KATZ, M.D., 126  
M.P.H., Deputy Director, Division of OTC Drug  
Products

Open Committee Discussion and Response to  
Questions

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

8:51 a.m.

ACTING CHAIR BRASS: Welcome to this morning's meeting of the Nonprescription Drugs Advisory Committee to discuss OTC Vaginal Antifungal Class Labeling.

I'd like to begin by apologizing for the delay. There was **some** confusion on the room set-up this morning, and I appreciate the efforts of all those who got us back on line promptly.

We're joined this morning by a number of representatives and consultants. I would like to begin by going around the room and asking everybody to introduce themselves, starting with Doctor **Neill**.

DOCTOR NEILL: My name is Richard **Neill**. I'm in the Department of Family Practice at the University of Pennsylvania.

DOCTOR GILLIAM: My name is Eddie **Gilliam**, I'm a Family Nurse practitioner with University Physicians in Tucson, Arizona.

ACTING CHAIR BRASS: And now I will remind everyone to please speak with the microphone in your mouth. Thank you.

DOCTOR SACHS: I'm **Hari Sachs**, and I'm a pediatrician here in Rockville.

1 DOCTOR 13' AGOSTINO: Ralph D'Agostino,  
2 Biostatistician with Boston University.

3 ?4s. SLINGLUFF: Beth Slingluff, Carondelet  
4 Occupational Health Services in Tucson, Arizona.

5 DOCTOR JOHNSON : Cage Johnson,  
6 Hematologist, Los Angeles.

7 DOCTOR RICE: Roselyn Rice, Senior Health  
8 Care Consultant, Preventive Medicine and Infectious  
9 Diseases.

10 DOCTOR DATTEL: Bonnie Dattel, Maternal  
11 Fetal Medicine, Eastern Virginia Medical School.

12 DOCTOR LEWIS: Vivian Lewis, Obstetrics and  
13 Gynecology, University of Rochester.

14 MS. NARRIGAN: Deborah Narrigan, Nurse  
15 Midwife, Nashville.

16 MS. KODA-KIMBLE: Mary Ann Koda-Kimble,  
17 Professor of Clinical Pharmacy, University of  
18 California at San Francisco.

19 EXECUTIVE SECRETARY STOVER: Rhonda Stover,  
20 FDA .

21 ACTING CHAIR BRASS: I'm Eric Brass with  
22 the Department of Medicine at Harbor-UCLA Medical  
23 Center.

24 DOCTOR McGRATH : Patricia McGrath,  
25 University of Western Ontario.

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1 Ms. HAMILTON: Kathleen Hamilton, Consumer  
2 Rep, Policy Advisor to California's Lieutenant  
3 Governor.

4 DOCTOR BLEWITT: George **Blewitt**, Industry  
5 Liaison Representative to Nonprescription Drug  
6 Advisory Committee.

7 DOCTOR **CHIN**: Ling Chin, FDA.

8 DOCTOR DAVIS: Dan Davis, Medical Officer  
9 with the FDA.

10 DOCTOR WINFIELD: Joe Winfield, Medical  
11 Officer with the FDA.

12 MR. GOLDBERGER: Mark **Goldberger**, Division  
13 of Special Pathogens, **FDA**.

14 DOCTOR KATZ: Linda Katz, Division of Over  
15 the Counter Drug Products, FDA.

16 MR. DeLAP: Bob DeLap, Office of Drug  
17 Evaluation V, FDA.

18 ACTING CHAIR BRASS : Thank you.

19 I'll now ask **Rhonda Stover** to read us the  
20 Conflict of Interest Statement.

21 EXECUTIVE SECRETARY **STOVER**: The following  
22 announcement addresses the issue of conflict of  
23 interest with regard to this meeting and is made a  
24 part of the record to preclude even the appearance of  
25 such at this meeting.

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1                   Based on the submitted agenda and  
2 information provided by the participants, the Agency  
3 has determined that **all** reported interests and firms  
4 regulated by the Center for Drug Evaluation and  
5 Research present no potential for a conflict of  
6 interest at this meeting with the following exception:  
7 **in** accordance with 18 USC 208(b) a full waiver has  
8 been granted to Doctor Ralph D'Agostino. A copy of  
9 this waiver statement may be obtained from the  
10 Agency's Freedom of Information Office, Room 12A30,  
11 **Parklawn** Building.

12                   In the event that the discussions involve  
13 any other products or firms not already on the agenda,  
14 for which an FDA participant has a financial interest,  
15 the participants are aware of the need to exclude  
16 themselves from such involvement and their exclusion  
17 will be noted for the record.

18                   With respect to all other participants, we  
19 ask, **in** the interest of fairness, that they address  
20 any current or previous financial involvement with any  
21 firm whose products they may wish to comment upon.

22                   ACTING CHAIR BRASS: Thank you.

23                   Doctor Katz?

24                   DOCTOR KATZ: Good morning.

25                   Before beginning actually today's meeting,

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1 I'd like to take this opportunity to hand out some  
2 certificates and to discuss, or actually thank some  
3 individuals who are **no longer** going to **be** sitting on  
4 our committee.

5 At this point in time, there are four  
6 members of the Nonprescription Drug Advisory Committee  
7 whose tenure has been terminated, and they are here  
8 today as consultants to the committee. We wanted to  
9 take this opportunity to thank them very much for the  
10 time and effort that they've put into this committee,  
11 for all their good work, and all the contributions  
12 they have made over the time of their appointment.

13 I'd like to hand out to them a certificate,  
14 as **well** as a letter signed by Doctor Woodcock for  
15 appreciation, and they will also receive a letter  
16 signed **by Doctor** Friedman, also for appreciation and  
17 for their contributions to this committee.

18 **If** those members **whose** names I mention  
19 **would** come up, I'd like to give them their  
20 certificates now. **The** first one is Doctor Ralph  
21 **D'Agostino**.

22 {Applause.}

23 DOCTOR KATZ: The next one is Doctor Cage  
24 Johnson.

25 (Applause.)

1 DOCTOR KATZ: The next is Beth **Slingluff**.

2 (Applause. )

3 DOCTOR KATZ: The last person is **not** here  
4 today, I will mention his name and he will be  
5 receiving these in **the mail**, he is **Doctor** Theodore  
6 Tong.

7 {Applause.}

8 DOCTOR KATZ: With that, I'd now like to  
9 begin the meeting and the discussion at hand. I'd  
10 like to take this opportunity to welcome members of  
11 the Nonprescription **Drug** Advisory Committees, the  
12 Reproductive Health Drug Advisory Committees and the  
13 Anti-infective Drug Advisory Committees, FDA  
14 consultants, industry representatives and other  
15 interested **people** who have come to participate in  
16 today's discussion for the vaginal antifungal class  
17 labeling.

18 Today we will hear presentations designed  
19 to give background information about the class of  
20 products for OTC use in this class. We'll discuss  
21 **class** labeling issues with specific regard to **the**  
22 carton and brochure, and we'll also talk about general  
23 consumer labeling concepts.

24 To set the stage, I'd like to begin with a  
25 brief introduction. **Vulvovaginal candidiasis, or VVC,**

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1 is one of the most common infections affecting women,  
2 with an estimated 13 million cases occurring annually  
3 in the United States. It is estimated that  
4 approximately 75 percent of all women will have at  
5 least one episode at some point in time during their  
6 lives. Of these, approximately 40 to 50 percent of  
7 women will have recurring episodes, and approximately  
8 five percent will go on to develop chronic recurrent  
9 vulvovaginal candidiasis.

10 Prior to 1990, all drugs intended to treat  
11 this condition were by prescription only. The  
12 clinical scenario would be, a woman would begin to  
13 experience a clumpy or curdy whitish discharge, may or  
14 may not have some itching or irritation, and call  
15 their physician or health care practitioner for advice  
16 as to what to do. The woman would be invited into the  
17 office for an examination, at which time a Wet Nap or  
18 KOH preparation would be obtained, and a diagnosis of  
19 vulvovaginal candidiasis would be made as a result of  
20 the classic findings on a slide of -- yeast or hyphae.

21 The woman would then be given a  
22 prescription for a product to treat and would go home  
23 and take the product. At that point in time, she  
24 would either notice an improvement or she would go  
25 back to her physician to seek further advice.

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1           In June of 1990, several commercial  
2 manufacturers approached the FDA about the feasibility  
3 of this class of drugs going over the counter. The  
4 reason for that was that there was approximately a 15-  
5 year prescription marketing experience of two such  
6 agents, **Clotrimazole** and **Miconazole**, which had a  
7 relatively *benign* at first event profile, and it was  
8 felt that women could probably self-diagnose and **self-**  
9 **treat** these infections **if** they had previously **been**  
10 given a diagnosis.

11           As a result, the Agency, **in June** of 1990,  
12 held an Advisory Committee to look at this class of  
13 drugs for OTC use, specifically discussing  
14 **Clotrimazole** and **Miconazole**, to begin looking at  
15 whether or not they would be safe for over-the-counter  
16 use.

17           The committee concluded that the **imidazole**  
18 topical antifungal products were safe and effective  
19 when used for seven days to treat **vulvovaginal**  
20 candidiasis. Further, the committee felt that women  
21 could easily recognize the symptoms if given a prior  
22 diagnosis by a physician or a **health** care  
23 practitioner.

24           Thus, they recommended that these **imidazole**  
25 topical antifungal could **safely** and effectively be

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1 used by women over the counter to treat recurrent  
2 episodes of vulvovaginal candidiasis, with  
3 appropriately labeled OTC drug products.

4 The first of the seven-day products was  
5 approved in 1990. In 1993, the first of the  
6 combination products, which consisted of the  
7 suppository and an external vaginal cream, both having  
8 the same active ingredient, was approved. In 1995,  
9 the first of the three-day products was approved, and  
10 in 1997 the first one-day product was approved for use  
11 for over-the-counter treatments.

12 Throughout its eight-year marketing  
13 history, the basic premise is that these products are  
14 safe and effective for OTC use with appropriately  
15 labeled consumer labeling. The part to emphasize is  
16 for women who have had previously diagnosed  
17 vulvovaginal candidiasis.

18 As I said, the emphasis is on a prior  
19 diagnosis of vulvovaginal candidiasis and not de novo  
20 users. However, a recent nationwide telephone survey  
21 conducted by Prevention magazine indicated that the  
22 portion of women who treated themselves without a  
23 prior diagnosis has increased from 38 to 45 percent  
24 over this past year. This could mean that either the  
25 labels we are approving are not conveying the *correct*

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1 message to women who are using the product, or that  
2 women have become fairly complacent about treating  
3 themselves with a problem that they feel is a  
4 nuisance, rather than one that could have consequences  
5 if not properly diagnosed or treated.

6 The issue, moreover, has become  
7 increasingly complicated as newer products with  
8 shorter duration have entered the marketplace. Not  
9 only do all of these labels contain statement of  
10 identity, uses, warnings, direction, but additional  
11 marketing-like claims have also begun to appear. The  
12 language also contains many words and phrases that may  
13 not be understood by the majority of women who need to  
14 rely on these labels to use the products  
15 appropriately.

16 The issue of comprehensibility will be  
17 dealt with in much great detail later this morning,  
18 but it emphasizes the need for simplistic language in  
19 order to convey the desired message.

20 It is also important to remember that over  
21 the past several years there has been an FDA  
22 initiative to make OTC product labels more consumer  
23 friendly. The FDA, in February of 1997, published in  
24 the Federal Register a proposal proposing a  
25 standardized format for the labeling of all OTC drug

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1 products. The Agency believes that this OTC labeling  
 2 initiative is critical to the successful use of OTC  
 3 products. It is this information that the consumer  
 4 again relies upon in easily understood language so  
 5 that appropriate self-selection and appropriate use of  
 6 the products may occur.

7 Similar products containing varying labels  
 8 may impose some consumer confusion. Thus, given the  
 9 current labeling for vaginal antifungal products with  
 10 widely different wording artificial differences among  
 11 products may be created when true differences may not  
 12 exist. Conversely, true differences may not  
 13 accurately be conveyed when they do exist. Thus, it  
 14 is felt that class labeling may be in the best  
 15 interest of the consumer to most effectively convey  
 16 important information about the use and differences of  
 17 these products.

18 In addition, the current labels fail to  
 19 provide an accurate expectation of benefit for women  
 20 choosing among drugs of varying duration, and  
 21 currently we have one, three and seven-day products  
 22 available. This information is also important to a  
 23 consumer for both appropriate selection and use of a  
 24 particular product and will play an important part in  
 25 our discussion for today.

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1           In summary, during today's discussion we  
2 would like for you to consider the following issues,  
3 particularly as they relate to the carton and  
4 educational brochure. The questions that we will ask  
5 the committee to address are as follows:

6           1.       Currently, one, three and seven-day  
7 products are available over the counter. How should  
8 information be conveyed to the consumer that will help  
9 them select among these products?

10          2.       What, if any, modifications should be  
11 suggested for the carton label and educational  
12 brochure?

13               I thank you for your attention, and with  
14 that I'll turn the meeting back over to Doctor Brass.

15               ACTING CHAIR **BRASS**: Thank you.

16               We'll have a series of presentations to  
17 provide us background information and additional  
18 opinions about these questions, and we will begin by  
19 a presentation by Doctor Joseph **Winfield**.

20               DOCTOR WINFIELD: Doctor Brass, members of  
21 the committee, and guest members of the other  
22 committees, industrial members, consumer  
23 representatives, consultants and guests, I'm Joseph K.  
24 Winfield, an Obstetrician and Gynecologist, and a  
25 Medical Officer with the Office of Drug Evaluation IV,

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1 Division of Special Pathogens and Immunologic Drug  
2 Products. Good morning.

3 It is, indeed, a pleasure for me to present  
4 to you some of the background information about **over-**  
5 **the-counter** drug products for the treatment of  
6 **vulvovaginal** candidiasis.

7 Actually, I am the one individual that has  
8 been very close to this and have been there since the  
9 beginning. I was the presenter from the Agency, from  
10 the original 1990 committee meeting, that went with  
11 the original switching from the prescription drug  
12 products to over the counter.

13 As was mentioned by Doctor Katz, in 1990,  
14 up until 1990, all of these products for the treatment  
15 of **vulvovaginal** candidiasis were by prescription only.  
16 And, at that committee meeting it was decided that due  
17 to the prevalence of the disease, and the relative  
18 benign nature of it with the **sequelae** that was found,  
19 that these products that were of seven-day duration  
20 could go over the counter, and the individual who had  
21 had a diagnosis made by her physician, if she had a  
22 repeated episode could actually make the diagnosis  
23 herself and self-treat. And, based on that, the  
24 **imidazoles** of the seven-day duration, that would be  
25 **Clotrimazole** and **Miconazole**, was then approved for

1 over-the-counter use.

2 The seven-day products that were first  
3 approved was **Gyne-Lotrimin** 1 percent cream for seven  
4 days, and **Gyne-Lotrimin** 100 milligrams inserts for  
5 seven days. **Gyne-Lotrimin** is a **Clotrimazole** product.  
6 **Monostat** 2 percent cream, **Monostat** 100 milligram  
7 suppositories, those are **Miconazole** nitrate products.  
8 **Mycelex** 100 milligram inserts and **Mycelex** 1 percent  
9 Cream, those are also **Clotrimazole** products.

10 It will be noted that these products, the  
11 seven-day products, did not present any additional  
12 studies. The approval for over the counter was made  
13 on historical, as well as the experience that had been  
14 -- we had had with these products for over 15 years,  
15 and we found that they were safe and effective.  
16 Therefore, no additional studies were required.

17 Following the approval of the individual  
18 products, we had the approval of seven-day combination  
19 products. With the combination what we mean is that  
20 you have the same ingredient in the product and the  
21 cream, and both of the products had been approved  
22 previously for the use in treating either cutaneous  
23 candidiasis or for the treating of intravaginal  
24 candidiasis. So, we had the **Monostat** 7 suppository  
25 plus cream, they had the same active ingredient of

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1 Miconazole nitrate, we had the Gyne-Lotrimin insert  
2 plus cream, which is Clotrimazole, and the Mycelex  
3 insert plus cream.

4 After about three years of being on the  
5 market, several sponsors then wanted to go with a  
6 shorter duration of treatment. This would provide,  
7 hopefully, better compliance, and in addition would  
8 get better cure rates. So, they applied for the  
9 shorter durations of therapy, that was the three-day  
10 therapies, to go over the counter.

11 The FDA decided that in order for this to  
12 be done we would require two adequate and well-  
13 controlled clinical trials that were expected to show  
14 that the investigational product was therapeutically  
15 equivalent to the seven-day product as previously  
16 mentioned, either the seven days of Miconazole nitrate  
17 or seven days of Clotrimazole.

18 The second requirement was that  
19 statistically, using a 95 percent confidence interval,  
20 the difference between the point estimates did not  
21 exceed -20 and the upper bound crossed zero.

22 Now, when we go back to the three-day  
23 products and the one-day products that were approved,  
24 we have Miconazole suppositories, 200 milligrams,  
25 three days, Miconazole cream 4 percent, three days,

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1 Clotrimazole insert 200 milligrams, three days,  
2 Butoconazole cream 2 percent, three days, and  
3 Tioconazole ointment 6.5 percent for one day.

4 I would like to share with you some of the  
5 data that we -- of how we approved these products that  
6 was previously mentioned, by giving you the data as  
7 analyzed by the medical officer, in most cases it was  
8 I, in terms of how we approved the products as was  
9 previously mentioned, just to give you some background  
10 so that you can give us some appropriate input of how  
11 we can convey this information to the consumer.

12 If we were to look at the studies, the two  
13 studies that were required for the Miconazole  
14 suppository, three day, it compares itself to the  
15 Miconazole cream, seven day, in study one you will  
16 find that we had a 51 percent cure rate for the  
17 suppository, three day, compared to a 59 percent cure  
18 rate for the seven-day cream, In the second study, we  
19 had a 67 percent cure rate for the three-day product  
20 and a 70 percent cure rate for the seven-day product.  
21 Both of the studies fell within the 95 percent  
22 confidence interval as defined.

23 For the Clotrimazole three-day insert, they  
24 compared themselves to the seven-day insert. Study  
25 one we got a 51 percent cure rate, compared to a 56

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1 percent cure rate with the seven-day product. Study  
2 two was 52 percent cure rate, compared with a 55  
3 percent cure rate for the seven-day products, and the  
4 confidence intervals are as indicated.

5 For **Butoconazole**, the three day was  
6 compared to **Miconazole** cream, seven day. We got a 69  
7 percent cure rate in study one, compared to a 63  
8 percent cure rate with the seven-day product, and in  
9 the second study it was the opposite, we got a 53  
10 percent cure rate, with a 59 percent cure rate with  
11 the seven-day cream.

12 The **Miconazole**, this is the most recent  
13 product that has been approved, it was a three-day  
14 product that was compared to the seven-day cream, and  
15 in this one it showed that we got a 72 percent cure  
16 rate with the three-day product, compared to a 62  
17 percent cure rate with the seven day, and almost  
18 identical cure rates in the second study, 59 percent  
19 compared to 58 percent.

20 The single one-day product that we have  
21 approved, the **Tioconazole** ointment, the 6.5 percent  
22 one-day product, was compared to a **Miconazole** cream,  
23 seven-day product, we got a 57 percent cure rate with  
24 the one-day product versus a 69 percent cure rate with  
25 the seven-day product. In the second study, a 55

1 percent cure rate versus a 70 percent cure rate with  
2 the seven-day product. If you will note, these are a  
3 little bit outside of the confidence interval that we  
4 had originally defined, and as I said, these are the  
5 figures that we got after the analysis was done by the  
6 FDA, which does not necessarily agree with the numbers  
7 that were provided by the company. But, after much  
8 discussion, and knowing enough about the product, the  
9 Agency felt that this could be approved and we could  
10 adequately describe this in the labeling, in terms of  
11 the results that are demonstrated here.

12 Now, based on the analysis of the FDA, in  
13 terms of the therapies for less than seven days, it is  
14 our general impression that the longer durations of  
15 therapy provide the best results if all the medicine  
16 is used correctly.

17 When we talk about labeling, historically,  
18 when we went from prescription to over the counter,  
19 initially the labeling was identical to the  
20 prescription product, except where it referred to over  
21 the counter. From there, it was modified about a year  
22 later, when HIV, we found that that was very prevalent  
23 among women who had WC, so we felt that HIV warnings  
24 should be included in the labeling and a letter was  
25 sent to all of the sponsors to include the HIV

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1 labeling, and this is the labeling that was first  
2 thought to be uniform throughout all of the products.

3 From there, we were moving to the  
4 standardized format for OTC products, and this is  
5 where we are today in terms of class labeling. We  
6 would like for all of these products, since they are  
7 of the same class, they are used for the same  
8 indication, and they are basically the mechanism of  
9 action is the same, therefore, we feel like we should  
10 have class labeling except for product specific  
11 information that would be allowed. Therefore, for  
12 class labeling we would hope that this would be for  
13 consistency, it would decrease confusion, and it would  
14 improve appropriate selection.

15 My comment to the committee would be, based  
16 on the information as we have presented this today, we  
17 are not asking you now to discuss this, but how can  
18 this information be best presented in the product  
19 labeling so that the consumer can make an appropriate  
20 selection in terms of duration of therapy?

21 Thank you.

22 ACTING CHAIR BRASS: I think we are going  
23 to hold general discussion until we get to the  
24 specific questions, but if there are specific factual  
25 or clarification questions for any of the speakers we

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1 will take them before they sit down. So, are there  
2 any specific questions for Doctor Winfield?

3 Yes.

4 MS. KODA-KIMBLE: Can you explain why the  
5 single-day, single-dose product was approved for use,  
6 since it did not meet the original criteria?

7 DOCTOR WINFIELD: In the definitions that  
8 was used and the data that was presented when the  
9 studies were conducted, as you can see there has been  
10 some evolvment in terms of how we define and how we  
11 look at studies, and from the original definitions of  
12 what we were going to use in terms of **evaluable**  
13 patients the sponsor had gone by the original  
14 definition, and when it came in for evaluation the  
15 definition had been changed somewhat.

16 Therefore, when I looked at the data and  
17 analyzed it, the data the was submitted, it was a  
18 little bit different from the data as submitted by the  
19 sponsor.

20 So, in going back and discussing with the  
21 sponsor, even though they had presented borderline  
22 data, if you would combine the studies and then use  
23 the statistical analysis, the studies would fall  
24 within that confidence interval.

25 so, based on that, it was a management

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1 decision that we could approve the product.

2 ACTING CHAIR BRASS: Yes.

3 EXECUTIVE SECRETARY STOVER: Were the  
4 patients that were selected for the studies self-  
5 diagnosed or doctor diagnosed?

6 DOCTOR WINFIELD: These were doctor  
7 diagnosed.

8 ACTING CHAIR BRASS: Please, go ahead.

9 MS. NARRIGAN: I just have a question about  
10 dosage for the study that you presented on **Miconazole**.  
11 The paper copy that we got has a different dosage for  
12 the three-day versus the seven-day treatment, but it  
13 didn't show on your slide.

14 DOCTOR WINFIELD: Oh, well, in general,  
15 with three-day products, what they have done is they  
16 have doubled the dose. Most of them are 200  
17 milligrams, and in the seven-day products it's usually  
18 100 milligrams. So, what is happening is, for the  
19 shorter durations of therapy the dose has been  
20 doubled, basically. All of the products of three-day  
21 durations are either 200 milligrams or 4 percent,  
22 versus the **Miconazole** nitrate that is usually two  
23 percent and the 100 milligram.

24 MS. NARRIGAN: Thanks.

25 ACTING CHAIR BRASS: Thank you, Doctor

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1 Winfield.

2 DOCTOR WINFIELD: Thank you.

3 ACTING CHAIR BRASS: Our next speaker will  
4 be Helen **Cothran** from the Division of OTC Drug  
5 Products.

6 DOCTOR BLEWITT: Eric, may I ask just one  
7 more question?

8 ACTING CHAIR **BRASS**: Yes.

9 DOCTOR BLEWITT: These numbers that you've  
10 presented here, these differ than from the data that  
11 were submitted by the sponsor, in other words, you  
12 analyzed them a different way, or are these the same  
13 summary data from the sponsor's numbers? That's what  
14 I can't figure out.

15 DOCTOR WINFIELD: If you were to look at  
16 what the -- the data was submitted by the sponsor, but  
17 the analysis, in terms of how many patients were  
18 included or excluded were different when I looked at  
19 them. For instance, I can give you a for instance,  
20 such as a window violation, in terms of returning for  
21 visits, where the company may have **used** 14 days or 14  
22 to 17 days, I may have varied that from 12 to 18 days.  
23 so, what is happening is I was including more patients  
24 and looking at them using the same criteria in terms  
25 of cure, whether it micrologically and clinically

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1 cured, but in most cases what happened, I included  
2 more patients than the sponsor had included and,  
3 therefore, the figures are a little bit different in  
4 some of the studies, but it doesn't vary that much.

5 We may be talking about a total of about  
6 ten patients, but in general I included -- expanded  
7 the **number** of patients that could be included so the  
8 figures are a little bit different.

9 DOCTOR BLEWITT: Okay, thank you.

10 MS. COTHRAN: Good morning.

11 In the Federal Register of February 27,  
12 1997, the Agency published a notice entitled, "Over  
13 The Counter Drugs for Human Needs, Proposed Labeling  
14 Requirements ." Because the draft guidance for OTC  
15 vaginal antifungal class labeling was developed in  
16 accordance with the February 27th proposal, I would  
17 like to present a brief overview of the February 27th  
18 label proposal. Later Doctor Chin and Doctor Davis  
19 "will discuss the specifics of the draft guidance, that  
20 is, the carton and the educational brochure.

21 The purpose of the OTC labeling proposed  
22 rule is to create label uniformity to increase safe  
23 and effective use of OTC drugs, and to improve  
24 communication of labeling information to consumers.

25 The OTC labeling rulemaking is a two-staged

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1 process. The first stage is the proposed rule, which  
2 is the February 27th document, and the last stage is  
3 the final rule. The label requirements I am speaking  
4 about today refer to the proposed rule, not the **final**  
5 rule.

6 I'd also like to mention that there were  
7 approximately 1,500 comments to the proposed rule.  
8 Ninety percent of the comments dealt with use of the  
9 terms doctor, health professional and pharmacist,  
10 others dealt with print size, listing of inactive  
11 ingredients, and use of the Poison Control Center **and**  
12 the Overdose --- The final rule that will address the  
13 submitted comments will be published in the near  
14 future.

15 Therefore, the final rule will include some  
16 labeling changes that are not in the proposed rule.

17 Once finalized, the OTC labeling  
18 requirements will be applicable to OTC drugs marketed  
19 under an OTC monograph, OTC drugs subject of a pending  
20 application, and OTC drugs marketed under approved  
21 NDAs . The requirements do not apply to **homeopathic**  
22 drugs, which are listed in the Homeopathic  
23 Pharmacopoeia of the United States.

24 There are five specific proposed labeling  
25 changes in the document. The first change is use of

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1 standardized headings and subheadings . The headings  
2 and subheadings would be presented in standardized  
3 order with a minimum six point type size, upper and  
4 lower case letters, certain graphical features such as  
5 contrast by ground color and the use of bullet points.

6 This is an example of proposed headings and  
7 subheadings for an OTC drug label. This labeling  
8 information would appear on the back or side panel of  
9 the outside container or wrapper, or if there is no  
10 outside wrapper it would appear on the immediate  
11 container. The headings are as follows: the active  
12 ingredient in each dosage unit, the purpose, for  
13 **example**, vaginal antifungal, the use or indication,  
14 the warnings and the warnings subheadings. Directly  
15 under the heading warnings would be any specific  
16 warnings that are required for certain products, such  
17 as the Rheyes syndrome warning for products containing  
18 **salicylates** or in the case of vaginal antifungal the  
19 warning that the product may damage condoms and  
20 diaphragms and cause them to fail. Do not use with  
21 the absolute contraindications, where consumers  
22 shouldn't use the product regardless of whether a  
23 doctor or health professional is consulted, or where  
24 consumers are told not to use the product unless a  
25 prior diagnosis has been made by a doctor, for

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1 example, bronchial dilators the warnings is, do not  
2 use unless a diagnosis of asthma has been made by a  
3 doctor.

4 The subheading, "ask a doctor before use, "  
5 would be used where consumers should not use the  
6 product unless a doctor is consulted, for example, if  
7 a Person has a preexisting condition such as high  
8 blood pressure or diabetes, or in case of vaginal  
9 antifungal if a person has been exposed to the HIV  
10 virus .

11 "When using this product" will be followed  
12 by side effects consumers might experience or  
13 activities to avoid while using the product, for  
14 example, "when using the product Use caution when  
15 driving a motor vehicle or operating machinery," or in  
16 the case of vaginal antifungal, "when using this  
17 product do not use tampons, douches, spermicides or  
18 other vaginal products."

19 "Stop use" and "ask a doctor" would be used  
20 for toxicity or other serious reactions that occurs  
21 that would necessitate stopping use of the product,  
22 for example, if nervousness or dizziness occurs.

23 This subheading is different from the  
24 wording in the proposal because at a previous NDAC  
25 meeting the committee recommended that the "stop use"

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1 and the "ask a doctor" should be contiguous, so we  
2 have implemented that change.

3 The vaginal antifungal example for this  
4 would be, "stop use and ask a doctor if symptoms  
5 remain after seven days."

6 Then we have the pregnancy/nursing warning,  
7 the keep out of reach warning, the directions, other  
8 information which would include information such as  
9 storage temperature, inactive ingredients, questions  
10 and a toll free number.

11 The second proposed labeling change in the  
12 February 27th document deletes connecting terms.  
13 Connecting terms are words or phrases which are in  
14 quotation marks in OTC drug monographs and in specific  
15 regulations.

16 Currently, all material in quotation marks  
17 must be written verbatim in the labeling. However,  
18 this proposal allows deletion of some connecting  
19 times, provided the deletion does not change the  
20 meaning of the labeling information.

21 Some examples of connecting terms are these  
22 -- "due to, " and "while taking this product, " and  
23 deletion of connecting terms is not required, but  
24 would be permitted to allow manufacturers to simplify  
25 the labeling information to accommodate the new

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1 labeling format.

2 The third change would expand  
3 interchangeable terms. This would allow broader use  
4 of terms to help manufacturers accommodate the new  
5 labeling format. Interchangeable terms are, examples,  
6 "avoid inhaling, " or "do not inhale, " "**discard**" or  
7 "throw away."

8 The fourth proposed labeling change would  
9 be to amend and simplify specific warnings. These  
10 would be warnings such as the pregnancy warning. The  
11 old or current warning is: "As with any drug, if you  
12 are pregnant or nursing a baby, seek the advice of a  
13 health professional before using this product." The  
14 reworded warning in the proposed rule is, "Pregnant or  
15 breast feeding, ask a health professional before use."

16 The old or current warning is, "Keep this  
17 and all drugs out of the reach of children. In case  
18 of accidental ingestion, seek professional assistance  
19 or contact the Poison Control Center immediately."  
20 The new warning in the proposed rule is, "Keep out of  
21 reach of children. If swallowed, get medical help  
22 right away." This warning has been further revised  
23 to, "**Keepout** of reach of children. If swallowed, get  
24 medical help or contact the Poison Control Center  
25 right away." As I mentioned before, there are many

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1 comments of warnings to keep the Poison Control  
2 Center, and actually an **NDAC** Committee recommendation  
3 agreed with that, and so we have made that change.

4 The fifth change proposes to preempt state  
5 and local requirements that establish different or  
6 additional format or content requirements. Thus,  
7 federal law would take precedence.

8 The OTC labeling final rule will be  
9 effective 30 days after the date of publication in the  
10 Federal Register. However, the implementation of the  
11 OTC labeling final rule varies according to the  
12 regulatory status of the product. The implementation  
13 is as follows: for OTC drugs marketed under an OTC  
14 final monograph, on or after the effective date of the  
15 labeling final rule, the implementation would be the  
16 effective date of the applicable OTC final monograph.

17 For OTC drugs marketed under an OTC final  
18 monograph or NDA before the effective date of the  
19 labeling final rule, the implementation would be two  
20 years after the effective date of the labeling final  
21 rule.

22 For OTC drugs subject to a pending NDA on  
23 or after the effective date of the labeling final  
24 rule, the implementation would be immediate. It would  
25 be concurrent with the initial product marketing.

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1 In conclusion, the OTC labeling proposal is  
2 the framework of how much the OTC vaginal antifungal  
3 guidance is based. Although some changes can be  
4 expected when the labeling final rule is published,  
5 the basic concepts and the standardized labeling  
6 format that I've discussed today will be included in  
7 the final rule. Accordingly, any changes made in the  
8 labeling final rule would also be incorporated into  
9 the OTC vaginal antifungal guidance.

10 Thank you.

11 ACTING CHAIR BRASS: Thank you.

12 Are there any questions for Ms. Cothran?

13 Yes.

14 DOCTOR BLEWITT: So, if I'm interpreting  
15 that right, drugs that are currently approved, they  
16 would have two years before they have to make the  
17 change? Why such a long time period?

18 MS. COTHAN: Yes, that is correct, they  
19 would have two years. This is to lessen the burden on  
20 the manufacturer, because there are already parts in  
21 the pipeline, and you provide them sufficient time to  
22 make the change.

23 ACTING CHAIR BRASS: Thank you.

24 Our next speaker will be Doctor Lechter,  
25 from the Division of Drug Marketing, Advertising and

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1 Communications.

2 DOCTOR LECHTER: Good morning.

3 Today I'm going to address the issues of  
4 literacy, and whether consumers can understand what's  
5 in the labeling, that is, the comprehensibility of the  
6 labeling.

7 I have a short quiz for you, and you will  
8 not get a grade on your answers. What percentage of  
9 adults aged 25 and over in the United States have a  
10 college degree? How many do you think -- Ling, I know  
11 you know the answer -- how many of you think it's 15  
12 percent? Twenty-five percent? Thirty-five percent?  
13 Forty-five percent? More than 45 percent? Well, we  
14 are not getting a lot of responders today, but if  
15 you'll go to the next slide you will see what the  
16 answers are.

17 Many of us here today, and, in fact, most  
18 people in the country, associate with persons of a  
19 similar education level, and it may come as a surprise  
20 to many of us that only about 25 percent of adults in  
21 the United States have a college degree.

22 According to 1997 Census data, eight  
23 percent have post college, graduate or professional  
24 education, 17 percent had a Bachelor's degree only, 24  
25 percent had some college or an associate degree, 34

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1 percent were high school graduates only, ten percent  
2 had nine to 12 years of schooling but did not have a  
3 high school degree, and seven percent had less than  
4 eight years of schooling.

5           Although it appears that 80 percent of the  
6 adult population over age 25 are high school  
7 graduates, the unfortunate fact is that education is  
8 not always a good indicator of reading ability. In  
9 one study, patients' reading levels were an average of  
10 4.6 grade levels below their education level. In  
11 another study, 40 percent of adult patients who had  
12 completed ten years of schooling read at the 8th grade  
13 level or below.

14           In 1993, the National Adult Literacy  
15 Survey, a nationally representative survey that can be  
16 projected to the entire U.S. population, sponsored by  
17 the Department of Education, reported that almost half  
18 the adults in the United States do not have the  
19 literacy skills necessary to function adequately in  
20 society. They are functioning at the two lowest  
21 levels of literacy on their scales.

22           They interviewed 26,000 persons aged 16 and  
23 over. Their purpose was to profile the English  
24 literacy of adults in the United States based on their  
25 performance on a wide variety of tasks that reflect

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1 the types of materials and demands that they might  
2 encounter in their daily lives.

3 The results are grouped into five literacy  
4 levels. Level one included 23 percent of the  
5 population. They can do simple matching and read  
6 brief, simple text. Level two was 25 percent of the  
7 population, they can locate a single piece of  
8 information in text and read low-level information.  
9 Levels one and two had difficulty integrating or  
10 synthesizing information from complex or lengthy text,  
11 and this represents 90 million people. Level three,  
12 which was 33 percent of the population, can perform  
13 information integration from relatively long or dense  
14 text, and levels four and five, which were 18 to 21  
15 percent of the population, can read long complex text  
16 and complex information that contains distracters.

17 Surprisingly, many people functioning in  
18 levels one and two believed that they had no problems  
19 with comprehension. Sixty-six to 75 percent in level  
20 one and 93 to 97 percent in level two perceived  
21 themselves as being able to read and write English  
22 well or very well. So, they don't even recognize  
23 their own limitations.

24 Therefore, with 48 percent of the  
25 population operating at the two lowest levels, it is

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1 imperative that we make every effort to simplify the  
2 comprehensibility of OTC drug labels. We may not be  
3 able to reach all of those in the lowest levels, but  
4 simplifying the labeling will most certainly make the  
5 information more accessible to them.

6 Here are some findings from some studies  
7 regarding how well patients understand medical terms.  
8 Research among patients has revealed that many common  
9 medical terms are not well understood. Here are some  
10 of the correct scores in one study. Thirty-seven  
11 percent understood what blood pressure was, 64 percent  
12 understood the word bowel, 69 percent nerve, 83  
13 percent orally. In another study of lower  
14 socioeconomic patients, all of whom were Native  
15 English speakers, only 63 percent of the definitions  
16 of medical terms were correct, 26 percent were vague  
17 or wrong, and for 11 percent there were no answers at  
18 all.

19 Here are some of the words and their scores  
20 in that study: abdomen, 70 percent got that correct;  
21 orally, 62; bowel, 52; hypertension, 44 percent got  
22 that correct; and only 24 percent understood stroke.

23 Although not everyone will be functioning  
24 at these low literacy levels, it is essential that  
25 drug labeling be comprehensible to the widest possible

1 audience.

2 In label comprehension studies conducted by  
3 drug sponsors as part of their application for  
4 switching prescription drugs to over-the-counter  
5 status, for most products there's a consistent pattern  
6 of the low literacy or low education consumers scoring  
7 lower than the general population consumers. There's  
8 usually, but not always, a pattern of about ten to 20  
9 percent lower scores for these people when they look  
10 at the draft labeling.

11 When we noticed this in our reviews of the  
12 studies, we tried to simplify the labeling further in  
13 these areas, and I'll give you some examples of some  
14 of the simplification that we've attempted.

15 Some of these label comprehension studies  
16 have been conducted at the lowest levels of literacy,  
17 that is, they test probably at the NALS Levels 1 and  
18 2. For example, the interviewer might ask a simple  
19 yes/no question about something in the labeling. For  
20 example, will you get skin irritation using this  
21 product, when the words skin irritation are clearly on  
22 the label. so, we don't always know how well  
23 participants truly understand the concepts in the  
24 label .

25 More recently, the Agency has encouraged

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1 sponsors to require the participants in their label  
2 comprehension studies to make inferences, to apply the  
3 information on the label to hypothetical situations.  
4 Participants appear to have trouble with some of these  
5 responses, particularly those requiring calculation of  
6 numbers, such as determining how many doses a day need  
7 to be taken, or how many cartons of a nicotine patch  
8 are needed to complete a treatment program.

9 Consumers have a variety of problems with  
10 other types of information, depending on the labeling  
11 itself and the nature of the product. For example,  
12 here's a list of products which participants from the  
13 general population had difficulty understanding in  
14 various label comprehension studies. They had  
15 problems with numerical concepts, such as duration of  
16 use, time to relief, comparative efficacy, which dose  
17 to choose, the maximum number of doses. They had  
18 problems with the involvement of health care  
19 providers, when to consult a doctor before use, when  
20 to consult a doctor during use. They had problems  
21 with medical concepts, treatment versus prevention,  
22 drug interactions, side effects, indications.

23 In these studies, persons who were at low  
24 literacy levels had particular problems with  
25 determining whether a product is appropriate for them

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1 to use, what to do if symptoms are not relieved, the  
2 time to relief and the duration of use.

3 Much of the health information that's been  
4 studied recently has a reading level beyond the 10th  
5 grade level of comprehension. That means it's  
6 inaccessible to 30 to 50 percent of the population.

7 Strategies that will help simplify the  
8 labeling include the following, which we have  
9 incorporated in our new proposed OTC formats, and  
10 which we have incorporated in the proposal you have  
11 before you today for the vaginal class labeling.

12 Our overall advice is to use clear core  
13 messages and use illustrations to fit the message, as  
14 we have suggested in the instructions section in the  
15 brochures. Also, avoid information overload.

16 In terms of language, we recommend using  
17 short words and simple sentences, use only one clause  
18 per sentence, avoid technical language and use  
19 language appropriate for the target audience.

20 In terms of organization, we should suggest  
21 that desired behavior be emphasized and that most  
22 important behavior be emphasized. Signal words, such  
23 as warnings, should be used. Titles and subtitles  
24 should be used to organize content, and print should  
25 be used that is sufficiently large.

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1           In developing labeling, we should always  
2 keep in mind the low literacy population who will need  
3 to use these materials. The reading level of text can  
4 be analyzed using readability formulas such as the  
5 **Flesch** Index or the Gunning Fog Index. These are  
6 based on the length of words and length of sentences.  
7 However, these readability formulas account for only  
8 one third of the variability and the difficulty in a  
9 set of passages. The most important factor in  
10 readability is the difficulty level of the vocabulary  
11 used. The second is sentence length.

12           Many short words are infrequently used and  
13 may produce an easy reading level score on such tests,  
14 but they may be unfamiliar to people and not very  
15 understandable. For example, the word prone and the  
16 phrase, "If you are prone to yeast infections . . . , "  
17 the word prone is short, it would get an easy  
18 readability score, but it's not a commonly used word  
19 and many people may have difficulty understanding it.

20           In a report generated by a group of  
21 consultants to the FDA over 15 years ago, the  
22 difficulty of understanding terms on OTC drug labels  
23 was recognized, and this group made some suggestions  
24 for simplifying language on OTC labels. Some of these  
25 suggestions are up here on the slide. They suggested

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1 using the word doctor instead of physician; call  
2 instead of consult; stop instead of discontinue; throw  
3 away instead of discard; returned instead of  
4 recurrence; long lasting in place of chronic; and  
5 lasts instead of persists.

6 Here are some examples of language from  
7 current WC product labeling that we believe could be  
8 simplified and which is presented more simply in our  
9 draft labeling. The original, and this is from a  
10 carton label, says, "Repeat this procedure daily for  
11 seven consecutive days." We think problems with this  
12 include difficulty understanding the words procedure  
13 or consecutive. We think it's better to have on the  
14 carton label, insert one, and then dosage form, into  
15 the vagina at bedtime for X days in a row.

16 Another example from the carton label is,  
17 if you do not improve in three days, or you do not get  
18 well in seven days, you may have a condition other  
19 than a yeast infection, consult your doctor. The  
20 problem here is that there are too many clauses.  
21 Other than and consult may be confusing to some  
22 consumers. We think a simpler and better way to do  
23 this would be to have a heading and bullets: stop use  
24 and ask a doctor if symptoms do not improve in three  
25 days, symptoms remain after seven days.

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1           The next example is from an educational  
2 brochure. The original says, "When a yeast infection  
3 occurs, the body responds with an increase in vaginal  
4 secretions. " The problem here is that responds may be  
5 difficult, vagina secretions may be difficult.

6           We think it would be better to do as we  
7 have done in our draft brochure, is to put the  
8 information in a question and answer format, and the  
9 question here would be, how can I tell that I have a  
10 vaginal yeast infection, and within the answer it  
11 mentions that you may have a discharge that is thick,  
12 white and lumpy like cottage cheese.

13           As you can see from these few examples, we  
14 still have difficulties in making comprehensibility  
15 completely simple. For example, some of the sentences  
16 we have suggested have more than one clause. It's  
17 difficult to find more common words to substitute for  
18 words like discharge or secretion. We might also want  
19 to substitute the word put for the word insert.  
20 Also, we may have lost some information in  
21 simplification, as in the advice about when to consult  
22 a doctor, on the carton label we left out the  
23 information that you may have a condition other than  
24 a yeast infection. However, we do provide this  
25 information in the brochure.

1           so, this is not an exact science, and we  
2 welcome your suggestions for further simplification.

3           It is not simple to simplify labeling, and  
4 a number of issues are unresolved, and they include  
5 the following ones that are applicable to the vaginal  
6 class labeling. If we wait for the lowest common  
7 denominator, we risk oversimplifying or in losing the  
8 meaning of the original message. Further, overly  
9 simply messages can be a turn off to good readers.  
10 Research shows that documents with low readability  
11 scores, or low reading difficulty scores rather, are  
12 negatively rated by good readers.

13           Further, some words or phrases are not  
14 amenable to simplification, such as names of body  
15 parts, medications that are contraindicated or  
16 diseases. Ideally, they would be explained or  
17 described, but there's inadequate space for this on  
18 most cartons for these products. Perhaps, some of the  
19 explanation can be included in the informational  
20 brochures.

21           And, for medications that must be measured  
22 by the consumer, how do we describe quantities, for  
23 example, the amount of external cream to be used by  
24 users of these vaginal products.

25           The use of graphics can be helpful, but

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1 they may be misinterpreted unless they are universally  
2 used. For example, if you see this graphic on a  
3 product label, do you think it means do not use this  
4 product if you are pregnant, or does it mean you'll  
5 not become pregnant if you use this product? There's  
6 quite a big difference in interpretation.

7 In conclusion, the regulations governing  
8 OTC drug products require that the labeling be stated  
9 in such terms as to render it likely to be read and  
10 understood by the ordinary individual, including  
11 individuals of low comprehension under customary  
12 conditions of purchase and use. And, that is why we  
13 are here today, to assure that the widest possible  
14 range of consumers can understand the labeling for  
15 vaginal candidiasis products, to enable them to use  
16 the products safely and effectively.

17 We welcome your suggestions for simplifying  
18 the labeling for these vaginal products.

19 Thank you.

20 Are there any questions?

21 ACTING CHAIR BRASS: Are there any  
22 questions? Yes.

23 DOCTOR BLEWITT: The women that use these  
24 products are going to be from their mid-teens to  
25 probably in their 40s, do you have any information on

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1 education out there, literacy of the people in just  
2 this age group, as compared to the society as a whole?

3 DOCTOR LECHTER: I know that the  
4 information is out there, I don't have it myself with  
5 me today.

6 ACTING CHAIR BRASS: Are there any other  
7 questions?

8 Thank you.

9 Our next speaker will be Doctor Chin from  
10 the Division of OTC Drug Products.

11 DOCTOR CHIN: Good morning, everybody.

12 ALL : Good morning.

13 DOCTOR CHIN: Okay. You didn't do too well  
14 on Doctor Lechter's class, but I thought you were  
15 going to flunk my reading test, and you have passed  
16 with flying colors.

17 Today we will be considering all the OTC  
18 vaginal antifungal products for treatment of  
19 vulvovaginal candidiasis, WC, as a product class. We  
20 will be making new footsteps as we further the  
21 development of class labeling for this product class  
22 for the benefit of the consumer.

23 My task is to present the carton label for  
24 all OTC vaginal antifungal products. I will be going  
25 over the content with you and will highlight some of

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1 the issues pertinent to this product class.

2 First, I'd like to show you some carton  
3 samples of currently marketed vaginal antifungal  
4 products. I'm not advertising for any of these labels  
5 shown.

6 As you can see, there are products for  
7 seven-day treatments, three-day treatments, and a one-  
8 day treatment. For most of these products, there are  
9 choices of dosage forms, such as the cream or vaginal  
10 insert. For the cream products, there are also  
11 choices for applicator types.

12 Now , I'd like to show you the back panels  
13 of these cartons. I'm just showing you the back  
14 panels to provide you with an overall sense of the  
15 variety in labeling, the differences in format,  
16 content and organization of the content. Don't try to  
17 read these word for word, the labels are included in  
18 your packet. I'm only providing a visual overview,  
19 setting the stage, so to speak, for class labeling.  
20 Here you see a back carton label for a seven-day  
21 product, a three-day product, and a one-day product.

22 And, here's a visual overview of the full  
23 carton back panel. This is the proposed class label  
24 for this class of products. It is in your packet, and  
25 has been available on the internet.

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1 With the multitude of vaginal antifungal  
2 products available OTC today, it becomes imperative  
3 that consumers are provided with fair and important  
4 information that will help them to self-select the use  
5 of these products appropriately. The Vaginal  
6 Antifungal Class Labeling Work Group was thus formed  
7 to develop OTC class labeling for all the products  
8 belonging to this class. The work group is a  
9 multidisciplinary team, involving four divisions, the  
10 Division of Over The Counter Drug Products, the  
11 Division of Special Pathogens and Immunologic Drug  
12 Products, the Division of Drug Marketing, Advertising  
13 and Communications, and the Division of Labeling and  
14 Nonprescription Drug Compliance.

15 The objectives of class labeling are to  
16 provide uniform information across this product class,  
17 that is, the vaginal antifungal, and also to conform  
18 to the proposed labeling requirements for OTC drugs.  
19 This is not to say that product differences will be  
20 lost as a result of class labeling. Where differences  
21 do exist, the specification of such differences will  
22 be allowed provided that the differences are supported  
23 by data.

24 The objectives of the carton label are that  
25 it provides all the information that the consumer

1 needs to self-select appropriately and to use  
2 appropriately.

3 Moving on to the use section. In 1990,  
4 when this product class was first switched to OTC, it  
5 was under the rationale that with Advisory Committee  
6 input that these products could be used OTC by women  
7 who had previously been diagnosed with WC by a  
8 physician and who subsequently recognized WC based on  
9 symptoms alone. Thus, this statement of current  
10 labeling: if this is the first time you have had  
11 vaginal itch and discomfort, consult your doctor. If  
12 you have had a doctor diagnose a vaginal yeast  
13 infection before and have the same symptoms now use  
14 this product as directed for a certain number of  
15 consecutive days.

16 We modified this statement because we  
17 wanted the label to convey a clear and direct message  
18 to the consumer with regards to having a diagnosis of  
19 WC first, and so the revision: see your doctor if  
20 this is the first time you have vaginal itching and  
21 discomfort to find out if you have a vaginal yeast  
22 infection. This modification left out the statement  
23 about using the product if the woman is having the  
24 same symptoms now as the previously diagnosed episode  
25 of Wc.

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1 This is where we would really welcome your  
2 input and suggestions as to how to clearly and  
3 strongly convey these messages to the consumer, since  
4 there is some indication that consumers are choosing  
5 to self-treat for symptoms without first having a  
6 doctor provide them with a definitive diagnosis of  
7 VVC.

8 In the August 17, 1998 tan sheet there was  
9 a report on a survey sponsored by Prevention magazine  
10 and the American Pharmaceutical Association. Results  
11 from the survey indicated that OTC vaginal yeast  
12 infection medications were used by 45 percent of women  
13 first, without consulting a physician. This was  
14 increased from 38 percent in 1997.

15 In a 1996 article in the Journal of Family  
16 Practice, et. al., reported that their questionnaire  
17 survey showed that one in five women who have used OTC  
18 antifungal products for WC have never previously  
19 received a clinical diagnosis of WC. Furthermore,  
20 women who have received a diagnosis of WC were more  
21 likely to incorrectly diagnose and inappropriately  
22 treat other urogenital infections with an OTC  
23 antifungal product, compared to women who have never  
24 received a clinical diagnosis of WC.

25 Now the use section. There are two

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1 statements on what the product is to be used for. The  
2 first is, to treat repeat vaginal yeast infections.  
3 This is to specify that the consumer is not having a  
4 first infection, but is having a repeat infection. We  
5 did not use the word recurrent because that has its  
6 own set of medical connotations and Doctor Davis will  
7 comment on that further. We also considered the use  
8 of the words infrequent or occasional to describe the  
9 vaginal yeast infection and would like to hear your  
10 specific suggestions as well.

11 Another use is to relieve external itching  
12 and irritation due to a repeat vaginal yeast  
13 infection. This use would be stated only for  
14 combination products with a tube of external cream and  
15 cream formulation products that come with a large tube  
16 of vaginal cream.

17 In the proposed rule for OTC labeling  
18 requirements, specific warnings for use of the product  
19 can come before warnings which are placed under  
20 standard subheadings. Here we wanted to clearly point  
21 out that these products are for vaginal use only, and  
22 the other specific warning is that the product may  
23 damage condoms and diaphragms and cause them to fail.  
24 The educational brochure provides more information on  
25 not relying on the use of these latex products to

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1 prevent pregnancies or STDS while using the antifungal  
2 product. Fungistat-X here is an imaginary name.

3 There are also standard subheadings  
4 pertaining to specific warnings about doctor contact,  
5 product use, stopping use, et cetera. For this  
6 product class, three subheadings were used for  
7 specific warnings. The first one is, ask a doctor  
8 before use if you have any of the following conditions  
9 or situations. The first two bullets are shown on  
10 this slide, and the next two will be in the following  
11 slide.

12 The concern here in the first bullet is  
13 that we provide safeguards in the labeling for  
14 misrecognition of symptoms, so that if the consumer  
15 had an infection other than a vaginal yeast infection,  
16 if they had any one or more of the **symptoms** of  
17 abdominal pain, fever, chills, nausea, vomiting, foul  
18 smelling discharge, they are referred back to the  
19 doctor.

20 The second bullet is in addition to current  
21 labeling. This is to bring consumers who are  
22 repeating their self-treatment too frequently back  
23 into the doctor's care for evaluation and proper  
24 treatment. Consumers requiring treatment as much as  
25 once a month or three in six months are, therefore,

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1 referred back to the doctor. They may have  
2 predisposing factors that may need to be addressed by  
3 a health care professional. Please provide comments  
4 about the frequency stated here.

5 The third bullet provides a specific  
6 warning to those who may have been exposed to the HIV  
7 virus.

8 The fourth bullet on the lower age limit is  
9 a carryover from the prescription labeling when  
10 **Clotrimazole** and **Miconazole** seven-day products were  
11 first switched. The definition in those days of an  
12 adult was anyone age 12 years and over. By **current-**  
13 **day** standards of care, it may be prudent to consider  
14 that adolescents aged 12 to 16 who are self-treating  
15 for repeat vaginal yeast infections may need to see a  
16 doctor who will evaluate and probe for reasons why the  
17 adolescent is getting repeat yeast infections. These  
18 reasons may require medical and social interventions  
19 and linkages to the health care system.

20 The next subheading, "when using this  
21 product, " provides for warnings during the use of the  
22 product, for optimal performance of the product the  
23 label states that the consumer should not use tampons,  
24 douches, spermicides or other vaginal products, and  
25 should not have vaginal intercourse. The first bullet

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1 cautions against possible interference from the use of  
2 other vaginal products, and the second bullet allows  
3 for time for the product to work and the consumer to  
4 get better, without adding further insult to the  
5 disease itself.

6 In the educational brochure, explanation  
7 about avoiding the use of other vaginal products and  
8 condoms and diaphragms are provided.

9 The last subheading, "stop use and ask a  
10 doctor if," guides the consumer back to the doctor  
11 during the use of the product. "Stop use and ask a  
12 doctor if symptoms do not improve in three days,  
13 symptoms remain after seven days, if you get abdominal  
14 pain, fever, chills, nausea, vomiting, foul smelling  
15 discharge or hives." Whether the consumer is self-  
16 treating for something other than a yeast infection or  
17 developing signs of a more serious infection which may  
18 no be WC, or the treatment is ineffective, all three  
19 bullets point the consumer back towards the doctor.  
20 This is another safeguard to ensure that the consumer  
21 receives proper clinical evaluation and treatment in  
22 the setting of OTC availability of these products.

23 The duration of time that should elapse  
24 before the consumer seeks medical care was carefully  
25 considered to achieve the optimal balance between

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1 consumers prematurely calling the doctor before the  
2 product has time to work and not delaying appropriate  
3 treatment for too long, especially in the setting of  
4 products being available for one-day, three-day and  
5 seven-day treatments.

6 There is also specific warning language  
7 required on the current monographs and regulations,  
8 and for this class of product it would be the  
9 pregnancy/nursing warning, "if pregnant or breast  
10 feeding ask a health professional before use," and the  
11 keep out of reach of children warning, "keep out of  
12 reach of children, if swallowed get medical help or  
13 contact a Poison Control Center right away." The  
14 language shown here reflects modifications to the  
15 proposed rule.

16 Under directions, only the general  
17 direction of inserting one dosage form at a certain  
18 time for a certain number of days, depending on the  
19 product, is in the carton label. For complete  
20 instructions, the consumer is referred to the  
21 educational brochure, which provides step-by-step  
22 instructions with illustrations for each specific  
23 product and dosage form.

24 There are also other pieces of information  
25 that go into the carton back label, and I'm not

1 showing them, but information such as storage and  
2 inactive ingredients will go here. If there is  
3 information about a toll free number, if a consumer is  
4 to call if they have comments or questions, it would  
5 be placed in this section as well.

6 And finally for your consideration, there  
7 were certain words that we discussed ad nauseam, and  
8 we would like your input on the following: repeated  
9 versus occasional, foul smelling versus bad smelling,  
10 abdominal versus palate, versus stomach, versus belly,  
11 vaginal intercourse versus vaginal sex and any other  
12 word you can think of. We would like to hear specific  
13 word suggestions for better word choices and, please,  
14 no legal definitions.

15 And, with that, I conclude this portion on  
16 class labeling.

17 ACTING CHAIR BRASS: Thank you.

18 Are there any questions for Doctor Chin?  
19 Yes, Beth.

20 MS. SLINGLUFF: I understand why a decision  
21 would have been made to choose the term in a seven-day  
22 product, if you are not better in three days, or if  
23 your symptoms aren't gone in seven, but when you look  
24 at one-day and three-day products what is the science  
25 that would substantiate at what time frame the patient

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1 should, in fact, be, (A) improved and, (B) cured, and,  
2 you know, truly logically it would seem that it would  
3 not be the same time frame.

4 DOCTOR CHIN: I'm going to take a first  
5 stab at it, give you a very general comment, and then  
6 Doctor Davis and Doctor Winfield can further comment  
7 on this.

8 The selection of the time frame of when to  
9 call the doctor first if you don't improve for all the  
10 products, whether they are one-day treatments, or  
11 three-day treatments, or seven-day treatments, is that  
12 you want to allow some time for the medication to  
13 work. Now, even for the one-day product, even though  
14 you are only inserting one dose of medication, that  
15 medication stays around, and so it needs time to work  
16 as well. So, you wouldn't necessarily want the  
17 consumer taking the one-day product to call the doctor  
18 the next day. So, that's the rationale for that.

19 But, if you want to add to that?

20 DOCTOR DAVIS : Yes, I mean, that's  
21 basically true, a one-day product still is active in  
22 the vagina for two to three days, and, therefore, the  
23 symptom relief really will take the same length of  
24 time that it would with a three or seven-day product.  
25 so, the advice really should be the same in our

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1 opinion.

2 ACTING CHAIR BRASS : Additional questions?

3 Thank you.

4 DOCTOR CHIN: Thank you.

5 ACTING CHAIR BRASS : Our next speaker is  
6 Doctor Davis from the Division of Special Pathogens  
7 and Immunologic Drug Products.

8 DOCTOR DAVIS: I'll start now. Good  
9 morning to the Advisory Committee.

10 ACTING CHAIR BRASS: I'm sorry, before you  
11 get started, do you have a full half hour  
12 presentation?

13 DOCTOR DAVIS: No, I have about ten  
14 minutes.

15 ACTING CHAIR BRASS: Okay, great, go ahead.

16 DOCTOR DAVIS: Good morning to the Advisory  
17 Committee, to the representatives of industry and  
18 other people in the audience.

19 I thought I'd be a little different on my  
20 first slide, so I included my E-mail address so if  
21 anybody would like to communicate with me by E-mail  
22 I've got my address up there.

23 I'm in the Division of Special Pathogens  
24 with Doctor Joe Winfield, and although Joe has really  
25 done probably 99 percent of the work with these

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1 products I have reviewed one product and been involved  
2 throughout this process of making the decisions about  
3 the class label for the carton and the educational  
4 brochure.

5 We have really covered class labeling  
6 pretty adequately, and the composition of the working  
7 group was presented by Doctor Chin, and it was the  
8 same group working on the carton label as well as the  
9 educational insert. I will go into more detail about  
10 some of the major content issues concerning the  
11 educational brochure and talk about some of the goals  
12 of the educational brochure with some detail and then  
13 point out some of the issues that came up with our  
14 advice about the instructions to be given as part of  
15 the educational brochure.

16 For class labeling, really, this has been  
17 covered by Doctor Winfield and Doctor Chin, but I  
18 simply will point out that for the educational  
19 brochure, which is inserted inside the carton and the  
20 package, each of the products really have different  
21 formats and headings, different instructions and  
22 illustrations that go with the instructions, and  
23 slightly different messages and word choices. So,  
24 clearly, what we want is a uniform consumer message  
25 that is simple and easy to understand, that's

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1 educational and informative, and that's really the  
2 goal, if you will, of our class labeling and having,  
3 hopefully, one educational brochure for all of these  
4 products.

5 Under major content issues, we,  
6 essentially, took all of the educational brochures  
7 that were already out there with the products and then  
8 assimilated what we thought was the best information  
9 from those brochures and came up with our topics and  
10 headings, and then with our warnings.

11 Under the topics and headings, we basically  
12 finalized that with 15 that were chosen, and I'll go  
13 into those further later, our format and wording was  
14 changed to generally be in the "I" format, in other  
15 words, how can I treat my infection, how can I prevent  
16 the infection, how can I use the product for best  
17 results, and we felt that this was consumer friendly  
18 and easy to understand.

19 For consumer comprehension, this was really  
20 always kept in mind as one of our goals, how can we  
21 get clear, simple information to the consumer so it  
22 can be easily understood? And, I think we did a good  
23 job of that, but it certainly required quite a bit of  
24 discussion and some controversy on word choices.

25 Under the concept of warnings, we basically

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1 have our warnings, obviously, specific to this  
2 product, that is, products for treating vulvovaginal  
3 candidiasis.

4 In 1992, a letter was sent out to all NDA  
5 holders, which talked about including some warning  
6 about HIV. That was because of the fact that  
7 certainly many women with recurrent infections were,  
8 in fact, HIV women, and it was felt by the FDA, the  
9 Agency, that there should be a warning included in our  
10 information.

11 In the educational brochure, there are, in  
12 fact, three different times where the HIV warning is  
13 given, so that we, in fact, have maybe over done it,  
14 but we felt it was more important to over do it on the  
15 HIV warnings, rather than to under do it. So, that's  
16 just a point that I would make in terms of our  
17 proposed brochure.

18 In terms of the actual brochure then, there  
19 are 15 headings, and the headings really cover these  
20 five major areas here, who should use the product,  
21 general information, best results, warnings and  
22 instructions. Under the first portion, about who  
23 should use the product, I think we've clearly made the  
24 message that this is not for first-time infections,  
25 and hopefully that is clear from the educational

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1 brochure, and it's also not for "recurrent"  
2 vulvovaginitis. I will make a quick comment about  
3 that, by medical definition most experts will call  
4 recurrent **vulvovaginitis** as four episodes of the  
5 infection within a 12-month period of time, and that  
6 is, as I said, a medical definition. Slightly later  
7 in the talk we'll go over the actual wording that we  
8 used and see if the Advisory Committee agrees with our  
9 choice of words as to what would still be an  
10 appropriate use of these over-the-counter products for  
11 women who happen to have repeated infections but do  
12 not have recurrent vulvovaginitis.

13 The brochure headings then, and these are  
14 basically in order as they appear in the educational  
15 brochure, the first four really deal primarily with  
16 who should use the product. The number one heading  
17 is, reasons I should use the **Fungistat-X**, which is the  
18 imaginary product. In this we simply state that it's  
19 really for the **vulvovaginal candidiasis** with a  
20 previous diagnosis made by a doctor for the vaginal  
21 infection. Number two, what is a vaginal yeast  
22 infection, this is a simple explanation that these  
23 infections are common, and caused by an overgrowth of  
24 the yeast forms, which may normally be present in the  
25 vagina. Who can get a vaginal yeast infection, we

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1 emphasize that it can occur at any age, that it's more  
2 likely, there are certain circumstances under which  
3 women are more likely to get the infection. Number  
4 four, how can I tell that I have a yeast infection,  
5 we, essentially, in this section have six bullets  
6 which list the most common symptoms of the infection.  
7 But, importantly, we mention the symptoms that are not  
8 associated with the infection, such as the fever,  
9 abdominal pain, and in that case our specific advice  
10 is to call the doctor or health care professional.

11 The next set of headings deal more  
12 generally with information about prevention and a  
13 little bit more about yeast infections. Why do women  
14 get repeated vaginal yeast infections, here  
15 specifically we have seven bullets which list  
16 associated conditions, such as antibiotic use,  
17 pregnancy, oral contraceptive use, diabetes mellitus,  
18 or here we do mention in a weakened immune system,  
19 which also is another form of the HIV warning. Number  
20 six, are vaginal yeast infections sexually  
21 transmitted? We essentially say no, but we add the  
22 advice that if the woman's partner has symptoms,  
23 meaning itching of the genital area, that the partner  
24 should seek care from a doctor or health care  
25 provider. Number seven, how can I prevent vaginal

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1 yeast infections? We really give advice to again go  
2 back to the doctor about current medications you may  
3 be taking, in terms of some prevention for the  
4 disease. This is not a lengthy section.

5 Can I use Fungistat-X during my menstrual  
6 period? The answer is yes, but we recommend that the  
7 woman should avoid tampon use while using the product  
8 if during their menstrual period. Can I use **Fungistat-**  
9 **X** with other vaginal products? The answer is a clear  
10 no, and we give the reasons why.

11 For best results in treating my infection,  
12 this is a somewhat larger lengthy section with 12  
13 specific **bulleted** recommendations, the most important  
14 of which is that we emphasize using all of the  
15 medication, even if the symptoms have cleared up, and  
16 then there are 11 other major points for best results.

17 Warnings and side effects, what warning  
18 should I know about using Fungistat-X? This is  
19 exactly the same format as appears on the carton  
20 label. There are really no changes or major  
21 additions, because that's really covered quite well on  
22 the carton label. However, we say to ask a doctor  
23 before use if, and it says "you get vaginal yeast  
24 infections often." Then we say in parentheses, "(such  
25 as once a month or three in six months.)" That might

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1 be interpreted to mean you could have as many as six  
2 infections in a year, but our intention is to say that  
3 this should be used for women who have a repeated  
4 infection, and we felt so comfortable with giving the  
5 advice of three infections in six months, but we did  
6 mean that that included the current infection the  
7 woman was being treated for. If members of the  
8 audience or Advisory Committee feel this is  
9 inappropriate, we would like comments.

10 Number 12, side effects that may occur, we  
11 talk about the actual fact that women may experience  
12 an increase in their vaginal symptoms, even first when  
13 using the medication, and then give advice about stop  
14 using the medication and talk to the doctor if, and we  
15 have the standard warnings of abdominal pain, fever,  
16 foul smelling discharge.

17 Under the instructions, which is the last  
18 portion of the educational brochure, we give **step-by-**  
19 **step** instructions under number 13, how should I use  
20 it, and I'll make some further comments about that  
21 shortly. What should I do if I have questions about  
22 the Fungistat? It's basically, call your doctor or  
23 the toll free number. Then under other information  
24 it's simply active and inactive ingredient and some  
25 storage information.

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1           On the instructions, we basically needed to  
2 deal with the fact that for formulation of these  
3 products there's either the cream or ointment, or the  
4 insert and suppository, and then under the  
5 suppository, which is where your delivery system is  
6 really the administration device where there are some  
7 products with a disposable applicator, some with a  
8 **prefilled** applicator, and others with a reusable  
9 applicator, so we have specific instructions for each  
10 of those combinations. And, in addition, with the  
11 combo pack we have both the internal product and the  
12 external product.

13           We did have discussions about the actual  
14 illustrations to go with the instructions, and we had  
15 to make decisions about how many actual diagrams to  
16 use, which ones to use, and how to label the diagrams.  
17 Some of the discussions centered around, again, word  
18 choice and actually what to label, vaginal versus  
19 birth canal, should you label the bladder and rectum,  
20 use of return uterus versus womb, urethra versus  
21 urinary opening, and vulva versus vaginal opening.

22           Other decision points or issues with the  
23 instructions had to do with the actual insertion of  
24 the applicator, where we wanted to try to get the  
25 message to insert the medication or applicator as far

1 back in the vagina as possible, and as far as it would  
2 "comfortably" go. There's also decisions about the  
3 lying down or standing position for use of the  
4 applicator, and then finally we had to make decisions  
5 about the external cream and how much to use.

6 I thought it would be good to use a little  
7 dab for the medicine, but that's because I'm older and  
8 I come from the **Brylcream** age, and I don't know if  
9 **Brylcream** is still out there now. Then we switched  
10 over to a dime's worth, but we sort of thought that  
11 was a little bit on the cheap side, but we felt that  
12 maybe a quarter's worth was, perhaps, too expensive,  
13 so we finally settled on "a small amount." It is  
14 interesting, if you think about how do you want to  
15 tell a consumer how much of this external cream to  
16 use, believe me, we probably spent 20 minutes or a  
17 half an hour making a decision, finally coming up with  
18 a small amount.

19 The educational brochure is in a draft  
20 form, subject to changes today. We welcome advice  
21 from the Advisory committee, comments from the public,  
22 and general discussion.

23 And, with that, I conclude my talk, and  
24 thank you.

25 ACTING CHAIR BRASS: Thank you.

1 Are there questions for Doctor Davis? Yes.

2 DOCTOR RICE: I have a question, Doctor  
3 Brass.

4 Hi, **Roselyn** Rice, two simple questions.  
5 Because we are charged to look at topics, headings and  
6 the warnings, do you have any information on the  
7 typical woman who would be the de novo user, for  
8 example, is the trend of data going up in OTC use, and  
9 the second question, do you have any data on the  
10 proportion of women who actually look at the package  
11 insert?

12 DOCTOR DAVIS: In terms of the **over-the-**  
13 **counter** use, my understanding is, yes, that it's many  
14 more women are going to an OTC product for treating  
15 the vaginal yeast infections, if that was your  
16 question. But, in terms of -- the second component of  
17 the question was?

18 DOCTOR RICE: How many actually read the  
19 package insert?

20 DOCTOR DAVIS: I don't have data, and I'd  
21 have to ask Ling or Karen Lechter if we're really --  
22 because that concerns us, you know, we've spent a lot  
23 of time on having this great educational brochure, but  
24 if it's not read then, you know, who are we helping?

25 For the specific instructions, they are

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1 only really included in the insert. So, that would be  
2 one clear reason why women might need to really read  
3 that, and then the only reason would really just be  
4 for their interest and their self-motivation, to want  
5 to know more about the disease and the infection.

6 And, I wish we had good data, but I would  
7 honestly say we don't.

8 ACTING CHAIR BRASS: Additional questions?

9 Thank you.

10 At this time, we will take a break, and we  
11 will reconvene promptly at 10:40. Thank you.

12 (Whereupon, at 10:28 a.m., a recess until  
13 10:42 a.m.,)

14 ACTING CHAIR BRASS: Our next speaking is  
15 Doctor David Soper, from the Medical University of  
16 South Carolina, I'm speaking slowly so you can come up  
17 to the podium and while people sit down, who will be  
18 speaking on duration of treatment.

19 DOCTOR SOPER: Well, clearly, I'm not going  
20 to have 30 minutes of a presentation, because I  
21 actually didn't realize I had a formal part in this,  
22 but I am prepared.

23 What has happened in the antifungal market,  
24 obviously, is that pharmaceutical companies have  
25 decreased duration of therapy and made these agents

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1 more consumer friendly. And, the issue, I think,  
2 becomes is this a good thing, and does -- and I think  
3 FDA is interested in, is there a need to bias, if you  
4 will, consumers possibly towards a longer duration of  
5 therapy because of studies that have been performed  
6 that tend to suggest maybe that longer is better than  
7 shorter.

8 The issue, as has already been alluded to,  
9 is mainly a formulation one, and that is that single  
10 dose or short-course therapies deliver high  
11 concentrations of the antifungal to the vagina, which  
12 then remain and slowly deteriorate over time, but stay  
13 long enough so that equivalent efficacy rates have  
14 been absorbed, and I'll share this data with you in  
15 just a second.

16 Compared to standard sort of treatment that  
17 was used many years ago, or the seven days, the lower  
18 dose intravaginal agent, that has always been shown in  
19 most studies to be a bit better but not statistically  
20 so .

21 of the five NDAs that have come before FDA  
22 and looked at short-course therapy for vulvovaginal  
23 candidiasis, and, therefore, ten studies, in only two  
24 of those studies have the new agent shown -- actually,  
25 they all showed equivalence, but only in two studies

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1 did the new agent actually surpass the comparator with  
2 respect to average response, both combined efficacy  
3 and mycological cure.

4 Again, if you just look at NDA data, it  
5 would suggest that 80 percent of the time the new  
6 agent isn't going to quite measure up, if you will, to  
7 a standard seven-day regimen.

8 But, at this time if I could have my first  
9 overhead, what I'd like to do is just kind of review  
10 you Susan Reef's study, which was published in the  
11 American Journal of Obstetric and Gynecology, and  
12 essentially is a review of all the vaginal antifungal  
13 treatment studies up until that point in time. You  
14 can see on the left side of the slide is the agent,  
15 Clo being Clotrimazole, Ter being Terconazole, Tio  
16 being Tioconazole, and But being Butoconazole, and you  
17 can see that I've divided it on this presentation to  
18 single dose, to a three-day dose, we are going to go  
19 to another overhead in just a second that shows six to  
20 seven-day therapy and then 14-day therapy.

21 And, what I really want you to glean from  
22 these data, really, is nothing more than that there's  
23 a heck of a lot of overlap, that there really isn't a  
24 lot of difference between combined efficacies or  
25 mycological cures in looking at single-dose therapy

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1 versus three-day therapy, and the confidence intervals  
2 are substantial.

3 Again, this is the study that I think panel  
4 members have in their handout, in their preparatory  
5 information, and, again, **looking** at these agents, Mic  
6 being **Miconazole**, you can see that combined efficacy,  
7 which is the most rigorous of standards, it compares  
8 those patients, essentially, describes those patients  
9 as failures if they are culture negative but continue  
10 to have symptoms, or if they are symptom free and are  
11 culture positive, SO YOU would expect **combined**  
12 efficacy rates to be lower than mycological cure  
13 rates, compared to what we are used to looking at,  
14 which is clinical cure rates versus mycological cure  
15 rates, which you tend to have a higher clinical cure  
16 rate than you do a mycological cure rate.

17 Again, just comparing, you know, combined  
18 efficacy and mycological cure on the seven and 14-day  
19 therapy, you can see there's tremendous overlap.

20 And then lastly is just an easier way of  
21 looking at these data. This is hardly a **metanalysis**,  
22 but this is a way of looking at **these data** in a more  
23 organized fashion, and this, essentially, reflects  
24 weighted means, that is that if you look at the data  
25 that's in Susan's paper, and you add up all the

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'1 participants in these studies, and that you look at  
2 efficacy rates, both combined efficacy and mycological  
3 cure, what you find for single-dose therapy is around  
4 70 percent combined efficacy, three-day therapy about  
5 65 percent, six to seven-day therapy a little bit less  
6 than 70 percent, and 14-day therapy about 76 percent,  
7 so if you look at the three most commonly durations of  
8 treatment, the single, three-day and seven-day  
9 therapies, and the most commonly studied durations of  
10 therapy, you can see that there is a -- difference and  
11 certainly no statistical difference between those  
12 courses of treatment.

-- 13 If you carry therapy out to 14 days, you  
14 start showing some -- as you and I well know about  
15 compliance, is that there's few individuals that will  
16 actually probably use seven days worth of therapy,  
17 much less 14 days worth of therapy,

18 That really is my comments on duration of  
19 therapy. I actually have others I'd like to make, if  
20 the committee would like.

21 ACTING CHAIR BRASS: Please, as long as  
22 they are semi-relevant to the topic on the table.

23 DOCTOR SOPER: They are actually relevant  
24 in that what you've already covered is what should be  
25 included in the handout to the patient.

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1 My big concern with over-the-counter  
2 medications for vaginal candidiasis is clearly related  
3 to self-diagnosis. Despite somewhat varying data to  
4 suggest that patients can be good as self-diagnosis  
5 **vulvovaginal** candidiasis, all the new information in  
6 this arena suggests that actually they are pretty  
7 doggone lousy about it, and it's a real concern of  
8 mine that there really isn't strong enough language in  
9 the package insert to have patients self-assess for  
10 risk of STD.

11 We kind of dance around it a little bit.  
12 We talk a little bit about HIV. We talk about what I  
13 would consider more severe symptoms that would suggest  
14 a diagnosis of pelvic inflammatory disease, such as  
15 abdominal pain, nausea, vomiting and fever, but  
16 recognize that the vast majority of pelvic  
17 inflammatory disease in this country is not associated  
18 with any of those symptoms and, therefore, it's  
19 important for consumers, particularly women less than  
20 the age of 25, and all they have to do is ask  
21 themselves two questions, do they have multiple sexual  
22 partners, or do they have a new sexual partner. And,  
23 those patients are probably not good candidates for  
24 self-treatment because of a risk of **chlamydial**  
25 infection, which can be asymptomatic, and may be

1 responsible for a symptom of abnormal vaginal  
2 discharge without associated vulvar pyrites.

3 And SO, it would be my recommendation to  
4 FDA and to industry, is that you try to protect,  
5 particularly, adolescent women who are going to have  
6 poor access to health care, who are not going to be  
7 very good self-diagnosticians, not that older women  
8 are any better, because they are not, and that we put  
9 some language in the consumer handout so that patients  
10 can self-assess their risk for more run-of-the-mill  
11 STDs, which probably are associated with a lot more  
12 morbidity than in a numbers game related to HIV,

13 There is a recent abstract at the American  
14 College of OB/GYN meeting by Jandel Allan Davis that  
15 I would refer you to, and essentially in women that  
16 called in with a self-diagnosis there literally was no  
17 agreement between what they self-diagnosed and what  
18 was their final clinical diagnosis.

19 Thank you.

20 ACTING CHAIR BRASS: Thank you.

21 I have a couple of questions about the  
22 duration of treatment question. Are you aware of any  
23 data that would relate the duration of treatment to  
24 either adverse effect frequency or recurrence rates,  
25 such as 30 days after course of treatment?

1 DOCTOR SOPER: No, I'm not.

2 ACTING CHAIR BRASS: Are there other  
3 questions for Doctor Soper?

4 Doctor D'Agostino.

5 DOCTOR D'AGOSTINO: I'm not sure I  
6 understand how this gets played out in practice,  
7 though. If somebody goes for one of the one-day,  
8 three-day treatments, and they deem it not to be  
9 successful, do they jump on a seven-day treatment?  
10 How does it actually play out in practice?

11 DOCTOR SOPER: Well, the way it actually  
12 plays out in practice is, first of all, the three-day  
13 issue about the persistence of symptoms is generally  
14 not helpful, because the vaginal cream is still going  
15 to be there three days. And so, the patient pretty  
16 much is satisfied that even if her diagnosis is wrong  
17 that she's improved.

18 And, it adds an additional problem for the  
19 clinician, because when she presents for diagnosis you  
20 can't get it, because what you are looking at  
21 microscopically is vaginal cream or suppository, and  
22 that's also going to alter the other tests that are  
23 important in the diagnosis of vaginitis, which are pH  
24 and immune order.

25 so, I think what happens practically is, if

1 patient self-treat, they have the diagnosis wrong,  
2 they come to the clinician, the clinician does the  
3 best they can, and two things happen. They change  
4 antifungal therapies, because they think that the  
5 possibility of resistance is present, when it is,  
6 indeed, not the case, or they assume that the patient  
7 had a bacterial infection and they start the patient  
8 on antimicrobial.

9 So, this kind of falls back to the issue of  
10 self-diagnosis in the first place. This country is in  
11 tremendous need of products that women can self-  
12 diagnose reliably vaginitis if they are going to use  
13 over-the-counter medications. I always find it kind  
14 of interesting, as I was talking in the back of the  
15 room, that we draw these diagrams on these product  
16 inserts because we think that women don't know where  
17 their vaginas are. Well, you know, women know exactly  
18 where their vaginas are, and they are used to putting  
19 tampons there, and they are used to putting penis'  
20 there, and there is actually, again, tremendous need  
21 for women to be able to do self-sampling of vaginal  
22 secretions, put that on, you know, something to allow  
23 them to have an accurate diagnosis, and then they can  
24 go and use an over-the-counter medication that would  
25 be much more specific than guessing.

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1 ACTING CHAIR BRASS: Yes.

2 DOCTOR SACHS: I guess a couple, there were  
3 actually two recent tests done on self-sampling of  
4 **chlamydia** and gonorrhoea in adolescent patients, and,  
5 you know, most of the women tested were between the  
6 ages of 15 and 25, very successful, and there are some  
7 new urine screens for gonorrhoea and **chlamydia** as well.

8 ACTING CHAIR BRASS: Other questions?  
9 Please.

10 DOCTOR LEWIS: I was just going to make a  
11 comment that it's not just patient misdiagnosis,  
12 because I think that a lot of patients are, perhaps,  
13 enrolled in health plans where they are required to  
14 call a nurse who may ask two or three questions and  
15 then tell the patient, try this product for a few days  
16 and call me if you don't get better. And, it's true,  
17 there's also a reassuring factor there too, I used  
18 this for a few days and seemed to get a little better,  
19 and, you know, even if it isn't the right diagnosis a  
20 lot of people will be partly treated, or improperly  
21 treated.

22 ACTING CHAIR BRASS: Yes.

23 DOCTOR DAVIS: I would just like to make a  
24 comment that would reinforce Doctor Soper's concerns  
25 about PID and the mild symptoms in PID. Literally, in

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1 this week's New England Journal of Medicine, there's  
2 a major article about chlamydia. I believe the study  
3 was 13,000 female military recruits into the U.S.  
4 Army, ages, whatever, 18 to about 25 predominantly,  
5 and the incidence of chlamydia, I think it was under  
6 ten percent, but it was like 9.2 or seven, but this  
7 was, basically, many, many, many of these women were  
8 asymptomatic, but should be treated to prevent the  
9 complications of the PID, the ectopics, the  
10 infertility.

11 so, it's a significant concern, and I'm  
12 glad that he brought it up.

13 ACTING CHAIR BRASS: I think that's  
14 absolutely right, but the issue is whether or not in  
15 an asymptomatic problem, whether the use of  
16 antifungal in any way complicates that issue at all.

17 So, I think the data you cite is extremely  
18 important from a public health standpoint, but how  
19 that interplays with individual consumers delaying  
20 treatment or not is the relevant concept here.

21 DOCTOR SOPER: I guess I'd argue that these  
22 are not asymptomatic patients if they are coming to  
23 the store to buy a product to relieve their symptoms.

24 ACTING CHAIR BRASS: Oh, no, I agree with  
25 that, but I'm saying that the 90 percent incidence

1 figure is not representative of the users of this  
2 population, or only to the degree that they are  
3 overlapping populations.

4 Other questions?

5 Our next speaker is Doctor William Soiler,  
6 who is Senior Vice President, Director of Science and  
7 Technology, Nonprescription Drug Manufacturers  
8 Association, who always bears gifts.

9 DOCTOR SOLLER: Could I ask the audio/video  
10 gentlemen, do we have a pointer or not? Okay, well,  
11 I'll do my best to describe.

12 Good morning, Mr. Chairman, members of the  
13 Committee, I'm Doctor Bill Soiler, I'm Senior Vice  
14 President and Director of Science and Technology for  
15 the Nonprescription Drug Manufacturers Association.  
16 NDMA is a 117-year old trade organization representing  
17 the manufacturers and distributors of nonprescription  
18 medicines by sales. Our members represent over 95  
19 percent of the OTC marketplace.

20 Our Vaginal Antifungal Task Group is  
21 comprised of members that market all of the national  
22 brand OTC vaginal antifungal products and a  
23 substantial number of the store brand or generic  
24 products in this category, and I'm here to provide  
25 NDMA's comments on FDA's proposed labeling guidance on

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1 OTC antifungal drug products.

2 What I'd like to do before getting to my  
3 outline on the second page is to answer a question  
4 first, if I could, follow up on Doctor **Gilliam** in your  
5 comments earlier, in general, on the labeling rule.  
6 You'll see as we get into these comments, and in the  
7 materials that were sent to you ahead of time, and  
8 it's in the blue-backed material and I hope you have  
9 those handy, because I will be referring to the  
10 Appendix A and the Appendix B, but I would like to  
11 have a general comment on FDA's labeling proposal and,  
12 specifically, the comment on the two-year or **three-**  
13 year implementation period.

14 We've asked for a three-year implementation  
15 period, and the question was, even on the two year  
16 that was talked about why such a long period, and I'd  
17 like to tell you. It's important to take a  
18 perspective on this. All the information that is  
19 required to be on the label for safe and effective use  
20 is there. Many, many of the label comprehension  
21 studies that were done on RX to OTC switch looked at  
22 paragraph format against the outline format and found  
23 that they were essentially comparable in terms of  
24 intent to heed. That's not to say we are not 100  
25 percent behind this proposal. You' ll see from our

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1 remarks, I hope when you reviewed our materials, you  
2 will understand that we are 100 percent behind making  
3 labels more consumer friendly, but we don't think  
4 there is a need to burn labels.

5 Let me provide a perspective on this. This  
6 is the largest change in labeling history, it's the  
7 largest change worldwide in label history at one time  
8 ever. Never have 300,000 SKU, shelf-keeping units,  
9 had to be changed in a specified period time. Keep  
10 that in mind.

11 Our companies are downsizing. We are asked  
12 to do more with less, and this will swamp resources,  
13 it is a guarantee. When you think about the labeling  
14 process itself, there are two basic elements, there's  
15 design and there's copy. That first draft, and what  
16 you are seeing are basically first drafts of labels in  
17 everything you've seen, has to be reviewed by  
18 marketing, legal, regulatory, a number of different  
19 elements within the company, and that process has to  
20 be repeated multiple times as we go down the sequence.  
21 There are lead times for getting the printing plates,  
22 or cylinders, or silk screens, they vary, and it's not  
23 necessarily -- we have concern, it's not necessarily  
24 a guarantee that when we order these particular plates  
25 in such a massive change that we necessarily will get

1 the same kind of return time from the vendors in terms  
2 of the basic printing materials. We don't know that.

3 Once the proofs are made, they come back to  
4 the company. We may have to go into a second round of  
5 printing because there are problems with that, or  
6 maybe there was a problem with the plate and we have  
7 to go into a full reproduction cycle of that plate.  
8 All of this has to be tested, and reviewed and looked  
9 it, and it's important, once all that is done, that we  
10 schedule that into the production process itself,  
11 remembering that some of these plants are making  
12 prescription drugs as well as OTC drugs. And, it's  
13 not always a guarantee that you could outside  
14 contract, because everybody will be thinking about  
15 outside contracting in this kind of situation.

16 And, I think simply stated, given the size  
17 and magnitude of this change, which, by the way, we  
18 are behind 100 percent, that we don't think that FDA's  
19 typical time of about two years is a fit for this  
20 situation. We think three years is a better fit,  
21 certainly for smaller companies that have label stock  
22 that will go out over three years sometimes in terms  
23 of the printing cycles for the small companies, that  
24 three year, they still would probably have to destroy  
25 some of the label, and for a company of that size

1 destroying \$25,000.00 worth of label is a major  
2 economic hardship. But, for the larger companies, the  
3 issue is resource, and the issue is thinking about a  
4 regulatory department and a product development  
5 department, and I came out of a company environment  
6 like that, is that you don't want a mistake to happen.  
7 And, given what we are trying to accomplish here, and  
8 what we need to do in order to have the consumer have  
9 a consumer friendly label, and we want that to happen,  
10 and, by the way, many of our companies are -- they are  
11 trying to get ahead of the game, they are trying to  
12 make these label changes already on non-NDA'd as well  
13 as NDA products, to improve the consumer friendly  
14 style, but those still will have to be changed. They  
15 are trying to train the personnel to make those  
16 changes when this final rate comes down. But, even  
17 so, there's no reason that we can't build in some kind  
18 of lead time, and lead time is the wrong term, some  
19 kind of time in here so that when mistakes happen, and  
20 invariably they will happen in such a complicated  
21 process, that when they happen there's time for a  
22 company to recoup and not have to petition the Agency  
23 and say, I need extra time in this particular area.

24 I think with the Agency's resources, you  
25 don't need that extra paper work, given the public

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1 health perspective on this, there doesn't need to be  
2 an overnight introduction of these particular labels,  
3 and we ought to see, knowing that this industry with  
4 an eight year history in label readability that I'll  
5 comment on momentarily, wants to have this happen and  
6 will likely in many cases get in there well before  
7 even a two-year time frame with some of the products,  
8 that we can't simply say, three years in terms of  
9 factory shipment is what will work and work very well,  
10 I think, in the partnership role that we've had so  
11 far.

12 so, long answer, but it's a very, very  
13 serious issue for us, and one that is in our 80  
14 companies that are representing 95 percent of the  
15 market that we have surveyed multiple times on how  
16 this proposal fits, what it would do to your  
17 production facilities and so on. We need three years.

18 DOCTOR GILLIAM: That said, my comment  
19 would be that, you know --

20 ACTING CHAIR BRASS: If we can hold off.

21 DOCTOR SOLLER : Okay, let's return to that  
22 if we need to.

23 Now, for the comments per se, and I have a  
24 laser here, the outline of my initial comments will  
25 talk about our general support for what FDA is doing,

1 our recommendation vis-à-vis our label readability  
2 guidelines that appear as Appendix B in the materials  
3 we sent you, specific comments on the carton and  
4 educational brochure, and per a discussion with Doctor  
5 Brass earlier I'll try and highlight some of the areas  
6 that, perhaps, are less refinements and more major  
7 issues for discussion as we go along, and then a  
8 summary.

9 The purpose of today's meeting is to review  
10 FDA's proposed labeling guidance, which is the first  
11 step in the Agency's initiative to take up OTC  
12 labeling of NDA'd OTCs, making them easier to read,  
13 more consumer friendly, and consistent across each OTC  
14 drug class. H<sub>2</sub>S may be next, I don't know which NDA  
15 may be next in front of an Advisory Committee, but, in  
16 general, making this consistency happen is something  
17 this Association, the members of our Association  
18 strongly support.

19 NDMA has had a long history of interest in  
20 improvement to the readability of OTC labels to make  
21 them more consumer friendly. Our commitment stretches  
22 back to the 1990 time frame with the senior citizens  
23 of California that helped us actually develop our  
24 voluntary program on label readability that was  
25 adopted in 1991. And, since that time, in roughly the

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1 two to three years post 1991 we changed over 37,000  
2 linear miles of labeling, all at the interest to make  
3 them more consumer friendly.

4 FDA , on many occasions, has endorsed our  
5 voluntary program in a variety of OTC review  
6 rulemakings, and we are gratified by that, we think  
7 they are good guidelines in terms of forming a  
8 perspective on this particular issue, but we knew when  
9 we adopted them, as we know now, that FDA action is  
10 needed for regulatory changes that will allow us to  
11 now change the content and change the format in a more  
12 specific way, and that's what you've seen presented  
13 today by FDA people.

14 Just a comment on Appendix B to our  
15 comments, the label readability guidelines, they  
16 provide an overview of the elements of good label  
17 readability. We are thinking of getting into a second  
18 edition of these that would also look at the low  
19 comprehension types of issues that were presented  
20 earlier by Karen Lechter. We'll talk about the  
21 principles of label readability and no single factor  
22 by itself can determine that readability, and then the  
23 various design factors from bullets, to white space,  
24 and all of that is being discussed today.

25 so, our recommendation, Mr. Chairman, to

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1 FDA is that when FDA now prepares these NDA label  
2 guidances for NDA'd OTC drugs, that they incorporate  
3 by reference our label readability guidelines. We  
4 think that this would be consistent with FDA's past  
5 endorsements, but more importantly for new people  
6 coming in to companies and looking at categories, and  
7 saying what has FDA done, and we try to reach out to  
8 them as well, I think these guidelines form the kind  
9 of perspective that can be helpful in having them  
10 think about label readability.

11 Remember, it's not just content and format,  
12 it can be the nature of the paper, the amount of  
13 bright that is bounced back to the eye, and a host of  
14 other factors that we're not even considering today,  
15 the kinds of issues that we bring forth in our label  
16 guidelines.

17 I'd like to turn now to a consideration of  
18 our model carton label and first give some background,  
19 the model carton label that FDA has proposed. FDA's  
20 label initiative started in 1993, Doctor Mike  
21 Weintraub called us up and said, "I'd like to talk  
22 about labeling."

23 And we said "Great, what part?"

24 And he said, "Everything."

25 And so, he came down to NDMA headquarters

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1 and that initiated a process of dialogue and  
2 communication with the Agency, a number of written and  
3 oral comments in the 1993 to '98 time frame, our most  
4 recent ones going in in July, including a presentation  
5 to NDAC which occurred last July 14th.

6 Many of the elements in our proposal to FDA  
7 are found in FDA's February 27th proposal that was  
8 reviewed earlier this morning, and they are in FDA's  
9 proposed labeling guidance for OTC Vaginal Antifungal  
10 Drug Products, that is the carton label that we are  
11 talking about.

12 These elements include a standard order of  
13 information and major headings, active ingredient and  
14 purpose, followed by uses, warnings, directions, other  
15 information and inactive ingredients, uniform warning  
16 subheadings, creating logical flow of information that  
17 starts with absolute contraindications, do not use,  
18 relative contraindications, ask a doctor before use,  
19 and then in use precautions, when using this, stop  
20 use, ask a doctor with, all with relative phrases that  
21 would appear under the warning subheadings or  
22 elsewhere in the label.

23 Now , this is the annotated label that  
24 appears on page ten of the handout, or as the first  
25 page of Appendix A in the materials that we sent you.

1 Those that want the color version look at the  
2 materials that we sent you. The black and white is in  
3 the handouts, and I'll be referring to this as we go  
4 through and speak to different sections and I'll pull  
5 that out separately in the slide for each of the major  
6 points.

7 By way of overview, we agreed basically  
8 with FDA's proposal in terms of the order of  
9 information, the major headings, the warning  
10 subheadings. We think that as FDA has presented it in  
11 its guideline with a box around the label that that's  
12 not needed when you consider a carton, that  
13 effectively that edge of the carton represents a box,  
14 we think that might have been an artistic rendition in  
15 the guidance. If it's not, we entered the comment  
16 that we don't think a special box around this adds  
17 anything, it only takes space away, and so we would  
18 recommend that that not be the case.

19 FDA has not made any comment in this  
20 guidance about type font, that will be made in FDA's  
21 proposal that will then be finalized we hear soon, but  
22 we would recommend that it be any sans serif type, not  
23 serif. This is sans serif type face, you'll notice  
24 there are not tiny serifs or little doodads at the end  
25 of and in corners of each of the letters. And, the

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1 reason you have serif is that in the larger fonts,  
2 when you are reading a word those serifs help you  
3 convey from letter to letter as you go through and  
4 capture that word in an image, but when you go to  
5 smaller type sizes, when you have those serifs they  
6 start having those letters blur together. And so,  
7 it's important to have sans serif. You'll note that  
8 the FDA guidance, the carton was printed in serif, we  
9 would recommend and make the point again that sans  
10 serif is preferred.

11 We also have a number of specific comments  
12 and refinements, and what I'm going to do is now go  
13 through that annotated label, pulling out separate  
14 sections one at a time.

15 First, on active ingredient and purpose, we  
16 support the use of the term "vaginal antifungal" as it  
17 would relate to this entire category. Second, we  
18 think that with replacing treat with cure most is  
19 appropriate. **Dawlings** defines cure as a successful  
20 treatment of a disease or wound, and in the topical  
21 **dermatologic** area, think athlete's foot, jock itch,  
22 ringworm that's covered under an OTC monograph, the  
23 verb cure is an allowed indication for those  
24 particular products, so it is consistent with other  
25 OTC labeling.

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1           In addition, we suggest that repeat be  
2 deleted. We think that's awkward. We think, just our  
3 group sitting around the table, and I know everybody  
4 can come up with a different opinion on it, but  
5 collectively that seems like a very awkward phrase.  
6 It's actually used as the term "repeated" in the  
7 brochure, not necessarily a problem there, but not  
8 quite a fit here. And, more importantly, when you  
9 think about it, the term "repeat" doesn't really fit  
10 for a first-time user.

11           Now, I know there were some questions about  
12 first-time users, but that's why we think adding an  
13 additional use precaution here, and I'll get to that  
14 in a moment, in addition with a revision of what FDA  
15 has proposed may help get around some of the concerns  
16 this morning.

17           The point that I'd like to make next  
18 relates to this use precaution, and use precaution, I  
19 think this is the first time it's probably been used  
20 publicly as a new term. I distinguish that from the  
21 in use precautions that appear as warning subheadings,  
22 but, clearly, we need some kind of nomer for placing  
23 something other than a short uses nomer within uses,  
24 and so we are calling these use precautions. We think  
25 it's more logical to have those use precautions follow

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1 the bulleted phrase "use," we think consumers look to  
2 see what the product is for, and then logically look  
3 down to say, what do I need to know about this  
4 particular product.

5           Importantly, by moving this from the first  
6 bullet here down into this particular area, we are  
7 suggesting a revision of this, "See your doctor" is  
8 FDA ' S version, we suggest starting with the  
9 conditional and highlighting that in bullet so it  
10 sticks out. And, when you see it on a label, and you  
11 look down under uses, actually, it creates curiosity  
12 and moves the eye to that particular bold, and that's  
13 one of the reasons why we think it's important to have  
14 it there. If this is the first time you have vaginal  
15 itching and discomfort, see your doctor, find out if  
16 you have a yeast infection, we think vaginal is  
17 superfluous here.

18           And then, a second use precaution that now  
19 occurs on the labels, but is not in FDA's proposal, is  
20 if you have had a doctor diagnose a vaginal yeast  
21 infection before and have the same symptoms now, use  
22 that dosage form as directed. We think that's an  
23 important direction, use precaution for the user that  
24 may have had an infection previously.

25           Turning to warnings, several points here.

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1 We've made the point for dermatologics in our comments  
2 on FDA 'S proposed rule that for a topical  
3 dermatologic, for example, it should say for external  
4 use, and that that should be allowed to be stated on  
5 the same line optionally with warnings. Our reason is  
6 simply a space consideration. We don't think it has to  
7 necessarily fit underneath, but that we should be  
8 given the option to put it up top here, and  
9 recognizing that there are products that are  
10 combination products with external and internal use we  
11 are suggesting for vaginal and external vaginal use  
12 only, and FDA uses this term "external vaginal" in the  
13 educational brochure.

14 The second major point here is that we are  
15 suggesting that this special warning or specialty  
16 warning about condom and diaphragm use, that that be  
17 placed under, logically, the in use precautions here,  
18 and that in addition it be highlighted across, it  
19 would be the only one as a full phrase here that would  
20 be highlighted, again, making it stick out ,  
21 particularly, in the label that has quite a number of  
22 spots where you have white space and allows things to  
23 punch out. It's also logical to have this particular  
24 placement in juxtaposition, do not have vaginal  
25 intercourse or whatever the other phraseology might be

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1 for that particular phrase.

2 We are suggesting that here vaginal be  
3 placed before foul smelling, but I would say, if you  
4 look at the warnings this particular issue of being  
5 able to put it on the same line is very important for  
6 us, in terms of making this fit on the label, and the  
7 second issue, Doctor Brass, further to you comments to  
8 me earlier, would be the placement of the  
9 condom/diaphragm warning highlighted in this  
10 particular position.

11 On directions, I hope these are considered  
12 housekeeping points. We think deleting education and  
13 information just makes a simpler phrase, before using  
14 Fungistat-X read the enclosed brochure for complete  
15 instructions, we think the others are superfluous. We  
16 agree that there should be a short and much shortened  
17 version of directions on the package carton itself and  
18 a more detailed description within the educational  
19 brochure. We probably wouldn't be able to fit on the  
20 outside carton very detailed instructions and  
21 diagrams, just from a space standpoint, so we agree  
22 with FDA's approach here. And, what we've added here  
23 is a suggested language, which we are merely  
24 suggesting, but it's the intent that I'm trying to get  
25 at that FDA, when you issue these guidelines, issue it

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1 for, not only the internal product, but a version that  
2 would be the internal and external product, that will  
3 make it much easier for the regulatory and legal  
4 managers within our companies when they are trying to  
5 interface with FDA on what that labeling might be. It  
6 provides more specific information.

7 Relative to the toll free number and other  
8 information in terms of storage, we would basically  
9 leave that blank, put it in brackets. The differences  
10 in the nature of the stability on these different  
11 products varies, that will be worked out when the  
12 company goes into FDA and specifying exact  
13 temperatures and so on is done, probably would not be  
14 all that helpful.

15 Secondly, in terms of the toll free number,  
16 we are suggesting it be 1-8XX, the reason being that  
17 there are -- 800 is not the sole province of toll free  
18 in terms of the exchange, it's 888, and other numbers  
19 probably will come along, but importantly, deleting  
20 the number of hours of operation. We think it's a  
21 disincentive to call when you put the hours of  
22 operation on, and as a practical matter a number of  
23 these 1-800 or toll free systems usually have some  
24 sort of electronic menu that will move you into a  
25 situation that you might actually say this is a

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1 medical emergency and you could hit that particular  
2 button and it's likely that you would get a voice in  
3 many of these particular systems. So, an hour of  
4 operation that's defined by a customer server that is  
5 there to ask general questions, versus medical  
6 emergency, doesn't quite make sense, and some of these  
7 numbers, obviously, have full 24-hour service.

8 so, if we look on page 16 and 17 of the  
9 handouts, or the second and third page of Appendix A,  
10 you'll see what I think represents a very nice, clean  
11 type of label. We've marked it up here with our  
12 recommended changes, and you'll notice that on page 16  
13 it's for the internal and external, i.e., the  
14 combination product, and for page 17, it's without  
15 external vaginal use directions, and we suggest to FDA  
16 that they place both types of model cartons into the  
17 guidance, that will make it easier as new people come  
18 into the companies and have to access these guidelines  
19 and then use them.

20 Now, yes, we have test driven this. This  
21 is a package that, as you can see here where the  
22 pointer is on the slide, that will be basically the  
23 carton, and what appears here is called a fifth panel  
24 or a riser card. And, when you have this kind of  
25 construct and quite a number of the national brands

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1 do, not all of them, certainly most of the generics do  
2 not, it is a rather easy fit with what appears to be  
3 some extra spacing in here between the lines, but this  
4 is done to scale and that's what it would basically  
5 look like in terms of what we have proposed to FDA.

6 I will mention, though, if you look up here  
7 on a couple of generic products, again, they don't  
8 have that riser card and it will be a much tighter fit  
9 in terms of trying to get this information located and  
10 may even require a wrapping of information into a side  
11 panel, so it will not necessarily look as clean as  
12 that riser card presentation.

13 I'd like to turn to a couple of comments on  
14 the model consumer education brochure. We basically  
15 support the layout and the guidance regarding the type  
16 of questions that might be included in the educational  
17 brochure and the Q&A type of format. Our comments  
18 relate to, first, when referring to the educational  
19 brochure, and this is not the title of it, titling it  
20 as the educational brochure makes sense, but when  
21 referring to it in the guidance itself we think this  
22 is a consumer education brochure, not a patient  
23 education brochure. We know that the individual  
24 should be seeing the physician the first time as a  
25 patient, but, ultimately, as there would be recurrent

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1 infections, this is a consumer kind of issue and that,  
2 I think, places the right kind of perspective, both  
3 within FDA and the companies as to who we are trying  
4 to speak to.

5 Secondly, relative to diagrams, FDA  
6 suggests two diagrams in the directions section. We  
7 think a mid-plane **sagittal view** is sufficient, and  
8 that one diagram should be required by FDA with the  
9 option of -- other diagrams, here as we lay it out, it  
10 just appears to us that less is more. You start  
11 getting too many diagrams and that actually can get  
12 confusing, we should be orienting them to one visual  
13 depiction of what we are talking about.

14 And, the second relates to using an arrow  
15 and not an X, and here FDA has, on page 16, stated,  
16 "Place an X over the urinary opening and rectum to  
17 indicate where the applicator should not be inserted, "  
18 and we suggest not using an X to mark where the  
19 product should not be inserted. I think it's in our  
20 lexicon that X marks the spot, that's a targeted kind  
21 of concept that we have, and we suggest that use of  
22 arrows would likely be a clearer way to do that.

23 So, with that, we have general support for  
24 updating the NDA'd OTC vaginal antifungal drug product  
25 labeling and other NDA labeling. The basic elements

1 of the proposed labeling we support, and we recommend  
2 a number of refinements to the proposed model carton  
3 label and consumer educational brochure.

4 Now, with that, what I would like to do is  
5 to turn to some brief comments that relate to the  
6 first question before you and, frankly, my preference  
7 would be not to have to make these comments, but since  
8 that question is before you, as our task group feels  
9 and as I feel, it's important for you to hear what the  
10 industry's position is with respect to what was  
11 presented in the materials sent to you, and I'm  
12 talking about, basically, that one page table that you  
13 saw with the confidence limits that were cited on the  
14 right-hand side of that table, basically, pulling five  
15 NDAs and 11 studies.

16 FDA's conclusion that was shared to us  
17 prior to the meeting, and here at the meeting as well,  
18 was that they had a general impression about the  
19 results and were concerned, and we seriously question  
20 the view that a general impression can or should be  
21 used to define OTC uses, directions, warnings,  
22 precautions or claims on labels. We think if this  
23 would have happened a very unfortunate precedent could  
24 occur.

25 That said, the issue rests, we think, on a

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1 determination as to what types of data are needed to  
2 support OTC labeled statements, what types of data?  
3 Is it sufficient that the information be based on a  
4 general impression of a retrospective reanalysis of  
5 data, or should the information really be held to a  
6 more rigorous standard? Most often, as it relates to  
7 OTC labeling, it is the latter.

8 Our discomfort with the use of  
9 retrospective reanalysis stems from the consideration  
10 of what information might be missing, the inherent  
11 variability of the available data, questions about the  
12 impact of some variables that may not have been  
13 considered, and what may be a dual standard, we hope  
14 that's not the case, in terms of the kind of  
15 information that FDA might put on the label versus  
16 what standard they would have for companies when they  
17 asked to put information on **NDA** labeling.

18 If you look at the '98 orange book, which  
19 has the list of approved products, we know that there  
20 are 23 approved drug applications, 13 **NDAs**, and ten  
21 **ANDAs**. The one-page overview talks about five of  
22 those **NDAs**. The 23 **NDAs** probably have well over 30  
23 trials involved in them. The five **NDAs** have about 11,  
24 so our concern is about the missing information.

25 And, even though some of these studies

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1 might be performed using the same protocols, I know  
2 from my experience in clinical work within the  
3 companies and our task groups that even executing the  
4 same protocols at different sites, different  
5 investigators, different monitors can cause -- and  
6 even by chance -- can cause slightly different  
7 changes. And, when you get to analysis, what you  
8 choose to be in the analysis, what you choose to be  
9 outside the analysis also can have very subtle  
10 effects, and even by chance appear to be systematic  
11 effects within those kinds of -- type of  
12 interpretations.

13 I'd like to add that we know from some of  
14 the companies in our task group, and we also heard  
15 today, that the rates given in the reanalysis are not  
16 the same rates calculated in the companies' analysis,  
17 and in reviewing some of the numbers just this morning  
18 with an individual that is very familiar with his  
19 company's clinical data, there are some 30 patients  
20 and various arms that are missing from some of the  
21 information that was cited, and that's disquieting to  
22 us, frankly.

23 Furthermore, if we were to assume, for the  
24 sake of argument, that there is this effect, and,  
25 Doctor Soper, notwithstanding your comments, but let's

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1 just assume this for the sake of argument, there's an  
2 additional policy issue as an industry that we are  
3 affected with and may not necessarily be the kind of  
4 thing that an advisory committee would look at, but  
5 let me share that, and that is that when you start to  
6 try and fiddle with the words that would sum up that  
7 assumption, and let's use FDA's words, longer  
8 durations, produce best results if all the medicine is  
9 taken correctly, that translate into a superiority  
10 claim. Implicitly or explicitly that is a superiority  
11 claim.

12 And, in numerous instances, as FDA, in  
13 advisory committees and elsewhere, and one that comes  
14 to mind is Janet Woodcock, who heads up the Center at  
15 the Arthritis Advisory Committee in February, '97,  
16 said that basically when you are dealing with these  
17 types of comparative claims the standard that FDA has  
18 for companies are two clinical trials head to head  
19 with both showing superiority. And, we don't think a  
20 general impression about data, Doctor Soper,  
21 notwithstanding your comments, but under this  
22 assumption we don't think that a general impression is  
23 something that translates into something that's  
24 consistent with FDA's policy.

25 And, the types of questions, frankly, that

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1 were going around our task group was, is FDA holding  
2 itself to a different standard than they hold us, and  
3 that's how we looked at what was happening from this  
4 type of issue, that, again, in an implicit or explicit  
5 way would likely create a superiority claim.

6 Now, a brief comment here relative to the  
7 amount of material that we were given and as a general  
8 point, we think that it would have been helpful if  
9 there had been more information, more of an analysis,  
10 and we don't know whether that's the case or not, but,  
11 again, I'll make an assumption that there is a written  
12 analysis that has been prepared that got to the point  
13 where FDA would ask you to answer that first question.  
14 We think that analysis should have been shared with us  
15 well in advance of the meeting, so that we could react  
16 to it and provide the kind of meaningful dialogue, as  
17 we get into an afternoon discussion that we would  
18 really like to give.

19 That hasn't happened, it's disturbing to  
20 us, and, again, one that I think we would have been  
21 helped by having a little bit more information.

22 So, in sum on this point, we believe that  
23 it's ill-advised to support a view that a general  
24 impression is sufficient to be the basis for OTC  
25 directions, OTC precautions, warnings or claims on NDA

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1 products. We think if that would have happened it  
2 would be an unfortunate precedent that could be  
3 established.

4 We think that OTC required labeling should  
5 be established through a rigorous process that ensures  
6 that label statements are scientifically documented,  
7 clinically significant and important for the safe and  
8 effective use of the product by the consumer, and  
9 overall, I think that's FDA's view as well, at least  
10 that's been my experience in this field.

11 We think that required labeling should be  
12 consistent with the CDER Drug Review Policy, think the  
13 superiority policy aspect, superiority claim policy  
14 aspect of this, and undertaken through the due process  
15 procedure that allows all the interested parties an  
16 opportunity to evaluate what analysis actually goes  
17 into this.

18 And, it's important when you start talking  
19 about trends in data, that you look at the inclusion  
20 and exclusion types of considerations that are going  
21 on.

22 So, Mr. Chairman, to FDA we would ask that  
23 you not ask the committee to translate the reanalysis  
24 into label language, that if you choose to create  
25 labeling based on that reanalysis, that you provide

1 that reanalysis for open public comment for, perhaps,  
2 a specified period of 90 days after this meeting, we  
3 think that would be important, and then clearly  
4 overall, it would help us if there was a general CDER  
5 policy that in working with advisory committees that  
6 when these kinds of medical reviews are undertaken and  
7 are presented to the committee that there's sufficient  
8 time for all interested parties to be able to have a  
9 chance to react to it.

10           Parenthetically, Linda, I will hand you  
11 copy of our comments and if you could place them in  
12 the docket I would appreciate it.

13           Well, let's go back to the first issue.  
14 This is our test-driven model of the carton label that  
15 FDA has proposed and has the refinements that we're  
16 suggesting, shown to you just previously.

17           And, what I have done here is to insert  
18 something that you haven't seen. This is Table 14 of  
19 the overheads. In thinking about this late yesterday  
20 afternoon when we got together to prepare for this  
21 meeting one last time, it occurred to us that as we  
22 looked at this that the labeling on the carton, and we  
23 know that some of the products at least have words to  
24 this effect, I'm not tied, and our committee is not  
25 tied to the specific words here, think the intent. We

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1 think it would be helpful that under directions that  
2 placing some sort of highlighted statement, whether  
3 it's important or not, but something that sticks out  
4 on the label that says, in order -- and we're not  
5 necessarily suggesting italics, that's harder to read,  
6 we used italic in our draft formats to show new  
7 wording, and that's why there are italics here, but a  
8 bold face sans serif type without italics is what we  
9 would be talking about -- important in order to kill  
10 these completely you must use the product the full X  
11 days, even if your symptoms are relieved sooner. And,  
12 I hope that, notwithstanding my immediately prior  
13 comments relative to the duration of use issue, that  
14 you can see that the particular task group that you  
15 are dealing with at NDMA is one that is willing to  
16 continually revise its thinking and try and think of  
17 the kind of language that would be important to be on  
18 the carton label for the consumer.

19 And, with that, Mr. Chairman, I thank you,  
20 and I'm happy to answer questions.

21 ACTING CHAIR BRAS S : Thank you.

22 Are there any specific questions or  
23 clarifications for Doctor Soiler? Beth.

24 MS . SLINGLUFF: Bearing in mind your  
25 comments about rich protected data, nevertheless, the

1 cartons here already display 800 numbers. I was  
2 wondering if you had ever collected any information or  
3 summarized it in any way about the kinds of questions  
4 you get from consumers now that would indicate  
5 problems that currently exist with labeling or  
6 information brochures that would suggest that needs  
7 fixed.

8 DOCTOR SOLLER: Beth, that's a great idea.  
9 No, I don't have that to present. It's quite possible  
10 that companies have done this, and I can tell you that  
11 in the initial development of these particular  
12 products that quite a lot of market research was done  
13 to fit in consumers' perspectives about what the  
14 labeling would say and product presentation and so on.

15 I would just add to anybody in our task  
16 group who is in the audience, raise your hand if you  
17 have any additional comments, but I think that's a  
18 great idea, and what I can promise is to pass that on  
19 to our task group in general, and it's probably a  
20 broader issue that affects other categories as well,  
21 and that makes -- that would be an interesting study.

22 ACTING CHAIR BRASS: Yes.

23 MS. NARRIGAN: I was interested in the use  
24 of the phrase "test driven, " related to this. Can you  
25 tell us what you mean by test driving it?

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1 DOCTOR SOLLER: Yes. I'm not talking about  
2 all the comprehension study, I'm saying test driven  
3 just to see if it fits.

4 MS. NARRIGAN: Fits the --

5 DOCTOR SOLLER: And, I will tell you that  
6 that is a major issue in this overall undertaking. We  
7 have 80 label coordinators, one for each of our  
8 companies, and all of them have been involved in the  
9 general OTC labeling rule. I'd say well over 50  
10 percent, maybe 60-70 percent, have test driven most of  
11 their products with FDA's original proposal, just to  
12 see if in that first drafting phase the requirement  
13 can actually fit on packaging.

14 The reason that's important, why we do test  
15 driving, and why we think it's important to show  
16 what's come up that doesn't involve packaging changes,  
17 that it changes the whole perspective in terms of how  
18 quickly it can be done and other things. And, all I  
19 meant to say is, it seems to be a fit.

20 MS. NARRIGAN: And, the second question,  
21 did you include a sample of your suggested consumer  
22 brochure? Am I missing it, or you didn't actually --

23 DOCTOR SOLLER: No, we thought FDA did such  
24 a great job, and we really didn't have a whole lot to  
25 say about it.

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1 MS . NARRIGAN: Oh, I see, okay.

2 DOCTOR SOLLER : And, in talking with Debbie  
3 Bowen about this before the meeting, she couldn't  
4 believe it, but I think FDA has done a great job in  
5 preparing the guidance overall.

6 I think there are some important issues for  
7 us in this, but by and large we are not talking about  
8 major overhauls, we are talking about two groups that  
9 are very close together.

10 MS. NARRIGAN: Thanks.

11 ACTING CHAIR BRASS: Other questions.

12 Doctor Gilliam.

13 DOCTOR GILLIAM : You still haven' t  
14 convinced me on the two-year thing.

15 DOCTOR SOLLER: Want to visit a company?

16 DOCTOR GILLIAM: I think there's something  
17 that's --

18 DOCTOR SOLLER: I'm serious.

19 DOCTOR GILLIAM: -- going to improve your  
20 sales, like putting new improved on it, that you could  
21 do it in a matter of months, but, you know, you  
22 haven't convinced me yet.

23 ACTING CHAIR BRASS: If I could comment  
24 before you comment. I think the discussion is  
25 legitimate. I don't want to cut it short, but I think

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1 it's important to emphasize that the meeting today is  
2 to focus on the class labeling for these products.  
3 The issues related to the overall OTC labeling  
4 strategy have been discussed extensively previously  
5 and will, unfortunately, be extensively discussed  
6 again, I have no doubt, and so when they are relevant  
7 to the class labeling I encourage you to bring it up,  
8 but I don't want to get us bogged down in the other  
9 issue.

10 DOCTOR SOLLER: By the way, see me at the  
11 break and I'll explain to you why this is a very  
12 different process. Okay?

13 DOCTOR GILLIAM: I do have -- I mean, I  
14 agree with most of the changes that you put in your  
15 proposed label, one comment I make is, I don't like  
16 cure most. I think, you know, when you say something  
17 is cured, you mean you are not going to get it again,  
18 you are not going to use the product again, and  
19 looking at your statistics these products are only  
20 working in 51 to, I don't know, 90 percent of -- I  
21 mean when you use the word cure, they are only  
22 treating 51 to 90 some percent of these infections.  
23 So, to me, that is not a cure.

24 And, when you put the word "most" next to  
25 it, you are contradicting what you just said. So, I

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1 totally agree with -- disagree with using cure most,  
2 and I think treat is better used in this case.

3 DOCTOR SOLLER: Okay. We don't think it's  
4 an over promise, because it doesn't say cures all, and  
5 we know that this particular drug has been used in the  
6 category for many years, in the **dermatologic** category.

7 ACTING CHAIR BRASS: Yes. We'll have some  
8 opportunity to discuss the details this afternoon, but  
9 I will point out that Doctor Winfield used the word  
10 "cure" in his presentation, describing the efficacy of  
11 these compounds. I don't know if that was accidental  
12 or intentional, but I did note that.

13 Do you have an additional comment?

14 DOCTOR WINFIELD: In terms of cure, when  
15 you are talking about the therapeutic cure rate in the  
16 theme in talking about the percentages, but I would  
17 like to make a comment because currently as the data  
18 was presented in terms of the five studies and the  
19 five products with the ten studies, I want to clarify  
20 for the committee that this was not any additional  
21 analysis than what was done with the original approval  
22 of each of the products when they were approved. This  
23 was the data that was analyzed and supplied in the NDA  
24 approval package.

25 In addition to that, the data, as had been

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1 supplied by the individual sponsors, were also  
2 included, so this data is available. It is not a  
3 separate or new analysis that was prepared just for  
4 this presentation.

5 Now, in general, if you were to go back to  
6 each of the **NDAs**, as I said before, in general, the  
7 data as presented and analyzed by the FDA was  
8 essentially the same results, in terms of cure rates,  
9 and what we meant by cure rates, we have a therapeutic  
10 cure rate. You have, for the individuals clinically  
11 asymptomatic and **mycologically** cured, and this is why  
12 the cure rates are in the low 50s, mid-50 range.

13 If you were to look at the individual  
14 clinical cure, where the individual is **asymptomatic**  
15 clinically, you are going to get a much higher  
16 clinical cure rate, and if you look at the mycological  
17 cure, where you look at that separately, it's going to  
18 be much lower, and almost will mirror the therapeutic  
19 cure rate.

20 But, these are not new figures, it's the  
21 same figures that were presented in each of the  
22 approved products.

23 ACTING CHAIR BRASS: Other questions or  
24 comments from the panel?

25 If not, thank you very much, Doctor Soiler.

1 DOCTOR SOLLER: Thank you.

2 ACTING CHAIR BRASS: We will take our lunch  
3 break at this time and reconvene promptly at 1:00.

4 (Whereupon, the meeting was recessed at  
5 11:44 a.m., to reconvene at 1:00 p.m., this same day.)

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

1:02 p.m.

ACTING CHAIR BRASS: Good afternoon. I'd like to get restarted.

We are going to begin the afternoon session with our open public hearing. We are aware of one individual who has requested the opportunity to speak to the Advisory Committee. I'd ask that individual to please be sure to identify her affiliation and any sponsorship that contributed to her joining us today.

Our first and last speaker will be Doctor Linda Alexander, from the American Social Health Association.

DOCTOR ALEXANDER : Good afternoon.

As mentioned, I'm Linda Alexander. I'm President and CEO of the American Social Health Association, and I am sponsored by the American Social Health Association.

Before I begin my prepared comments, I'd like to just make a couple of points, and particularly applied to the comments this morning that were made regarding the need to break down complex information into language that's easily understood by mainstream America.

This is a challenge that we face on a daily

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1 basis, trying to translate complex information about  
2 sexually-transmitted diseases to individuals who  
3 predominantly utilize public health clinics. The  
4 challenges in this arena are enormous.

5 But , the caveat that I'd like to emphasize  
6 is that in our attempt to simplify and distill  
7 information down to specifics about use and personal  
8 treatment, that we not fail to educate women about  
9 other arenas that are related to yeast infections, and  
10 that's going to be the theme of what I'm talking about  
11 today.

12 First, I'd like to thank the committee for  
13 the opportunity to speak on this important issue.  
14 It's one that affects millions of women in the country  
15 today.

16 The American Social Health Association is  
17 a national non-profit organization founded more than  
18 80 years ago, and our mission is to stop the spread of  
19 sexually-transmitted diseases. Among our primary  
20 activities are patient advocacy and patient education.  
21 We have a particular interest in the subject of over-  
22 the-counter medications, because the desire to use OTC  
23 medications is especially strong in the case of  
24 genital infections due to the embarrassment and stigma  
25 often associated with STDS.

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1           Understandably, patients may prefer to  
2 attempt to self-treat instead of seeking an accurate  
3 diagnosis from a health care provider. While there  
4 are situations in which self-treatment with OTC  
5 medications may be entirely appropriate, we strongly  
6 believe that patients must have enough information to  
7 ensure that both the diagnosis and the treatment are  
8 correct. Women who incorrectly self-diagnose and  
9 self-treat an infection in the genital area may be  
10 unaware that they have acquired a sexually-transmitted  
11 disease.

12           Vaginal infections are extremely common.  
13 Among physicians in private practice alone, it is  
14 estimated that vaginitis accounts for more than 10  
15 million office visits a year, and that number does not  
16 include publicly-funded clinics. Furthermore, the  
17 number of office visits for vaginitis has increased  
18 sharply in the last 30 years. These infections  
19 include **trichomoniasis**, yeast and bacterial vaginosis.  
20 Vaginal discharge may also be due to gonorrhea,  
21 **chlamydia** and other sexually-transmitted diseases.  
22 Left untreated, a vaginal discharge may, at a minimum,  
23 cause itching and discomfort. Later, it may lead to  
24 more serious health complications, causing pelvic  
25 inflammatory disease and resulting in complications

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1 such as tubal ovarian abscess, atopic pregnancy and  
2 infertility. In pregnant women and their unborn  
3 children, these infections may be especially  
4 destructive.

5 An accurate diagnosis leads to appropriate  
6 treatment, as well as a baseline to gauge success of  
7 the treatment. With accurate diagnosis of vaginal  
8 symptoms, treatment is often early enough to prevent  
9 pelvic inflammatory disease and other complications.  
10 Furthermore, proper treatment of vaginal symptoms can  
11 prevent vertical transmission during pregnancy.

12 From a disease control perspective,  
13 accurate diagnosis also allows for treatment of sex  
14 partners, who if untreated can infect other partners  
15 as well as reinfect the original patient. Clearly, in  
16 the case of STDs, in accurate self-diagnosis and  
17 treatment can have many adverse consequences.

18 A study reported in the July, 1997 issue of  
19 Obstetrics and Gynecology found that nearly 3/4s of  
20 women with chronic vaginal symptoms had self-treated  
21 with OTC medications. In another study reported in  
22 the June, 1996 issue of the Journal of Family  
23 Practice, women had previously been diagnosed with  
24 yeast infection scored poorly on a test to assess  
25 their knowledge of symptoms of yeast as compared with

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1 those of STDS and other infections. A 1992- '93 study  
2 of 111 randomly selected women with suspected  
3 vaginitis revealed that approximately 50 percent had  
4 confirmed diagnosis of candida infection. Within this  
5 study, women correctly diagnosed themselves 42 perter.t  
6 of the time, 58 percent incorrectly diagnosed  
7 themselves.

8 Perhaps more disconcerting, the same  
9 investigators compared physician diagnosed based on  
10 presenting symptoms, with physician diagnosis based on  
11 physical and laboratory examination. Of the 62  
12 physician pre-examination diagnosis of candida, 20, or  
13 32 percent, were incorrect.

14 What we know then is that the diagnosis of  
15 vaginal yeast infections is not necessarily  
16 straightforward. Organisms other than candida may  
17 present vaginal symptoms. Furthermore, some of these  
18 other organisms can cause severe morbidity if not  
19 recognized and properly treated. We must encourage  
20 women, not only to learn more about vaginal symptoms,  
21 but also to be more alert and sensitive to the  
22 possibility that they could have an STD.

23 The labeling of OTC medications for yeast  
24 infections offers a crucial opportunity to educate  
25 women about these important issues at the point of

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1 purchase. In addition to the labeling currently  
2 required, the package should list the following:

3 1. Yeast infection is only one of many  
4 possible infections that cause symptoms in the vaginal  
5 area;

6 2. Other vaginal infections include bacterial  
7 vaginosis and trichomoniasis;

8 3. STDS such as gonorrhea and **chlamydia** may  
9 present with a discharge;

10 4. STDS can have a variety of other symptoms  
11 and signs, including rashes, blisters, warts, bumps  
12 and odorous discharge, or they may cause no symptoms;

13 5. If untreated, STDS can cause pelvic  
14 inflammatory disease, tubal pregnancy and infertility;

15 6. The National STD Hot Line, and we have the  
16 800 number, can provide more information; and last

17 7. Women should consult their health care  
18 providers the first time they have vaginal symptoms  
19 and any time the symptoms are unusual.

20 Specifically, we propose the following  
21 changes to the draft guidance of 6/19/98. Page three,  
22 the carton label, under warnings, the warnings about  
23 PID symptoms should be strengthened. Current carton  
24 labels need to be more forceful and are, therefore,  
25 preferable. For example, the warning could say, do

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1 not use if you have abdominal pain, fever or foul  
2 smelling discharge, contact your doctor immediately.

3 On page four, the patient education  
4 brochure, under "The following 15 questions, " question  
5 four, a new question should be inserted, perhaps,  
6 between questions four and five, asking what else  
7 causes a vaginal discharge? With this new question,  
8 the answer could be, you may have a small amount of  
9 normal vaginal discharge at certain times of the  
10 month. This kind of discharge may be clear or  
11 slightly white. It does not itch, smell bad or hurt.  
12 Besides vaginal yeast infections, many other  
13 infections can cause vaginal discharge, and each of  
14 these requires prescription medication from a health  
15 professional . Bacterial vaginosis and trichomoniasis  
16 are two different infections that can cause a vaginal  
17 discharge that may be milky white, gray, yellow or  
18 green, and may have an unpleasant, foul or fishy odor.  
19 Itching and burning may also be present. If  
20 untreated, these infections can cause complications  
21 for women, and in pregnant women problems in  
22 pregnancy. Other serious infections that can cause  
23 discharge include gonorrhoea and chlamydia. The  
24 discharge may be yellow, gray, green or white, but  
25 often these sexually-transmitted diseases cause no

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1 symptoms. Because of this, women may develop  
2 complications, including PID, before they are  
3 diagnosed.

4 Beyond the diseases that cause discharges,  
5 women may experience vaginal irritation from **sexually-**  
6 transmitted diseases, such as genital herpes and  
7 genital warts, and this is in bold, it can be  
8 confusing for you to know what a discharge means, and  
9 for this reason it is very important that you receive  
10 an accurate diagnosis and the correct treatment any  
11 time you have a vaginal discharge.

12 On page six of the patient education  
13 brochure, under, "How can I tell that I have a yeast  
14 infection, " the last bullet states, "painful vaginal  
15 intercourse (sex)." We would encourage you to  
16 consider removing this bullet. Painful intercourse  
17 due to vaginal irritation is implied in the third  
18 bullet.

19 Under page six of the patient education  
20 brochure, "How can I tell that I have a vaginal yeast  
21 infection, " the note after the last bullet should be  
22 expanded. If a new question is inserted asking what  
23 causes the vaginal discharge, as we suggested, the  
24 reader could simply be referred to this question and  
25 answer. If not, this point needs to be strengthened

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1 and/or put in bold type.

2           Again, on page six in the patient education  
3 brochure, under "Why do women get repeated vaginal  
4 yeast infections," insert a comment or note,  
5 preferably in the beginning, stating if you still have  
6 a vaginal discharge after being treated for a yeast  
7 infection you may have another kind of infection, and  
8 see the new question that we suggested, what else  
9 causes a vaginal discharge?

10           Again, on page six in the patient education  
11 brochure under "Are vaginal yeast infections sexually  
12 transmitted," this is a good opportunity to add, if  
13 your partner has, or has had a discharge (or drip, or  
14 puss) from his penis, both of you should see a doctor.  
15 Even if his drip goes away, you should see a doctor  
16 since you could have a sexually-transmitted disease  
17 and many women have no symptoms at first.

18           On page seven, again in the patient  
19 education brochure, under "How can I prevent repeated  
20 vaginal yeast infections," in the first bullet add a  
21 sentence saying, do not stop taking antibiotics that  
22 were prescribed for you.

23           Further, we suggest that there be a section  
24 in the patient educational brochure on understanding  
25 vaginal infections, giving more detailed information

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1 on these infections and listing the signs and symptoms  
2 of STDs. We have prepared an attached table in the  
3 handout that is available to the panel.

4 The American Social Health Association's  
5 own studies have shown low levels of knowledge and  
6 awareness of STDS in this country. The fact is, most  
7 men and women assume that STDS happen to other people,  
8 and they themselves are not at risk. For women, the  
9 lack of understanding of why they are at risk for  
10 STDS, coupled with the expense, the inconvenience and  
11 the embarrassment of a clinic visit to get a  
12 professional diagnosis, are very strong motivators to  
13 self-diagnose an infection as yeast and to buy an  
14 over-the-counter medication.

15 We believe that these motivators should be  
16 counterbalanced by clear and compelling information  
17 about STDS on the medication package. Alerting women  
18 to the fact that their symptoms could indicate an STD  
19 is a responsible action to lower the risk of wrongful  
20 self-diagnosis and treatment and to encourage women to  
21 seek professional health care for potentially  
22 dangerous infection.

23 Thank you very much.

24 ACTING CHAIR BRASS: Thank you.

25 Are there any questions for Doctor

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1 Alexander?

2 Doctor Katz, would you like to summarize  
3 and charge the committee?

4 DOCTOR KATZ: Good afternoon.

5 In the time remaining, I'd like to give a  
6 brief summary and charge to the committee, before we  
7 entertain the questions that are put at hand for  
8 further discussion.

9 We have spent this morning discussing  
10 specific issues relating to the vaginal antifungal  
11 class labeling. We have provided background  
12 information, OTC product labeling format issues, and  
13 specific issues related to the consumer labeling, as  
14 well as for the carton and the educational brochure.  
15 We've talked about language, language that may be  
16 confusing to consumers, and all of these will go into  
17 play with our discussion this afternoon. We have  
18 heard comments from industry, as well as from  
19 interested parties, about the information at hand.

20 In the time remaining, I'd like to focus  
21 your attention back to the questions. The first  
22 question is, currently, one, three and seven-day  
23 vaginal antifungal products are available OTC, how  
24 should information be conveyed to the consumer that  
25 will help them to select among these products?

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1                   Question two, what, if any, modifications  
2 would you suggest on the carton label?

3                   And three, what, if any, modifications  
4 would **you** suggest in the consumer educational  
5 brochure?

6                   At this point, I'd like to go back a little  
7 bit to question one, because just to clarify what the  
8 intent was of our committee in posing this question to  
9 the committee here to address during the discussions  
10 and deliberations today.

11                   Question one is designed to look at  
12 expectation of benefit. The expectation of benefit is  
13 not made in any way to create -- we are not looking  
14 for a comparative claim, and I want to make that  
15 clear. What we are looking for is some way to suggest  
16 and to provide some useful information to a consumer  
17 who might happen to be in a drug store, supermarket or  
18 wherever else you may purchase these products, so  
19 that, when she sees a one, three and seven day there  
20 will be something on the package that might help her  
21 as to determine what product would be most appropriate  
22 for her and why.

23                   What is intended by this again is not a  
24 comparison on the label of the one, three or seven-day  
25 product, but if I can kind of familiarize or bring

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1 people back to prescription drugs that people may be  
2 more familiar with, that in those labels there are  
3 expectations of benefits that are provided in terms of  
4 either a clinical trials design section or a clinical  
5 pharmacology section, where results of clinical trials  
6 are provided to a physician so that a physician can  
7 make a determination as to what the product might do  
8 for the patient who he's prescribing it for.

9 In this question, we are asking sort of the  
10 same concern, is there some information that we should  
11 provide to a woman about a specific product that she  
12 is buying to help her to make a decision as to what  
13 she may or may not want to buy, and, again, not making  
14 comparisons amongst the different products.

15 Now , what I also want to emphasize with  
16 this as well is that we did not put this section in  
17 our carton label or our educational brochure that we  
18 disseminated because we, as an Agency, did not know  
19 how to make these kinds of statements, and we're  
20 looking really for you as a committee to give us  
21 guidance.

22 If, in fact, there's no information that  
23 people feel would be useful to contain in such a  
24 section, that's fine, too. We're open to entertain  
25 it, but thought it was a worthwhile question to

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1 address, and I hope that that will clarify at least  
2 what it is that we are looking for with the advice for  
3 this particular question.

4 With regard to the questions two and three,  
5 I think those are fairly self-explanatory. During the  
6 discussions, when we get to those questions, we do  
7 have overheads available that we will show, so that  
8 way it will make it easier to go through some of the  
9 language or comments that people may have.

10 And, with that, I'll turn the meeting back  
11 over to Doctor Brass.

12 Thank you.

13 ACTING CHAIR BRASS: Thank you.

14 I'd like to go through -- suggest we go  
15 through these questions individually, and, in  
16 particular, when we get to questions two and three  
17 we'll look at the labeling in blocks to try to focus  
18 our discussion.

19 so, to begin with, would anybody like to  
20 comment on question one, with respect to additional  
21 labeling with respect to the product?

22 MS. HAMILTON: I'd like to make a general  
23 observation focusing on an aspect of the one-day,  
24 three-day, seven-day labeling that hasn't been  
25 addressed directly, but as a consumer rep concerns me.

1 I think that it is likely that consumers,  
2 who are not as familiar with language related to  
3 dosing, but are more comfortable with language related  
4 to alleviating their symptoms, are very likely to  
5 think that the one - day product will provide  
6 symptomatic relief in one day, and that a three-day  
7 dosing product will provide some relief in three days,  
8 and seven days and ongoing. So, one of the questions  
9 that I would like to raise, is there a way to clarify,  
10 to distinguish between a one-day dose, where symptoms  
11 may still appear, there may be still, as discussed  
12 earlier, three to seven days before there's any  
13 effective relief. That's a concern to me.

14 ACTING CHAIR BRASS: Beth.

15 MS . SLINGLUFF: If I understand the  
16 information that's been presented thus far correctly,  
17 there really is no substantial difference in the  
18 efficacy of one-day, three-day or seven-day  
19 treatments.

20 Therefore, it is very difficult for me to  
21 see how I could really make a recommendation on  
22 labeling as to which product a woman should use, since  
23 I don't really have a scientific basis on which to do  
24 that.

25 It becomes much more of an issue, as

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1 Kathleen has just pointed out, of trying to clearly  
2 delineate for the consumer in what time frame she  
3 should expect improvement .

4 ACTING CHAIR BRASS: If I can just,  
5 perhaps, interpret, if I understood Doctor Katz  
6 correctly, for a number of products we have  
7 recommended including things like bar graphs or other  
8 things that illustrate the expected response rate for  
9 products as a guide to consumers to help them know  
10 what to expect.

11 And, one interpretation of what your  
12 comment was is whether there is value in providing  
13 such information in this setting, particularly, if  
14 failure to respond has public health concerns and  
15 should not be interpreted by the consumer as the  
16 natural history of things, but some people don't  
17 respond to this treatment.

18 Are there any thoughts on utility of such  
19 additional information?

20 DOCTOR SOPER: When I -- I think your  
21 concern is real, and I think maybe in an illusion back  
22 to the single-dose antimicrobial therapy for urinary  
23 tract infection is illustrative, and that is, it's  
24 been my observation that few clinicians use that any  
25 longer. And, even though it has been shown to be

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1 quite effective, you could almost guarantee yourself  
2 a Phone **call** on day two because it just took a few  
3 days for the symptoms to go away and the patient was  
4 uncomfortable not being on therapy at the time that  
5 the symptoms had not resolved.

6 Therefore, similar expectations are going  
7 to follow some of those vaginal antifungal therapy,  
8 and it's going to be incredibly important to make sure  
9 that patients are informed that even though you use  
10 this single dose that it can take, and the average is  
11 about two and a half days for symptoms to resolve,  
12 and, of course, that's a mean, and there's confidence  
13 intervals on both sides of that, some more promptly  
14 and some less promptly resolve their symptoms.

15 And **so**, I think there probably needs to be  
16 something added to the patient education.

17 ACTING CHAIR **BRASS**: Doctor Soiler, if you  
18 could go on your knees, please.

19 DOCTOR SOLLER: I think I have many times  
20 in the past.

21 Just to comment first on, I think you  
22 mentioned bar charts or something, let me just address  
23 that. There was a study done by WCE, it's an  
24 associate member of **NDMA**, they are in the label  
25 comprehension business, have done a lot for the

1 different switches, looking at the bar charts and the  
2 H<sup>2</sup> blockers, and finding that paragraph format is  
3 generally better understood than charts, just to weigh  
4 in on that. Okay, so that's something to think about.

5 But , in the materials that we've sent to  
6 you, if you look at, I think it's the second to last  
7 page, the materials from FDA, you have the label,  
8 okay, I'm reading from Vagistat-1, when can you expect  
9 symptom relief, and my understanding, I can't speak  
10 for the company, I don't know specifically, but my  
11 understanding is that in the one-day product that was  
12 an issue because you are moving from a seven, to a  
13 three, to a one, and the company didn't want to be in  
14 a position where people were thinking that their  
15 product wasn't providing relief. And so, that's part  
16 of the approved NDA labeling worked out between the  
17 company, and I think the other products don't have it,  
18 and certainly that's not in the guidelines.

19 But , I have it in the packet. We have a  
20 different cover that we put on it, but it's the second  
21 to last page, Vagistat, Kathleen, do you have that?

22 MS. HAMILTON: I do.

23 DOCTOR SOLLER: And, you can see in the --  
24 it's kind of folded down here because it's difficult  
25 to pull out of this, but it's number five, item number

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1 five, "While Vagistat-1 is a one-dose treatment, most  
2 women do not experience complete relief of their  
3 symptoms in just one day. Most women experience some  
4 improvement within one day and complete relief of  
5 symptoms within seven days," something longer than you  
6 had mentioned, Doctor Soper, to just encompass that  
7 time period, and then if your symptoms don't improve  
8 in three.

9 Now , I'd also add that in the proposed  
10 carton it says, "Stop use and ask a doctor if . . ."  
11 first bullet, "symptoms don't improve in three days, "  
12 so the implication is that something is going to  
13 happen in three days.

14 And, Kathleen, I don't know whether this  
15 gets it where you were going, but certainly there's  
16 something different for that one product already out  
17 there.

18 MS. HAMILTON: No, actually, the carton is  
19 also different than the other examples that we have,  
20 in that it refers to one dose on the front of the  
21 carton. It doesn't say one day, three day, seven  
22 days, so it's actually clearer from the outset, and I  
23 guess that's the point that I'm making, is it seems to  
24 me that there's a difference for the consumer of this  
25 product to understand, this is a product you will take

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1 one time, or that you will administer three times,  
2 which is very different than a three-day treatment.

3 ACTING CHAIR **BRASS**: Thank you very much.

4 I think in that context, and, again, the  
5 one thing we are not going to do is try to write, as  
6 a committee, a label, I assure you of that, the one  
7 thing that might be considered is whether wordsmithing  
8 to change that carton phrase to a clearer figment of  
9 expectation linked to the three and seven-day consult  
10 a physician block, to incorporate those expectations  
11 more clearly.

12 Any other thoughts on the one, three? Sir,  
13 if you could identify yourself when you come to the  
14 microphone, please.

15 MR. **GARUDI**: Ron Garudi, Sharon Plow  
16 **Healthcare** Products. I think the intent behind the  
17 question is admirable. We all want to convey more  
18 information to consumers, but I'm not sure it's the  
19 right question, and I'm not sure you stop there.

20 There may be other important variables as  
21 well. I mean, why not advise a woman about the subtle  
22 differences, perhaps, between choosing an insert and  
23 a cream? There clearly are some **bioavailability**  
24 differences there. We are silent on that. There may  
25 be differences between the efficacy of the different

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1 antibiotics themselves.

2 So, I appreciate the spirit of it, but I'm  
3 not sure where you go with it.

4 ACTING CHAIR BRASS: Again, I certainly  
5 have a sense of the, committee and a strong opinion  
6 myself that it is not an attempt based on the  
7 available data to differentiate between products of  
8 one, three and seven, in terms of their efficacy or  
9 adverse effects, but to ensure that consumers are not  
10 mislead unintentionally by the significance of the  
11 one, three and seven days, and that, I think, is what  
12 Kathleen was suggesting, to anticipate  
13 misinterpretation.

14 I don't think there's going to be consumers  
15 worried about the differences in bioavailability.

16 DOCTOR SOLLER : Bill Soiler. Our group may  
17 have missed the assignment. Okay. We saw that  
18 question, and the only thing we could link it to in  
19 the packet was the three pager, okay, which I  
20 understand didn't come from the OTC Division.

21 And, the way we looked at it was in the  
22 context of a comparative claim.

23 I'm very gratified to hear your view on  
24 that, and I'm trying to understand exactly what's  
25 being asked. I don't know that we have specific input

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1 that we can provide today, because we may have missed  
2 the intent of that, but is it that you are asking for  
3 some sort of statement similar to the Vagistat-1  
4 statement that would say for the three-day product you  
5 can expect symptom relief within a -- most women can,  
6 and if you don't do this, and with the seven day you  
7 can say, you can expect symptom relief to begin, but  
8 if she doesn't get relief by then something like that.  
9 So, the expectations relative to the symptom relief,  
10 as it would relate to the one, three and seven day, is  
11 that what you are asking? I'm not getting the exact  
12 question.

13 ACTING CHAIR BRASS: Well, the sense is  
14 that -- well, again, my sense, and the experts can  
15 correct me if I'm wrong, the expectation for symptom  
16 relief, in fact, would not be different between the  
17 one, three and seven-day products, and that a single  
18 statement --

19 DOCTOR SOLLER: And so that the difference  
20 is largely a convenience issue for the woman. I'm  
21 just trying to work through it so we get the  
22 assignment right, and we can easily come back to FDA  
23 with thoughts.

24 ACTING CHAIR BRASS: Again, I think we are  
25 learning through this as well as you, and I think what

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1 members of the committee, I have heard them say, is  
2 their concern about mixed differential expectations  
3 that may not be grounded in scientific data based on  
4 the different therapies, and to avoid that.

5 DOCTOR SOLLER: Well, maybe this helps the  
6 discussion, I don't know, we don't have specific  
7 quantitative information on the consumer perception,  
8 but I can share with you qualitatively what comes out  
9 of many focus groups in this area and how women talk  
10 about this.

11 And, the sum of it is that generally when  
12 they get to the shelf, and they get to the package,  
13 they've already made up their mind as to what they  
14 want to use, and it breaks out because they have gone  
15 to a physician, if it's a seven-day product, and most  
16 physicians are suggesting the seven-day product, so  
17 many first-time users are under the seven-day product  
18 type of mode, or they've suffered before and it's  
19 worked, and they may have some suspicions as to  
20 whether the shorter duration really is, you know,  
21 whether that really makes sense for them. That  
22 characterizes the seven-day user population.

23 The three-day user is looking for  
24 convenience. They've tried it, it worked, they are  
25 going to try it again, and they have some suspicions

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1 as to whether a one - day product would work,  
2 remembering that there's a sequence in marketing  
3 reduction here and getting used to that on the  
4 consumer marketplace.

5 And , the one day is simply motivated by  
6 convenience, and they want the relief, they want it --  
7 or they have used it and it works for them.

8 And SO, I don't know whether that helps in  
9 terms of getting the perspective, but the sense is  
10 that women come with very strong preconceived notions  
11 to the retail shelf when they are studying to take the  
12 product. Some of it is driven by the physician, a lot  
13 of it is driven by their own experience.

14 ACTING CHAIR BRASS: Thank you.

15 And, again, one of our concerns is that we  
16 don't doubt the preconceptions, we would just like to  
17 correct the false ones.

18 Yes, please.

19 MS. NARRIGAN : There is a difference in  
20 price that no one is talking about.

21 ACTING CHAIR BRASS: That's not generally  
22 an issue we worry about.

23 MS. NARRIGAN: Okay. All right,

24 DOCTOR SACHS: As a pediatrician dealing  
25 with a lot of adolescents, the big question I get is,

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1 you know, what's different about them or whatever, and  
2 the one thing that I think should be clear, and this  
3 may move us to the next part of the talk, is what the  
4 preparation actually is, and, you know, whether its  
5 purpose is to help someone select, seeing that it's an  
6 insert, or it's a **prefill**, or it's a cream, is  
7 actually important, and **it's not clear** on all of the  
8 packages what it is.

9 ACTING CHAIR BRAS S: Any other thoughts  
10 about the overall theme of the differentiation of  
11 product or clarification of instructions and  
12 expectations?

13 DOCTOR DAVIS: Doctor Davis here, I guess  
14 I'd like to ask Doctor Soper, and he doesn't have to  
15 answer if he doesn't want to, but in your actual  
16 clinical practice do you actually feel that a one-day  
17 product does have the same efficacy as the three and  
18 as the seven-day product?

19 DOCTOR SOPER: Yes, in a word. I think  
20 that, as has been pointed out, that patients use  
21 different products for different reasons, and patients  
22 and consumers do have choices, and in actual clinical  
23 practice you give patients choices and they can make  
24 a lot of these decisions themselves.

25 And so, from mild to moderate **vulvovaginal**

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1 candidiasis that's not recurrent in nature, single-  
2 dose therapy is very reasonable.

3 And , just to emphasize actually again  
4 what's already been pointed out, it's a very important  
5 part of the treatment in patients that are taking  
6 single-dose therapy of anything to educate them about  
7 the relief of symptoms. Otherwise, you will get a  
8 kind of a false positive failure rate, if you will,  
9 because patients will have expectations that they  
10 should respond more rapidly.

11 ACTING CHAIR BRASS: Thank you.

12 If there are no other comments -- oh,  
13 please, Doctor Chin.

14 DOCTOR CHIN: Doctor Chin. I'd like to  
15 follow up to that question. I guess the question is  
16 in people who are having repeat infections, and we're  
17 going to have to discuss the frequency of how many in  
18 what time frame, in clinical practice at which point  
19 do you make a decision that a one-dose therapy may not  
20 be the treatment of choice, and that the longer  
21 duration therapies are much more appropriate?

22 ACTING CHAIR BRASS: Before Doctor Soper  
23 answers, I would just like to interject that I'm a  
24 little uncomfortable in the direction the questioning  
25 is going, because if we are going to start addressing

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1 fundamental questions of efficacy, based on anecdote,  
2 and without an opportunity to review the data, and if,  
3 in fact, what you are asking us to do is reopen the  
4 approval process for the one-day treatment to see if  
5 we made a mistake with the recommendation, I really  
6 don't think the drift is one that I'm comfortable  
7 with.

8 so, with that admonishment, I will ask  
9 Doctor Soper to answer the question.

10 DOCTOR SOPER: Well, just to amplify what  
11 the Chairman said, I think that the information that  
12 we have in the management of these infections is that  
13 you have data that treats patients with acute mild to  
14 moderate disease that within a given window have not  
15 been pretreated.

16 And then, you have another group of  
17 patients that have true recurrent disease, which means  
18 they have a minimum of four or more episodes a year.

19 Everybody else is kind of in between and  
20 are not specifically studied for me to give you any  
21 actual feedback, so what you are really asking for, as  
22 the Chairman suggests, is my own personal preferences  
23 and some anecdotes.

24 So, I think that what you are saying when  
25 you say repeat, really, is probably what happens, you

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1 know, if 75 percent of women have at least one  
2 infection and 40 percent of those 75 may get a repeat  
3 at some time in their life, only five percent actually  
4 have chronic recurrent disease. So, it will be that  
5 many women have occasional repeat **vulvovaginal**  
6 **candidiasis** episodes, which should promptly respond to  
7 any one of the antifungal that have been approved  
8 through the FDA process, and that what you are asking  
9 for is a specific comment on the patient maybe that's  
10 having multiple, relatively frequent infections, and  
11 that's a different problem altogether.

12 ACTING CHAIR BRASS: Yes, and because you  
13 are not Doctor Winfield, if you would identify  
14 yourself.

15 MR. LEISSA: Brad Leissa, FDA.

16 One of the comments that was very helpful  
17 I think came from you, Ms. Hamilton, the issue about  
18 as we would be working on class labeling we'd want to  
19 apparently stay away from issues of three-day  
20 treatment and seven-day treatment, because that would  
21 give a different expectation. So, that is actually  
22 very helpful, as we would continue to work on this  
23 document, not to introduce that if it were to come to  
24 us .

25 ACTING CHAIR BRASS: Thank you.

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1 Cage.

2 DOCTOR JOHNSON: I just want to add a  
3 comment about the ability of the consumer to identify  
4 what the therapy is, and some of the packages actually  
5 have, the fifth panel ones, particularly, have a  
6 picture of either the troche for insertion, or the  
7 applicators, and the one I'm looking at now has the  
8 three applicators that are going be used, and that  
9 kind of information, I think, relevant to this  
10 question, would be very useful.

11 And, I would really want to agree with what  
12 Ms. Hamilton said, that I think the possibility of  
13 introducing to the consumer the expectation that the  
14 therapy is going to respond to the **number** of  
15 treatments is possibly an area that we really want to  
16 work hard at not to give that kind of presumption.

17 ACTING CHAIR BRASS: Okay.

18 I'd like now to turn our attention to the  
19 carton label, and if we could have the carton label up  
20 on the screen. This is the FDA's proposed carton  
21 label.

22 What I'd like to do is review this in the  
23 large blocks incorporated into the format, and simply  
24 ask the panel based on the variety of opinions they  
25 have heard, and what they have reviewed themselves,

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1 whether they have any suggestions . And , for  
2 completeness sake, I'll start at the top, and anything  
3 in the first three lines related to the product  
4 identification, active ingredient or purpose that  
5 anybody would like to comment on.

6 MS . NARRIGAN : I'd like to comment on  
7 purpose.

8 ACTING CHAIR BRASS: Please.

9 MS. NARRIGAN: Maybe I'm not understanding  
10 exactly what the purpose of the purpose is, but  
11 vaginal antifungal is the class of drug, it's not the  
12 -- it doesn't tell a consumer in, (A) language they  
13 can understand what it is, or (B) what the purpose is.  
14 I mean, it does, but --

15 ACTING CHAIR BRASS: This goes back, and  
16 Doctor Katz can correct me if I'm wrong, to the global  
17 '97 proposal of formatting.

18 MS. NARRIGAN: Okay, it has to be that way?

19 ACTING CHAIR BRASS: And, it was just in an  
20 area on the carton to identify in one area commonality  
21 between classes along products, so that in one area  
22 they would --

23 DOCTOR KATZ: That's correct. What it is  
24 intended to do is to be the statement of identity, so  
25 that all products of the same class would have the

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1 same statement of identity. And, that's where the  
2 purpose was translated.

3 It may be sort of a misnomer, but that was  
4 how it was published in the proposal in 1997 as  
5 purpose, but it really is synonymous with statement of  
6 identity, and it was felt that statement of identity  
7 wouldn't mean anything to the consumer either, that  
8 purpose might be simpler, and it might get more of the  
9 message across.

10 MS. NARRIGAN: I guess the word purpose is  
11 clear, but the language -- I mean a consumer certainly  
12 can't understand those two words.

13 ACTING CHAIR BRASS: But, we see it on  
14 multiple cartons.

15 MS. NARRIGAN: Okay, it's strange language.

16 DOCTOR KATZ: It will be there on every  
17 carton. If you pick up a carton of a different  
18 product, let's say you pick up an over-the-counter  
19 analgesic, you'll see purpose, pain reliever, or fever  
20 reducer, and that's the statement of identity.

21 ACTING CHAIR BRASS: The same place on  
22 every carton.

23 MS. NARRIGAN: So, is there then some  
24 leeway to change those words under, that describe the  
25 purpose or not?

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1 DOCTOR KATZ: Well, you could if you feel  
2 that there's another terminology that might best  
3 describe this class of drugs, but what we wanted to do  
4 was to keep something simplistic that would get the  
5 message across.

6 Other statements of identity that would  
7 again be listed under purpose would be pain reliever,  
8 fever reducer as examples, cough/cold preparations,  
9 and that we chose vaginal antifungal because we  
10 thought that that might get the message across more  
11 clearly. But, if you have a better suggestion we'd be  
12 glad to hear it.

13 MS. NARRIGAN : Treat vaginal yeast  
14 infection.

15 DOCTOR KATZ: Well, see, you don't want --

16 MS. NARRIGAN: And, have a verb.

17 DOCTOR KATZ: -- you don't add the verb in,  
18 it's really just the descriptor.

19 MS. NARRIGAN: Okay.

20 ACTING CHAIR BRASS: Doctor Soiler.

21 DOCTOR SOLLER : Soiler, **NDMA**, active and  
22 purpose first, as we have originally proposed, was in  
23 part for professional counseling issues at the point  
24 of purchase, turn it up, it's got it right there, you  
25 know what the ingredient is, and the health

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1 professional is looking at that purpose.

2 I think that's also important for the  
3 consumer, though, and Linda has correctly said, think  
4 of it as -- it's easier to think of sort of aspirin,  
5 you know, pain reliever, and then the use is for the  
6 temporary relief of, and you go through headache and  
7 so on. And, it's one of the reasons, I didn't mention  
8 it in the presentation, why we think that two bullets  
9 under uses, to treat or cure most, however you made  
10 out on that, but those two bullets that explain what  
11 the indication is should be higher under uses, so you  
12 move from active ingredient, to purpose, to cure most,  
13 and you have that triad.

14 There was a suggestion at the last NDAC  
15 meeting that there might be information inserted  
16 between actives and purpose and uses, and we strongly  
17 opposed that because we think it's a logic and  
18 conceptual triad that needs to exist. And, in this  
19 case it's the reason why we think the two bullets need  
20 to be higher than the use precautions.

21 ACTING CHAIR BRASS: If there are no other  
22 comments, we will move on to uses, and there were a  
23 number of points directly and indirectly made relative  
24 to that portion of the carton.

25 Doctor Sachs.

1 DOCTOR SACHS: In that first section under  
2 uses, "See your doctor if this is the first time you  
3 have vaginal discomfort, " to find out if you have a  
4 vaginal yeast infection, and maybe some -- or, two,  
5 you have a vaginal yeast infection as opposed to an  
6 STD, because that is the issue, that is why they are  
7 seeing the doctor.

8 MS. KODA-KIMBLE: It seems that the first  
9 statement in bold really is a warning, and in my  
10 opinion ought to occur under ask the doctor before  
11 use, except I would make that stronger, I would say,  
12 do not use and see a doctor if: this is your first  
13 whatever, or if you have multiple sexual partners, or  
14 have a new sexual partner, anything that cues to an  
15 STD, have abdominal pain.

16 So, really, it's a strong warning, do not  
17 use, as opposed to putting it under use. It just  
18 doesn't feel right under that section.

19 ACTING CHAIR BRASS: I think the philosophy  
20 there is that it was strongly felt that this product  
21 was only appropriate if you were previously diagnosed.

22 MS. KODA-KIMBLE: Right.

23 ACTING CHAIR BRASS: Whatever is currently  
24 being used. And, the earlier that was said, the  
25 higher the low probability is that the consumer will

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1 actually see that and take it seriously. So that, I  
2 think any time you switch it from the top to further  
3 down, you may be decreasing the likelihood that it  
4 will be looked at before purchase.

5 MS. KODA-KIMBLE: I understand the  
6 rationale for it, but it seems to me there are other  
7 -- when we are talking about absolute  
8 contraindications there is sort of a hierarchy there,  
9 then maybe the whole labeling ought to be rethought,  
10 because if that's what you want them to see first, as  
11 opposed to use, then let's put that up on top.

12 ACTING CHAIR BRASS: Yes, please.

13 DOCTOR LEWIS: Yes, actually, I wanted to  
14 say that I think that it's good to have that sort of  
15 warning under uses, and I would go a little bit  
16 further and maybe just add a sentence that other  
17 sexually -- no, not other -- certain sexually-  
18 transmitted diseases can cause vaginal itching and  
19 discharge, you know, call your doctor, something to  
20 that effect.

21 ACTING CHAIR BRASS: Yes.

22 DOCTOR DATTEL : I'm going to echo that, but  
23 maybe I'll even take it one step further. I think  
24 that warning should be the first thing on the whole  
25 package. The whole discussion today, all the issues,

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1 all the objections, everything that's been raised, has  
2 been about the issue of masking serious other  
3 conditions, all of which can present with the same  
4 symptoms of vaginal itching and other complaints, and  
5 women are self-diagnosing incorrectly.

6 So, the very first thing should be warning,  
7 just like it is on a package of lye, you know,  
8 warning: don't splash this in your face. You know,  
9 it should be the very top thing underneath the title  
10 of what it is, and then you can put all the other  
11 things down there, but, I mean, maybe I'm taking it a  
12 step too far, but it seems that all of the concerns  
13 are focused on this one issue, and that is universal  
14 between all of the over-the-counter treatments, and  
15 that would be the one thing that would make sense to  
16 me and that addresses everyone's concerns.

17 ACTING CHAIR BRASS: I appreciate your  
18 reinforcement. Just again, in terms of background for  
19 those members who are not on the NDAC, the issue of  
20 the ordering and these kinds of issues have been  
21 discussed and will continue to be discussed endlessly,  
22 and there is, was, probably will be a rationale for  
23 the conformity and for most products moving the  
24 warnings can be justified, particularly, from a health  
25 care provider perspective. And so, I appreciate your

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1 comments, but be assured that those have been  
2 discussed a lot.

3 DOCTOR DATTEL: Oh, I'm sure.

4 MS . NARR IGAN : I have another comment on  
5 this particular sentence. Neither the industry  
6 suggested wording or the FDA's are very clear about  
7 actual use. In other words, it says, make some kind  
8 of contact with your health provider, but it doesn't  
9 tell you not to self-treat. It just says, well, you  
10 know, it's not your first, you better call somebody.  
11 But , if I were in the drug store I would probably buy  
12 and, or what I mean is, it doesn't say don't use this,  
13 and maybe it needs to be stronger in that direction.

14 ACTING CHAIR BRASS: Doctor Alexander?

15 DOCTOR ALEXANDER: Hi. Linda Alexander,  
16 ASHA . I would just emphasize the point that we made  
17 out that to reinforce what you are saying. We really  
18 thought the warning should be very bold, do not use if  
19 you have abdominal pain, fever or foul smelling  
20 discharge. Contact your doctor immediately.

21 ACTING CHAIR BRASS: And, again, we are  
22 still on the uses section.

23 DOCTOR ALEXANDER: Right .

24 DOCTOR SOLLER: Soiler again. Could I  
25 suggest turning to section A, the second of the

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1 materials we sent you, it has the blue back.

2 DOCTOR ALEXANDER: I'm looking at it.

3 DOCTOR SOLLER: Are you looking at the  
4 second one under A?

5 DOCTOR ALEXANDER: No, I'm looking at the  
6 first one, the annotated.

7 DOCTOR SOLLER: Not the annotated, just to  
8 give you kind of how to look at the label and how  
9 highlighting is used when you are thinking about  
10 readability, and how, in presenting information you  
11 want to create a curiosity through the highlighting,  
12 and that's part of where our thinking is coming. We  
13 think that actives, purpose and use form a very  
14 important conceptual triad in a counseling situation,  
15 when a pharmacist is there and he's holding it up and  
16 he's able to take a quick read on the product as he's  
17 talking to the individual, what different ingredients  
18 are there.

19 so, we strongly advocate that you could  
20 support that, because it will apply across other  
21 categories as well.

22 Now, whether the bullets are first under  
23 uses or after what we think it should be, to cure or,  
24 let's say, to treat, let's not get into that part of  
25 it. The point is that there's a highlighted phrase

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1 right at the top of the label. It's likely that a  
2 consumer will move through the active and purpose very  
3 quickly into the uses. They look for uses first. If  
4 you want that first information, then -- and we think  
5 it should be the conditional first, if this is the  
6 first time you have vaginal yeast and discomfort,  
7 maybe it's do not use and see your doctor, something  
8 like that, but I would recommend that you keep that  
9 uses because that's how the consumer is going to use  
10 the label.

11 ACTING CHAIR BRASS: Cage.

12 DOCTOR JOHNSON: I'd like to emphasize the  
13 fact that I think this particular warning does belong  
14 high up in the uses, and, perhaps, to get at the other  
15 question that we are all concerned about, is if you  
16 have a yeast infection to add rather than another type  
17 of vaginal infection.

18 ACTING CHAIR BRASS: So, I think what I  
19 sense from the committee is an effort to complete the  
20 logic of that, whether it's with STD or other  
21 infection in appropriate languages seems to be a  
22 consensus.

23 I'm still a little troubled about the first  
24 time use clarity issue. I mean, it doesn't say use  
25 only if you had it previously, I mean, there's not an

1 active descriptor, but kind of this see your doctor if  
2 it's the first time. It doesn't say this is not for  
3 use for the first time in a positive kind of way, and  
4 whether consumers understand that it's not for first  
5 time use and are simply ignoring that, or truly don't  
6 understand whether it's not for first time use is  
7 quite questionable, but, clearly, the data would  
8 suggest that message is not coming across properly.

9 Beth.

10 MS . SLINGLUFF: That's true, we've heard  
11 that there are certainly de novo users, but really the  
12 reason that I think this line was in here was, again,  
13 speaking to the issue to assume that the woman had  
14 already been to her health care provider so, in fact,  
15 an accurate diagnosis was made, so that when she used  
16 this the first time around she would know that's what  
17 I need to use, and then subsequently would say these  
18 are the same symptoms, I can go back to the drug store  
19 and get this stuff.

20 I'm not really convinced that it has to say  
21 first time users there are not able to use this  
22 product. I think that if you do say let's complete  
23 the concept, don't think that just because you have a  
24 vaginal discharge and itching you have a yeast  
25 infection, here are other things that present the same

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1 way, not in that language, then you've accomplished  
2 what you need to accomplish, and you don't really have  
3 to get hung up with, you know, tell her, **you** know, she  
4 can't do it the first time she has these symptoms.  
5 What you do is, you just use the rest of the logic  
6 instead.

7 ACTING CHAIR BRASS: Other thoughts? Yes.

8 DOCTOR DATTEL: I'm going to agree with  
9 that, because I think we've heard ample evidence that  
10 even people who have been diagnosed with a yeast  
11 infection before are wrong the next time. So, it  
12 really seems, although I understand that's the FDA  
13 approved indication for use, but it seems like that's  
14 an emphasis probably of no great utility to anyone.

15 ACTING CHAIR BRASS: Okay.

16 Nobody wants to comment on treat versus  
17 cure ?

18 DOCTOR JOHNSON: I prefer treat,  
19 personally.

20 MS . HAMILTON : Yes, I'm concerned by the  
21 use of the term cure. I think in sort of colloquial  
22 parlance it sort of suggests a vaccine of sorts, that  
23 this will never happen again, and clearly we are  
24 talking about a condition that may have a tendency to  
25 repeat. And so, the offer of a cure strikes me as

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1 particularly distinct, again, obviously, I'm talking  
2 about parlance not understanding what the correct  
3 medical definition of a cure versus treatment would  
4 be, but I'm entirely comfortable with treatment, and  
5 not at all comfortable with cure.

6 DOCTOR GILLIAM: George.

7 DOCTOR BLEWITT: But it does cure most, and  
8 I think that's the fact of the matter. If you take  
9 cure in the purest sense, and just the word cure, well  
10 then that's a problem, but if it cures most, then I  
11 think that's a different context altogether.

12 ACTING CHAIR BRASS: Well --

13 DOCTOR BLEWITT: I'd ask FDA's comments,  
14 since it does appear on all of these packages as well,  
15 and how they felt about it.

16 ACTING CHAIR BRASS: -- let me just  
17 emphasize, and I have in analogous conversations in  
18 the past with this committee, that we be very careful  
19 not to impose our own values and interpretations on  
20 what these words mean, and what is very clear to us,  
21 or even within the Agency when we discuss those words,  
22 may not convey what is intended to the consumer.

23 And, I'm not saying it doesn't either, I'm  
24 just concerned that just because it is clear to us  
25 shouldn't be interpreted as evidence that it's clear

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1 to the consumer.

2 DOCTOR BLEWITT: Oh, I understand that,  
3 yes.

4 ACTING CHAIR BRASS: Doctor Davis.

5 DOCTOR DAVIS: I would like to comment on  
6 that. I was one person that was very upset about  
7 reading this, "cures most yeast infections, " and I  
8 didn't like the word cures, but I also equally did not  
9 like the word most, because I, quite frankly, do not  
10 know what the word most means, even to myself, and I'm  
11 sure I don't know what it means to anybody else in the  
12 room, because I don't know if that means greater than  
13 50 percent, that it means 70 percent, if it means 80  
14 percent, I really, truly have no idea what most means.  
15 so, I really -- so, I have a strong objection to the  
16 word most, because I don't know how you define that.

17 And, I think you made the point, we really  
18 don't know what that means to the consumer, and,  
19 therefore, I think that's a poor choice, and that's  
20 why I really felt strongly it should not be there.

21 ACTING CHAIR BRASS: Doctor Soiler.

22 DOCTOR SOLLER : Soiler, NDMA.

23 I don't think the interpretation of most is  
24 necessarily that important that we have to quantify  
25 it. I think it's a general impression that's being

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1 conveyed to the consumer.

2 One of the reasons these products were  
3 switched was that there were treatments that women  
4 were using before they were switched which masked  
5 symptoms, topical products, as well as external  
6 topical products, as well as continuous douching. And  
7 so, perhaps, trying to think about a way where that  
8 kind of verb is where we were coming from would help  
9 distinguish this category from another category where  
10 you really might have a concern in terms of masking  
11 symptoms.

12 And, it's not every -- of the OTC  
13 foundational concept for effectiveness in the OTC  
14 world is a reasonable expectation that you are going  
15 to get an effect, those are exact words used. So, I  
16 think it fits in there, I think it makes sense. I  
17 don't think most has to be **quantitated**, I think it's  
18 an impression that there can be, you know, it's  
19 implied that there will be a benefit. If there  
20 **wasn't**, why would it be there?

21 ACTING CHAIR BRASS: Yes.

22 MR. LEISSA: Brad Leissa. The historical  
23 perspective was asked from FDA, and at some point, I  
24 don't know when, but the issue of cures most was  
25 actually included on the carton and it's been there

1 until today. And, in various discussions that we've  
2 had with sponsors about choosing -- changing over to  
3 treat, the response we've frequently heard back is,  
4 well, make everybody else change, too, because it is  
5 seen as a promotional difference, and that there is an  
6 advantage about having cures most on the label versus  
7 treats.

8 ACTING CHAIR BRASS: Yes. That's one of  
9 the overall goals of standardization anyway.

10 If there are not other comments about the  
11 uses section, going once, going --

12 DOCTOR SOLLER: Doctor Brass, we have an  
13 extra warning in there, too, if you could take that  
14 up. We propose an extra warning under uses.

15 ACTING CHAIR BRASS: Yes.

16 DOCTOR McGRATH: I'm sorry, I thought you  
17 were asking if there was anymore comments about cure  
18 versus treat.

19 I would like to discuss the word repeat a  
20 little bit, only because I wonder how someone  
21 determines that they fall in the repeat range versus  
22 the range of frequency that would constitute a  
23 contraindication. So, I'm not sure if you want to  
24 deal with this in this section or further down on the  
25 carton.

1                   ACTING CHAIR BRASS :    Yes.  I think it's  
2 really two separate issues, because I have a concern  
3 about how recurrent is defined lower down, and repeat  
4 is undefined, and, again, what repeat means to a  
5 reader is subject to our conjecture.

6                   Theoretically, it means not the first one,  
7 but whether it means anything other than that, or even  
8 that, I don't know.

9                   Doctor Sachs.

10                  DOCTOR SACHS:    If you put, you know, if  
11 it's the first time da-da-da, and then you follow it,  
12 to treat vaginal yeast infections, then you don't need  
13 to write repeat, because you've written to the first  
14 time in that sentence and emphasized it, and it also  
15 means that if, you know, someone goes and sees their  
16 doctor who says you do have a yeast infection, and  
17 they feel comfortable using it even if it's the first  
18 time, and that way I don't think you lose anything.

19                  DOCTOR GILLIAM:  One last comment on cure.  
20 If it is implied that these products work, which you  
21 just said, then why do you even have to have to cure  
22 in there at all, cure most, or to treat.  I know it's  
23 getting picky, but --

24                  ACTING CHAIR BRASS:  Well, no, in fact,  
25 treat is the -- I mean, treat is the use without a

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1 value judgment in either direction.

2 Yes, Doctor Neill.

3 DOCTOR NEILL: I thought we weren't going  
4 to committee edit this.

5 ACTING CHAIR BRASS: We are not, no, we are  
6 not committee writing this.

7 DOCTOR NEILL: I'm going to make a couple  
8 of generic comments that don't relate to any specific  
9 section, so that those comments are heard now as  
10 opposed to later, namely, in the industry  
11 recommendation that we adopt by reference their  
12 current use guidelines which allow 4.5 point size  
13 type, no, 4.5 point size type is too small. Second,  
14 in reference to their recommendation that any sans  
15 serif font be acceptable, no.

16 ACTING CHAIR BRASS: Again, I'm trying not  
17 to discuss the '97 overall recommendations, and those  
18 points refer to the '97 global recommendations. I'd  
19 like to focus on the class labeling today.

20 I realize that Doctor Soiler took advantage  
21 of the opportunity to reinforce some of those  
22 opinions, but I really don't want to --

23 DOCTOR NEILL: Fortunately, those were the  
24 only two comments related to that.

25 ACTING CHAIR BRASS: Okay.

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1 DOCTOR NEILL: All the remainder have to do  
2 with class labeling.

3 Regarding the phrase "if this is the first  
4 time, " I would both keep that in the uses section,  
5 also bold or all capitalize that. There is a  
6 recommendation that apparently currently some of that  
7 wording is all capitalized, and as I've perused some  
8 of the package labels I note that there is a great  
9 degree of variability from one manufacturer to another  
10 about what is **bolded**, what is all capitals, what is  
11 upper/lower case, and to the extent that there needs  
12 to be some uniformity keep it within that phrase and  
13 specifically keep that phrase so that the entire  
14 phrase, not just the first preposition, but the entire  
15 phrase is emphasized.

16 ACTING CHAIR BRASS: Again, I'm sorry, just  
17 for clarity, caps are gone. Caps have been decided as  
18 not aiding clarity, and in the February, '97  
19 recommendations that's included.

20 DOCTOR NEILL: Okay. Then keep the phrase,  
21 and keep the entire phrase, or make the entire phrase  
22 bold faced.

23 That's it regarding uses.

24 ACTING CHAIR BRASS: Thank you.

25 And, Doctor Soiler pointed out that nobody

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1 commented on their suggested additional bullet that  
2 was added to the uses section in their draft that's  
3 included in Appendix A.

4 MS. NARRIGAN: Can I just ask a procedural  
5 question? Are we reviewing both of these  
6 simultaneously?

7 ACTING CHAIR BRASS: No, we are only  
8 reviewing the FDA proposal.

9 MS. NARRIGAN: We keep kind of going back  
10 to what the industry is suggesting.

11 ACTING CHAIR BRASS: Only to make sure that  
12 nobody wants to comment on it.

13 MS. NARRIGAN: So, we are looking at both  
14 of them.

15 ACTING CHAIR BRASS: We're only going to go  
16 through once this section, so that if any -- and,  
17 again, we are using this as the template, so if  
18 there's any points from any place that are relevant to  
19 this template --

20 MS. NARRIGAN: Okay.

21 ACTING CHAIR BRASS: -- that's why I'm  
22 trying to keep us on line and do it once.

23 MS. NARRIGAN: Thanks.

24 ACTING CHAIR BRASS: No comments on the  
25 additional point. Okay.

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1                   Moving on to warnings. Comments about the  
2 proposed warnings section of the carton label. Doctor  
3 **Neill.**

4                   DOCTOR NEILL: In reference to the comments  
5 that Ms. Alexander has made, the single most important  
6 warning is absent from the label, which is, you may  
7 have symptoms of some other more serious problem, see  
8 your doctor, and we haven't made any suggestions --  
9 well, we've made several suggestions, haven't arrived  
10 at any agreement about what that wording ought to be.  
11 But , within the warnings specifically, there's the  
12 reference to the condoms and diaphragms, and for  
13 vaginal use only, and I think warnings ought to  
14 include that specific warning related to misdiagnosis.

15                   ACTING CHAIR BRASS: So, the section --

16                   DOCTOR NEILL: Am I missing something?

17                   ACTING CHAIR BRASS: -- the section in the  
18 warning that's under "ask a doctor before use if you  
19 have one or more of the following, " you would like to  
20 take out the ask a doctor and move it into the above  
21 section?

22                   DOCTOR NEILL: Or, alternatively, within  
23 the add a doctor before if, or even in the -- one of  
24 the suggestions was, there's a question within the  
25 educational brochure, which I understand we are not

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1 discussing, but one of the suggestions was, there's a  
2 question that's not being asked, which is, do I have  
3 a vaginal yeast infection, there needs to be someplace  
4 in any of those, and I don't know where it needs to  
5 go, that suggests to the consumer that itching and  
6 irritation can be a sign of another more serious  
7 problem and you need to be aware of the risks of  
8 ignoring that, and need to have an appropriately low  
9 threshold for contacting your doctor, and, I'm sorry,  
10 I don't have a good way to say that, or even a  
11 suggestion as to where it's supposed to go within that  
12 warnings.

13 But, it seems so important that it ought to  
14 be emphasized either by moving it up underneath the  
15 "for vaginal use only" warnings, or black boxed, or  
16 something, I don't know. And, on the outside of the  
17 box .

18 ACTING CHAIR BRASS: Doctor Sachs.

19 DOCTOR SACHS: Other symptoms to contact  
20 your doctor in the setting of a vaginal discharge that  
21 might be very important, which we are not mentioning,  
22 are painful periods and painful intercourse, which are  
23 also signs of PID.

24 ACTING CHAIR BRASS: Cage.

25 DOCTOR JOHNSON: I'm confused as to whether

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1 this warning is in addition to the warning about the  
2 specific symptoms that might be related to the other  
3 pelvic inflammatory diseases or other vaginal  
4 infections . I'm just confused about what you are  
5 trying to get at.

6 DOCTOR NEILL: Women simply with a vaginal  
7 discharge, and without abdominal pain, fever, or, for  
8 that matter, without any symptoms at all, but we are  
9 presuming these women have at least vaginal itching or  
10 some symptoms. All we know is they've arrived in a  
11 drug store and they are looking for something for a  
12 symptom that they have. They many not even have  
13 vaginal itching or vaginal discharge, they might not  
14 have any of those symptoms, but they are in the drug  
15 store looking for some relief from something, and  
16 there's nothing within the warnings section which  
17 conveys that there are serious conditions that can be  
18 -- again, I'm sorry I don't have a good way to say  
19 this, but --

20 ACTING CHAIR BRASS: Well, I think, and  
21 several people have pointed this out, and I think one  
22 approach on the carton may be some succinct syntax  
23 under the "stop use and ask a doctor if," in terms of  
24 the persistence, because what you are pointing out,  
25 and what Cage is confused by, is that you do have a

1 section that says there are other syndromes, but even  
2 this clinical presentation might be something else,  
3 and under what conditions, even if you have this  
4 clinical syndrome, should you call a doctor and why,  
5 to complete the logic, so adding the STD or other  
6 vaginitis, appropriate syntax, might fit into that  
7 space.

8 DOCTOR NEILL: Yes. I think it could, I  
9 guess my concern is about the relative lack of  
10 emphasis on the severity of the potential  
11 complications that's implied by the absence of their  
12 mention.

13 ACTING CHAIR BRASS: Well, I would suggest  
14 we haven't heard a lot of data to say how big a  
15 problem that really is. We all acknowledge it can be  
16 a problem, but, in fact, we are talking about if  
17 symptoms persist a one week delay, assuming that the  
18 threshold for seeing a doctor on day one would have  
19 been equivalent to the threshold of buying an over-  
20 the-counter product, which I'm not at all convinced  
21 of, and so, the biggest danger is a transient STD  
22 **symptomatology** that the symptoms go away on day seven  
23 but the STD infection persists, and now the person  
24 might not seek attention. But again, they might not  
25 have sought attention anyway if the symptoms went away

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1 in a week spontaneously.

2 DOCTOR NEILL: I think that's not the only  
3 difference, because there is a wide degree to which  
4 patient preference ought to play a role in the  
5 decision about whether or not to use this, and if  
6 patients aren't informed about the potential severity  
7 of consequences, whereas, one patient might see a  
8 worded warning, vaginal itching and discharge could  
9 potentially be symptoms of, see that warning and say,  
10 oh, my gosh, I didn't even know that, I think I just  
11 want to see my health provider now anyway. Another  
12 patient might say, oh, but I think I'm aware of what  
13 they are talking about, and I know that that's not  
14 what I have, or my doctor has told me not to worry  
15 about that, and at this point there's a lack of  
16 information to allow the patient to make an informed  
17 decision about that.

18 ACTING CHAIR BRASS: Yes.

19 DOCTOR DATTEL: I was just going to say  
20 that I think it is separate from these warnings,  
21 because we are just talking about the symptoms that a  
22 woman would seek over-the-counter treatment for being  
23 misdiagnosed by her, separate from having abdominal  
24 pain, chills, fever, all of that. So, I would say as  
25 my box that I was going to put at the top, it could go

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1 here in bold, if that's going to be more in fitting,  
2 that these symptoms may mean another **sexually-**  
3 transmitted disease if -- and Doctor Soper had to  
4 leave, but that was his one comment that he wanted to  
5 bring forward also.

6 ACTING CHAIR BRASS: And, again, let me  
7 also point out that for those who have not spent much  
8 time dealing with these labeling issues with **NDAC**,  
9 that that space on the carton is at a premium, and  
10 that we have to pick truly these kinds of critical  
11 issues to advocate that appropriately succinct wording  
12 be developed for, and then other educational type of  
13 information can go into the other enclosure.

14 DOCTOR DATTEL: I think that's probably the  
15 most important warning that we are advocating here.

16 ACTING CHAIR BRASS: Good .

17 MS. KODA-KIMBLE: I think part also of the  
18 confusion is, you have this big thing called warnings,  
19 which is a big title, and the first thing you see is  
20 for vaginal and external use only. I mean, if they  
21 took this by mouth nothing would much happen.

22 And then, the next thing is about condoms  
23 and diaphragms, when we are really saying some of  
24 these other issues are far more important to the  
25 consumer.

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1 I would also ask the committee to consider  
2 adding under warnings, see your doctor, or whatever,  
3 if you have diabetes, because the **fungal** infection  
4 either could signal poorly controlled diabetes, and  
5 the **fungal** infection could worsen diabetic control.  
6 It was not at all discussed today, but it's a concern  
7 of mine.

8 ACTING CHAIR BRAS S : Yes, Kathleen.

9 MS. HAMILTON: Well, I just want to second,  
10 I think, the general view of the committee that I  
11 think the appropriate place for an STD warning is  
12 above the, "ask a doctor before you use," to me, it  
13 falls in the category of very significant general  
14 information to the patient population who is likely to  
15 be looking at this product, and that it is a good use  
16 of carton space.

17 It occurs to me, having heard a little bit  
18 of the data presented on who the population is, that  
19 we ought to be particularly troubled by suffering with  
20 **STDs**, is potentially a younger group of women who may  
21 not have direct access to medical care, or may be  
22 embarrassed to seek it, or may be confused, and so it  
23 strikes me that the consumer who is going to be in the  
24 pharmacy looking at these products may have, you know,  
25 generic vaginal discomfort, irritation, and might very

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1 well be significantly educated by a warning in bold  
2 print that says, you know, STDS may have the same  
3 symptoms that this product was intended for, but they  
4 may not, and you really, really need to be aware of  
5 that. It strikes me as really important.

6 And, the second issue on the warnings that  
7 I wanted to just touch on is the language that's been  
8 suggested dealing with condoms and diaphragms. In a  
9 general way, I guess one of my questions is, have we,  
10 in the course of the labeling discussions, and  
11 research, and especially from the literacy  
12 standpoint, ever sort of tested consumer knowledge of  
13 a whole range of both body parts, and symptoms, and  
14 treatment potentials?

15 Even this new label, which I know is a  
16 product after a couple of years of really trying to  
17 get the language down to be simple, it still seems to  
18 me that we occasionally have verbiage that comes up  
19 that isn't as simple as it could be, and to say that  
20 condoms and diaphragms, you know, this product may  
21 cause them to fail, why wouldn't we say birth control  
22 devices, such as condoms and diaphragms, won't work in  
23 conjunction with this product, cause them to fail  
24 seems unnecessarily --

25 ACTING CHAIR BRASS: Yes, I think condoms

1 and diaphragms won't work is just --

2 MS . HAMILTON : Yes, you know, and let's  
3 call them what they are. If you are using birth  
4 control in conjunction with this product, check with  
5 your doctor, they won't work, you'll get pregnant.

6 ACTING CHAIR BRASS: Yes.

7 I just want to make two comments about this  
8 section. First of all, I absolutely agree that it's  
9 disproportional to have the Fungistat may damage  
10 condoms and diaphragms in the larger second line as  
11 compared to some of the other warnings. I would guess  
12 this is a really secondary level concern, compared to  
13 some of the other things we are talking about.

14 But also, I thought dissociating it from  
15 the "do not have vaginal intercourse" statement was  
16 confusing at least, and bizarre at best. So, I think  
17 that there has to be -- there might be some  
18 integration or parsimony or linkage there that would  
19 save space.

20 And , while I completely agree with the  
21 concern about STD, I think in the interest of  
22 perspective, the data we have about inappropriate use  
23 did not identify, other than some trichomoniasis  
24 cases, and they didn't look for it well in the studies  
25 we have available to us, whether missing STD diagnoses

1 was a major problem with misuse, that it was no  
2 infection, and other problems, that dominated the  
3 numeric issues, but clearly, the STD issue, which I am  
4 in complete agreement with, is the most serious danger  
5 of misuse that we have discussed.

6 DOCTOR NEILL: If I could make a comment to  
7 that.

8 ACTING CHAIR BRASS: Please.

9 DOCTOR NEILL: I don't think I want to wait  
10 to see data that suggests that we've missed a big  
11 problem.

12 ACTING CHAIR BRASS: Any other thoughts or  
13 comments about the warnings section?

14 Doctor Sachs.

15 DOCTOR SACHS: Under "ask your doctor, " I  
16 just want to reiterate, I still think it would be a  
17 good idea to say something about if you have a new  
18 partner or multiple sex partners.

19 The other issue, as a pediatrician and  
20 adolescent person, is it says not to use if under 12,  
21 we might want to actually raise that to 16, or 18, I  
22 mean, you guys can debate about that, but given that  
23 the consequences of PID in adolescents is particularly  
24 burdensome, you know, that is just something that  
25 should be considered.

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1           ACTING CHAIR BRASS : I agree with that, and  
2 I think the issue of justifying the appropriateness of  
3 12 year old's self-selecting the product needs to be  
4 seriously thought through.

5           Another issue I was concerned about in the  
6 warnings is the apparent discrepancy, and, perhaps,  
7 our experts can help me with this, in the definition  
8 of recurrent WC is defined in the literature we  
9 provided, as four per year, versus tolerating once a  
10 month or three in six months, and three in six months  
11 is, I think, going to be a hard thing for the consumer  
12 to understand, that that seems to have a much higher  
13 threshold of concern than the literature would have  
14 suggested raise the flag of recurrent WC in practice.

15           Do any of our gynecologists have a comment  
16 on that?

17           DOCTOR DATTEL: Well, I think Doctor Soper  
18 used the standard accepted definition of recurrent for  
19 that.

20           ACTING CHAIR BRASS: Which is four a year.

21           DOCTOR DATTEL: Four a year.

22           MS. NARRIGAN : I also think giving two  
23 examples is actually confusing, and the consumer then  
24 has to stop and think about both of those conditions,  
25 and also, a year is a commonly accepted span of time.

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1 So, I would vote for the four.

2 ACTING CHAIR BRASS: Doctor Davis.

3 DOCTOR DAVIS: We did spend quite a bit of  
4 time trying to figure out the language here, and what  
5 we came up with was what we thought would be sort of  
6 common language, such as once a month. Now, that's  
7 not a medical term, by any stretch of any imagination,  
8 because we are saying such as rather than definitely  
9 or specifically once a month, and we felt that going  
10 out to the one-year window, stating four in one year,  
11 we were then saying, well, now, how many women are  
12 really going to remember what's happened in the past  
13 12 months in terms of these yeast infections, I mean,  
14 did I have three, did I have four, did I have two.

15 And so, that is simply our rationale, non-  
16 scientific, if you will, for coming up with a phrase  
17 of such as once a month or the three in six months.

18 Now, the reason we did not choose two in  
19 six months is that technically the woman assumes she  
20 has an infection now, so that's number one, so if she  
21 had an infection five months ago, or four, or six  
22 months ago, well, that's two in six months  
23 technically, and then it's saying don't use this  
24 product. And, we really felt that it was appropriate  
25 for women, under those circumstances, to use these OTC

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1 products, infection now and then an infection five  
2 months ago, four months ago, so that's why we said  
3 three in six months.

4 But, we really would like comments from the  
5 committee, because nobody in our group is saying we  
6 absolutely know we've got the best statement there.

7 ACTING CHAIR BRASS: I just think it's  
8 really confusing, and you talked about the kind of  
9 concepts that consumers have trouble extrapolating  
10 from a label, they have to be able to understand that  
11 they have to have had more than one, can't be the  
12 first, but they can't have had more than -- you know,  
13 and none of that may be important enough to worry  
14 about, as was pointed out for the first time, but it  
15 seemed to me from reading that there was a health risk  
16 in not seeking attention if you were truly having what  
17 was called recurrent WC, and to err on the side of,  
18 a prompting to that medical concern was more important  
19 than not.

20 DOCTOR McGRATH: Patricia McGrath. I would  
21 just like to say that I think there should be only one  
22 number choice too, that that's confusing, but I also  
23 find that we're still not really informing the  
24 consumer, we are almost quasi informing them about  
25 facts, and then asking them to infer if they fit into

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1 those categories the seriousness, in essence, of why  
2 they shouldn't use the product, or should go see a  
3 doctor.

4 And, I'm wondering if we can move to being  
5 much more bottom line. You used the words  
6 "significant health risks, " I believe, Eric, and just  
7 say something very clear that this, this and this may  
8 indicate that your symptoms mean this, see a doctor,  
9 and that that would be a much cleaner way of informing  
10 somebody that they are at risk, and that unless they  
11 know they have a yeast infection they maybe should  
12 seek health professional advice.

13 I'm concerned that we're giving all of  
14 these clauses, but never really connecting the  
15 importance of falling into those categories with the  
16 seriousness of the problem.

17 ACTING CHAIR BRASS: Any last thoughts on  
18 warnings?

19 Yes, Doctor Chin.

20 DOCTOR CHIN: I just want to make a comment  
21 about the disjointed nature of the carton label. It  
22 does seem that way. In the development of labeling,  
23 we have always felt that, well, if you say something,  
24 if you explain about it, then that tells the consumer  
25 why they should be doing something or not be doing

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1 something.

2 And, moving towards the standardized  
3 format, what's happened -- and also, with the balance  
4 between not having a lot of space to put a lot of  
5 information, we then went from a label that had under  
6 each bullet, really, an explanation for each bullet,  
7 where all the explanation was removed and that's why  
8 it was very important to then say that the brochure  
9 had additional information, and they should read that.

10 And, whether or not people do is a  
11 different matter, but a lot of the information went  
12 into the brochure, and so, it was taken out, and the  
13 placing of some of these warnings, you know, it may  
14 damage condoms and diaphragms and cause them to fail  
15 had other explanations to it, and it was with the do  
16 not have vaginal intercourse too, but in playing with  
17 a lot of that and removing some of the explanations,  
18 it was reordered. So, we welcome all of your comments  
19 on it.

20 ACTING CHAIR BRAS S : Yes.

21 DOCTOR LEWIS: I was just going to say that  
22 I think the industry's placement of some of those  
23 things makes a little more sense, like the warning  
24 about condoms and so on, it's down underneath  
25 intercourse, right next to intercourse, and also

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1 eliminating the phrase, "if you have one or more of  
2 the following, " just if you have and then listing the  
3 symptoms.

4 You could just put see brochure or  
5 something like that, you know, ask your doctor, see  
6 brochure.

7 ACTING CHAIR BRASS: Doctor Dattel.

8 DOCTOR DATTEL : Are we going to be done  
9 with this section, so we should talk about intercourse  
10 now ?

11 ACTING CHAIR BRASS: Yes.

12 DOCTOR DATTEL : I had a problem using the  
13 word intercourse. I think that it does not  
14 necessarily apply to all women who will be buying  
15 over-the-counter products, and vaginal sex would be a  
16 better term than intercourse, which implies  
17 male/female relations and a certain type of sexual  
18 activity, as opposed to placing other things in the  
19 vagina or having other types of sexual activity.

20 MR. LEISSA: One question for  
21 clarification, Doctor Soper's comments about with  
22 **STDs**, whether they didn't offer specific wording, but  
23 the issue about if a woman had vaginal symptoms and  
24 she's had multiple sexual partners, or a new sexual  
25 partner, whether that would be a message we'd want to

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1 see here.

2 DOCTOR LEWIS: I think that is something  
3 that most OB/GYNS feel very strongly about, and other  
4 health care providers to women do also, it's a  
5 standard warning that women get.

6 ACTING CHAIR BRASS: And, you feel  
7 strongly, again, just for clarity sake, you feel  
8 strongly it's a carton issue, not an educational  
9 enclosure issue.

10 DOCTOR DATTEL: I think that wording is a  
11 carton issue. Some of the other things, you know, for  
12 example, we make -- I run all the HIV clinics, so I  
13 have this issue about HIV is highlighted, but it's  
14 highlighted in a way on this that really makes no  
15 sense, it's basically saying, if you have HIV you  
16 can't use this. Well, sure you can. You just ought  
17 to find out if you have HIV, I mean, HIV patients get  
18 yeast infections commonly, and know it and often treat  
19 themselves. So, to me, that's something that doesn't  
20 need to be there.

21 However, more importantly, if you have a  
22 lot of sexual partners then you see your doctor and  
23 then you get tested for HIV, and maybe that's why you  
24 have the yeast infection.

25 So, if I was going to remove something, I'd

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1 put that in the brochure, and I'd put the thing about  
2 multiple sexual partners and see your doctor, because  
3 that gets the same message across that you want about  
4 HIV being the ultimate sexually-transmitted disease,  
5 and its relationship to yeast vaginitis.

6 ACTING CHAIR BRASS: Beth.

7 MS. SLINGLUFF: Yes. Actually, if you were  
8 going to drive at trying to **save space on cartons**,  
9 things like causing diaphragms and condoms to fail  
10 could be part of the educational brochure. That  
11 doesn't have to be on the carton. The consumer, at  
12 the time of purchase, doesn't have to see that on the  
13 label .

14 ACTING CHAIR BRASS: Particularly, if you  
15 are told not to have sex.

16 MS. SLINGLUFF: Right, exactly, but that  
17 kind of stuff.

18 The other point was, and I admit it, it's  
19 anecdotal, I worked for some time in a **federally-**  
20 **funded STD clinic**, women's definitions of multiple  
21 partners, new partner vary. One of our standard  
22 questions was, do you have a new partner? Oh, no.  
23 How long have you been with this partner? A week.  
24 That might bear further explanation in the brochure.

25 ACTING CHAIR BRASS: Yes. Again, this goes

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1 back to what's clear to us requires careful thought  
2 when the final language is synthesized by the Agency.

3 MS. NARRIGAN: I had questions for beyond  
4 intercourse. The language under "stop use and see a  
5 doctor if symptoms do not improve in," I would vote to  
6 change that to after, to be consistent with after in  
7 the seven-day phrase directly below it, because in  
8 three days could be anywhere from five minutes in the  
9 three days to the end of the 72nd hour. And, I think  
10 the meaning is that it's the full three days.

11 I wonder about, God forbid adding words,  
12 but after three days of use, because when I first read  
13 this myself, I thought after three days of finishing  
14 the therapy, or after three days of using it, or what?

15 ACTING CHAIR BRASS: Yes. Well, again, it  
16 can't be in use because of those single-dose products.  
17 so, it would be three days after first dose or  
18 beginning therapy.

19 MS. NARRIGAN: Oh, after starting.

20 ACTING CHAIR BRASS: Yes, after starting or  
21 something like that.

22 DOCTOR DATTEL: Which is also true for the  
23 seven day, you begin to get relief.

24 MS. NARRIGAN: Right .

25 ACTING CHAIR BRASS: Again, that goes back

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1 to what we talked about earlier, trying to incorporate  
2 some language about expectations more clearly into  
3 that section.

4 Any other things about warnings? Okay.

5 Directions. Again, just to remind people,  
6 the industry suggested included the cream external  
7 directions on the carton at that section if  
8 appropriate.

9 DOCTOR SOLLER: We had an additional phrase  
10 on that single one pager that was handed out to you.

11 ACTING CHAIR BRASS: Yes, use the full X  
12 days direction was suggested to be added.

13 Thoughts? Comments? Doctor Sachs.

14 DOCTOR SACHS: Having had lots of kids that  
15 have no clue what to do with this stuff, and, you  
16 know, picking it up, something simple like this  
17 product is used much like a tampon, or whatever, would  
18 actually be quite helpful, and would also disqualify  
19 someone who is uncomfortable using tampons or putting  
20 anything else in their body.

21 ACTING CHAIR BRASS: Again, you are going  
22 back to your earlier point about having any idea  
23 what's in the carton before you buy it.

24 Cage.

25 DOCTOR JOHNSON: I hate todo this, but I'd

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1 like to disagree, because I think if you put that  
2 there then the woman is going to be forced to read the  
3 instructions, you see, because she'll already know how  
4 to use a tampon and, therefore, can skip the  
5 instructions. I would rather have her read a booklet  
6 than not read the booklet.

7 ACTING CHAIR BRASS: But, I think the  
8 theme, that's why I linked it to your earlier comment  
9 which I think is quite appropriate, that having some  
10 idea what type of device or product is in the carton,  
11 how that's identified I think thematically is a valid  
12 point.

13 DOCTOR DAVIS: Well, but when the  
14 manufacturer does their final carton label, it will  
15 say insert one suppository into the vagina at bedtime  
16 for three days in a row, or one day in a row. I mean,  
17 those blanks will be filled in, or it will say, it  
18 could say, one **prefilled** applicator into the vagina at  
19 bedtime, or it could say one reusable applicator. I  
20 mean, I'd have no problems with that.

21 So then, if the person is reading the  
22 product, and I'm sure on the labeling it says it's a  
23 disposable applicator, reusable applicator, or  
24 **prefilled**, I know it says on the **prefilled**, and that's  
25 really in pretty large font, not right here on the

1 label, but on the back flap, side flap, or whatever,  
2 front panel. So, I don't think --

3 ACTING CHAIR BRASS: I guess what's being  
4 suggested is what an applicator is may not convey  
5 anything to a first-time user of these kinds of  
6 products.

7 DOCTOR SACHS: If you look on some of the  
8 labels, the pictures are really clear, I mean, without  
9 plugging Vagistat or whatever, it had a very clear  
10 picture, where like the Monostat-1 you have to look in  
11 the corner, for the creams you have to read under the  
12 label that this is a cream. I mean, you know, I would  
13 say in the population I see, you know, that's not so  
14 obvious, and if they have to read the whole thing to  
15 figure out what they are supposed to buy they'll  
16 probably walk away without it.

17 ACTING CHAIR BRASS: No other thoughts  
18 about the directions or the proposed changes?

19 Yes, Kathleen.

20 MS. HAMILTON: I like the FDA proposal and  
21 would like to discourage eliminating the words "and  
22 information" that was proposed earlier. Initially,  
23 I'm not sure I had much of a sense of that, but I  
24 think as this discussion moves along it's clear to me  
25 that we are going to be providing information, not

1 just instructions on how to use the product that we  
2 believe is really important.

3 MS. NARRIGAN : What about external use  
4 directions? There was a discussion about --

5 ACTING CHAIR BRASS: I asked that.

6 MS. NARRIGAN: -- I guess I --

7 ACTINGCHAIR BRASS: Yes, no, comments, you  
8 think they should be added, shouldn't be added?

9 MS. NARRIGAN: Well, if I missed it, then  
10 I don't get to make a comment.

11 ACTING CHAIR BRASS: No, YOU do, YOU do.

12 MS. NARRIGAN: I blanked out.

13 I don't know what to say, there are pros  
14 and cons to putting it on. I think -- I don't know.

15 DOCTOR CHIN : The external use  
16 instructions, the general instructions, will not be  
17 excluded, it's just that in doing the model, it's  
18 true, we listed both uses up there and in the  
19 directions we didn't have that second choice.

20 For all products that have the external use  
21 indication the instructions will be there, for  
22 products where that is --

23 ACTING CHAIR BRASS: Thank you for that  
24 clarification.

25 DOCTOR CHIN: -- not going to be, it will

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1 not be there.

2 ACTING CHAIR BRASS: Thank you for that  
3 clarification.

4 And, any comments, again, about -- going  
5 once, going twice, about the need to specify use the  
6 product until it's all gone, or use for X days? Okay.

7 DOCTOR SOLLER : Is that agreement?

8 ACTING CHAIR BRASS : Indifference,  
9 unanimous indifference. Okay.

10 MS. NARRIGAN: Can I ask about the wording  
11 for external use?

12 ACTING CHAIR BRASS: Yes.

13 MS. NARRIGAN: Anatomically there is no  
14 external vagina. The wording in another place says  
15 "skin around, " skin around the vaginal opening, around  
16 the vagina, I would vote for that language rather than  
17 the use of external vagina.

18 DOCTOR DAVIS: As it is stated here on the  
19 industry proposal, it says, "Gently apply the cream  
20 onto the itchy, irritated skin outside the vagina  
21 twice daily." I think that's anatomically correct.  
22 So, you are referring to what?

23 MS. NARRIGAN: Higher up in the proposal  
24 that's from NDMA, they say under warnings, their  
25 suggestion is to use the word external vagina use

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1 only, and I believe that was referring back to  
2 actually the FDA's use of that term.

3 DOCTOR SOLLER: That's right, we chose --  
4 -Soiler, NDMA -- we chose FDA's term, and the reason we  
5 chose it was that when we sat around the table we  
6 couldn't come up with short, pithy way of getting to  
7 that because you don't want, you know, a phrase that  
8 now gets longer, and we thought, well, external  
9 vaginal, not the best, but probably gets the meaning  
10 across.

11 ACTING CHAIR BRASS: It seems like skin  
12 around isn't a bad alternative.

13 MS. NARRIGAN: It's more letters.

14 DOCTOR SOLLER: Yes, but try for vaginal  
15 use only, and now put into a combination product and  
16 try to have it be short and succinct.

17 ACTING CHAIR BRASS: Just replace external  
18 with skin around vagina, or something, I don't know.

19 DOCTOR SOLLER: We'll work on it.

20 ACTING CHAIR BRASS: Other information,  
21 everybody like the temperature cite.

22 Inactive ingredients and the global  
23 acceptance of new 800 -- non-800 toll-free numbers.

24 What about the hours for the toll-free  
25 number? Cage.

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1 DOCTOR JOHNSON: I think the industry  
2 suggestion is very good.

3 ACTING CHAIR BRASS: To delete the hours  
4 for the toll-free number.

5 DOCTOR JOHNSON: Yes, to delete the hours  
6 and allow the consumer the freedom to interact with  
7 whatever menu they have.

8 As Doctor Stover pointed out, some of them  
9 even have 24 hours.

10 ACTING CHAIR BRASS: No, but the question  
11 is whether there are some where the phones absolutely  
12 aren't answered at some hours, where it just rings.

13 DOCTOR LEWIS : It's a toll-free call, if  
14 the consumer calls and they don't get the information,  
15 then they can probably figure it out, call back  
16 during, you know, other hours.

17 ACTING CHAIR BRASS: Okay.

18 DOCTOR DATTEL: By the same token, I think  
19 the suggestion by Doctor Alexander's group of  
20 including an 800 number for STDS on the back,  
21 underneath that, is excellent. I think that provides  
22 another avenue for a consumer to get information about  
23 what our main focus is.

24 ACTING CHAIR BRASS: And, again, you like  
25 that on the carton rather than in the educational

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1 brochure?

2 DOCTOR DATTEL : I mean, I would put it in  
3 both places, but I think if you are going to have that  
4 toll-free number, you know, you can say, or for  
5 information about STDS 1-800 --

6 DOCTOR NEILL: I would respectfully  
7 disagree, just because industry is going to have no  
8 say over either who answers that other phone, what's  
9 said on that other phone. While I have no doubt about  
10 the voracity of the organization that stands behind  
11 the number, and it sounds like a wonderful thing, I  
12 think it would be putting an undue burden on industry  
13 to assume responsibility and accept responsibility for  
14 an organization that they have no connection with at  
15 all .

16 ACTING CHAIR BRASS: And an implied  
17 endorsement that we know what is said on that phone,  
18 and we happen to think it's worthwhile.

19 DOCTOR NEILL: Yes, it's a good idea, but  
20 not workable.

21 ACTING CHAIR BRASS: Yes, Doctor Chin.

22 DOCTOR CHIN: I think there's room for  
23 compromise on that one. In the educational brochure  
24 on some of the information for the HIV, there is the  
25 800 number for more information about HIV. So, if

1 there is a better source of information about STD, it  
2 could be placed in the educational brochure.

3 DOCTOR NEILL: Yes, the distinction being  
4 that unless I missed one of those HIV phone numbers,  
5 all of those phone numbers referred to numbers run by  
6 CDC or other government agencies.

7 DOCTOR DATTEL: I think the National STD  
8 Hot Line is also --

9 DOCTOR NEILL: I'm sorry, is that funded by  
10 the government?

11 DOCTOR DATTEL: Isn't it through -- their's  
12 through the CDC?

13 DOCTOR NEILL: Not that I'm aware of.

14 ACTING CHAIR BRASS: Certainly, the Agency  
15 can look into that.

16 MS. NARRIGAN: Can I ask the Chairman to go  
17 back to the warnings section for 30 seconds.

18 ACTING CHAIR BRASS: Certainly.

19 MS. NARRIGAN: I apologize.

20 ACTING CHAIR BRASS: No problem.

21 MS. NARRIGAN: My brain is too many places.

22 I'm interested in the pregnancy language,  
23 and not being on the OTC Committee I think I'm getting  
24 the drift that there is a standard **speel**, it's got to  
25 look that way, is that correct?

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1                   ACTING CHAIR BRAS S :    The "if pregnant or  
2 breast feeding"?

3                   MS. NARRIGAN:    Yes, I mean, there are no  
4 choices.

5                   ACTING CHAIR BRAS S :    That is a standard  
6 generalized syntax, yes.

7                   MS. NARRIGAN:    It's a shame, because it's  
8 kind of ironic that when you are pregnant you are much  
9 more likely to have candida, and you have to go to  
10 extra steps, or there's actually an extra barrier to  
11 use with a safe drug.

12                  ACTING CHAIR BRAS S :    Again, the issue was  
13 the risk -- my sense is that the risk of misdiagnosis  
14 was felt to be sufficiently higher, that that was not  
15 a self-diagnosis.

16                  MS. NARRIGAN:    Misdiagnosis?

17                  DOCTOR NEILL:    Bacterial vaginosis in  
18 preterm pregnancy, specifically.

19                  ACTING CHAIR BRASS:    Yes.

20                  DOCTOR NEILL:    For a woman who may have a  
21 vaginal discharge, without itching or other symptoms,  
22 who presents wondering, could this be yeast, could it  
23 be bacterial vaginosis, I think that that's a  
24 sufficiently higher level of concern that I would have  
25 that's more time limited.

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1 ACTING CHAIR BRASS: Right .

2 DOCTOR NEILL: More specifically related to  
3 the condition, I would keep the uniform language.

4 ACTING CHAIR BRASS: Doctor Katz.

5 DOCTOR KATZ: I also want to emphasize that  
6 point, is that the language is standard, standard  
7 language, and it also intended, remember, that this is  
8 for very certain conditions that this product is not  
9 intended for as an over-the-counter product for a  
10 consumer to go and select it.

11 If a physician is telling her to go buy an  
12 over-the-counter product, that's different, and a  
13 pregnant woman should be under the advice and guidance  
14 of a physician or a health care practitioner, whoever  
15 she is seeing for her pregnancy, to be told to go use  
16 the product, and then it would be appropriate. But ,  
17 it wouldn't be appropriate for us to tell a pregnant  
18 woman to go and buy the product without being seen  
19 first.

20 MS. NARRIGAN: No, but the rules -- not the  
21 rules, but the regulations would be the same, pregnant  
22 or non-pregnant, if you haven't had it before, get  
23 care, et cetera, but I won't go into that.

24 ACTING CHAIR BRASS : No, just for  
25 information sake, if we felt the product should be

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1 used with self-diagnosis during pregnancy we can elect  
2 not to put that in there, but that's not the case  
3 here. So that, if there's going to be a pregnancy  
4 warning, this is the standard syntax, and it was the  
5 feeling that this is not a self-diagnosed --  
6 appropriate self-diagnosed self-treatment during  
7 pregnancy.

8 MS. NARRIGAN: Okay.

9 ACTING CHAIR BRASS: Did that address the  
10 points Doctor Chin and Davis had on this? Okay.

11 Doctor Katz, have we addressed the issues  
12 with respect to the label to your satisfaction?

13 DOCTOR KATZ: Yes, you have. The only one  
14 question that I do have, and I'm going to go back  
15 again, and I know that we talked about not  
16 wordsmithing, but going back to the uses, if anyone  
17 can think of a way to craft the statement that's been  
18 kind of bantered as to where it should be, "if this is  
19 the first time you have had vaginal itching and  
20 discomfort, see your doctor, " and including an STD  
21 warning in that, we would appreciate that as well.

22 ACTING CHAIR BRASS: Yes, that's the kind  
23 of thing where, perhaps, if people thought about it  
24 they could E-mail suggestions directly to Doctor Katz,  
25 and they could then take the best suggestions and play

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1 with them and come up with an optimum.

2 Okay. If we could have the 15 questions  
3 from the educational brochure up on the screen, and  
4 rather than going through these individually, I think  
5 there will be less controversy here, it was earlier  
6 suggested that the educational information, with  
7 respect to **STDs**, be strengthened in this educational  
8 brochure, whether it's a separate point, there are  
9 several ways to suggest it. I think there was a sense  
10 of consensus about the importance of adding that type  
11 of information to the educational brochure.

12 Are there other points about the  
13 educational brochure, points that should be further  
14 emphasized, new points, or points that are  
15 unnecessary?

16 DOCTOR BLEWITT: I just had a comment we  
17 were discussing earlier and I thought that I had with  
18 regard to what draws a consumer to -- what draws a  
19 consumer's attention to the brochure, and wondered  
20 whether the term educational might actually turn some  
21 people off, and wonder whether some more user friendly  
22 term, like consumer aid materials or something like  
23 that, as opposed to educational. Educational could  
24 have the context that, well, if I wanted to learn  
25 something more about that then I can read this

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1                   However, it sounds like, from the  
2 discussion today, that the label and the brochure are  
3 very much joined at the hip, so what you'd want to do  
4 is to be able to draw people over to the brochure and  
5 think of ways to better do that.

6                   So, I would just open up the name of this  
7 product for discussion.

8                   ACTING CHAIR **BRASS**: To somehow imply that  
9 it does include the directions.

10                   Yes, Doctor Katz.

11                   DOCTOR KATZ: Basically, the consumer  
12 educational brochure is really kind of a holdover or  
13 tie-over from the patient educational leaflet that  
14 goes along with some prescription products. And, we  
15 actually are open to suggestions of a better way to  
16 try to convey the message.

17                   We also agree with the earlier comment that  
18 **NDMA** made, it's not a patient information leaflet or  
19 whatever it is, it's a consumer leaflet. And, we are  
20 open to suggestions as to what else to tag on with  
21 consumer.

22                   DOCTOR BLEWITT: Or, important facts to  
23 know, or something like that.

24                   ACTING CHAIR **BRASS**: Doctor **Neill**.

25                   DOCTOR NEILL: The distinction between the

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1 phrase consumer and patient speaks a legal ease to me,  
2 which implies that somehow there's a difference if I,  
3 as a physician, tell my patient, who has now had a  
4 second infection, please go and pick this up and have  
5 it done, and the distinction is that the relationship  
6 between the patient and myself, as a provider of care,  
7 is provider/patient, but somehow the relationship  
8 between the company that's made this and put it out  
9 and the buyer of that product is consumer and product,  
10 and that if, as Prevention magazine tells me, 45  
11 percent, you know, of the patients go out and use this  
12 for the first time without the advice of a physician,  
13 or a provider, or being treated, that somehow makes  
14 the relationship different. I don't know.

15 I looked through each of these to see  
16 whether any place on the papers it said patient, it  
17 doesn't, it doesn't say consumer either, so it's  
18 fairly semantic and FDA can call it whatever you want  
19 to, I guess, but there is -- there's a distinction  
20 certainly in what I'm responsible for legally, if the  
21 person in my office is a consumer versus a patient.

22 ACTING CHAIR BRASS: Hasn't your hospital  
23 administrator told you that yet?

24 Yes, Kathleen.

25 MS. HAMILTON : I like the idea a lot of

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1 maybe getting away from using the educational brochure  
2 and think that it's really worth spending some time  
3 on. I think women, especially younger women, might  
4 actually be drawn to read it in a way that we know  
5 right now one of our biggest struggles **is** to get  
6 people to read this information, if it **was packaged in**  
7 **a way**, and this is not intended to be facetious, but,  
8 you know, like out of Glamour magazine, you know, four  
9 women that knew, you know, whatever, something that's  
10 really packaged in a way that would be very consumer  
11 friendly, appear very readable, minimum legal ease and  
12 medical ease, that it actually might could be a very,  
13 very useful tool.

14 ACTING CHAIR BRASS: Yes, Beth.

15 MS. SLINGLUFF: Some of these points have  
16 actually already been made. First off, there is  
17 material that's suggested for the carton right at the  
18 moment that I think some of those bullets can simply  
19 be placed in the brochure, saving yourself room on the  
20 carton for more important messages, like there are  
21 other things that can cause vaginal itching and  
22 discharge, you need to be sure of what you are  
23 treating.

24 Secondly, I actually like **NDMA's** suggestion  
25 about **sagittal** use only, and I like arrows, I think

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1 arrows are good, and I very much like the idea that  
2 came from American Social Health Council about  
3 additional information about what else can cause  
4 similar symptoms.

5 ACTING CHAIR BRASS: I would just again  
6 observe that the linking of the no sex and condoms  
7 fail applies here as well.

8 Yes, Doctor Gilliam.

9 DOCTOR GILLIAM: I just, on getting them to  
10 read the whole brochure, this is maybe misleading the  
11 consumer a little bit, and we could still come up with  
12 a better title, but still just putting directions for  
13 use, then they have to go through all the other  
14 information and they eventually get to the actual use  
15 directions, but at least they would look through some  
16 more things, they would at least look through all the  
17 questions.

18 ACTING CHAIR BRASS: Maybe wishful  
19 thinking, yes.

20 Yes.

21 MR. LEISSA: I think part of our intention  
22 here with this page four, which, you know, has the  
23 title of "Patient Educational Brochure," with the  
24 points is really more for the committee, not to  
25 anticipate that this would even necessarily have that

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1 title.

2 As you know, there's a similar initiative  
3 underway for prescription drugs, what they are calling  
4 patient package inserts, so I'm not sure we even need  
5 to -- but, we need a name so we can call it when we  
6 are talking to each other in the companies about  
7 modifying the carton versus whatever that thing is  
8 inside.

9 ACTING CHAIR BRASS: Doctor Neill.

10 DOCTOR NEILL: The patient package,  
11 whatever these things were that we got in the actual  
12 package, one of them, Gyne-Lotrimin-3, it was glued,  
13 **as** are many of the patient inserts, package inserts,  
14 for the prescription sample drugs that I get, and it's  
15 clear from the form of many of these, using small  
16 print as they do, and using somewhat smaller than,  
17 say, a standard 8-1/2 x 11 form, absent for the most  
18 part color or half-tone imaging, that there are a lot  
19 of things that could be done to improve readability,  
20 but for a lot of probably very good reasons related to  
21 conserving paper, and minimizing packaging, et cetera,  
22 they are not.

23 If there's a way for FDA to prohibit the  
24 gluing of these, which seems to me to be a singular  
25 barrier to reading them, great, do it.

1           And then, specifically related to the  
2 contents, since that gluing probably has more to do  
3 with the overall thing that we are not supposed to be  
4 talking about, the first question, why should I use X,  
5 it seems to me that the more important first question  
6 on the brochure, given that the patient has already --  
7 the consumer has already bought the product, is should  
8 I use X, not why should I use. The text may be  
9 entirely similar, this product X is intended for use  
10 to treat XYZ, but somehow the question implies that it  
11 is okay for there still to be some doubt in the mind  
12 of the patient, whereas, the current phrasing, why  
13 should I use implies the opposite. You know, the  
14 patient is being sold here.

15           ACTING CHAIR BRASS: Doctor Katz, have we  
16 addressed all the issues for the educational brochure  
17 that you had in mind?

18           DOCTOR KATZ: Yes, you did.

19           MS . NARRIGAN : I just -- I'm sorry, I'm  
20 talking an awful lot, I have just a general concern  
21 about the sense of redundancy with some of the  
22 material. One example is under who can get a vaginal  
23 infection, there's a nice paragraph describing kind of  
24 HIV risk issues, on the next page there is, under  
25 weakened immune system, something that's kind of

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1 similar under why, and I would just vote for kind of  
2 tightening down. I mean, there's a point to  
3 redundancy sometimes, people don't get it the first  
4 time and it applies in different situations, it's  
5 answering different questions, but this really seems  
6 like a lot to read.

7 DOCTOR DAVIS: I would like to address your  
8 concern. It was a concern of our's too, except that  
9 we felt that probably nobody would read this whole  
10 thing from front to back.

11 MS. NARRIGAN: Okay.

12 DOCTOR DAVIS: And, therefore, we figured,  
13 well, let's have some headings, and if the woman  
14 really was interested in, are these infections  
15 sexually transmitted, hopefully, she -- and, that's  
16 her focus, and then how do I use this, you know,  
17 instructions, fine, she'd do that. If she was  
18 interested in, how can I tell that I really have a  
19 vaginal yeast infection she can go to that section.  
20 So, we are totally aware of the fact that some things  
21 are said three times over, many things are said twice  
22 over, but we felt that that sort of overkill was,  
23 perhaps, better than only stating everything once, and  
24 then people not selecting that information.

25 But , again, we didn't have -- we don't know

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1 what's right or wrong, but that was the reasoning that  
2 we used and the fact that we are well aware of the  
3 fact that there's some duplication and triplication.

4 ACTING CHAIR BRASS: Yes, Mary Ann.

5 MS. KODA-KIMBLE: I noticed some things in  
6 this piece that were in conflict with Doctor Sobel's  
7 article, and I'd be interested in the opinions of the  
8 OB/GYNs . I also thought that wearing tight layers or  
9 moist clothing predisposed to candida, but he, in his  
10 article, his review article said there is no evidence  
11 that that is the case. And SO, it seems to me, if  
12 there is no evidence linking these two things, that  
13 maybe we shouldn't perpetuate the myth, and I'll just  
14 turn to all of you.

15 DOCTOR DATTEL: It is a common myth, and  
16 there isn't any scientific data to support it, but  
17 everybody thinks it. That's all I can say.

18 ACTING CHAIR BRASS: That's a good point.

19 DOCTOR DAVIS: I will make a comment, I  
20 mean, I was in private practice for 20 years, 20 to  
21 25, Joe Winfield is still -- has a private practice  
22 small time, and he's been in practice for I think over  
23 30, and I just can only say **anecdotally**, I do  
24 personally, honestly feel that the wet clothing is a  
25 factor in some women getting a yeast infection.

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1 DOCTOR DATTEL: Well, certainly it's true,  
2 you know, obese women, women where there might be a  
3 high moisture factor, there seems to be a high  
4 predisposition to that, but there's never been any  
5 rigorous scientific data to support it.

6 I agree with you, I live in the south.

7 DOCTOR DAVIS: So, and I agree with you,  
8 too, that if you look at the literature --

9 DOCTOR DATTEL: We can't find anything.

10 DOCTOR DAVIS: -- it's very hard to find  
11 that.

12 ACTING CHAIR BRASS: You are laying the  
13 threshold that you want to put it in, or whether it's  
14 one of those things to let the health care provider  
15 tell them.

16 DOCTOR LEWIS: It is common, and the other  
17 thing is, if you are starting to get symptoms and you  
18 wear tight clothing it will make you more  
19 uncomfortable.

20 DOCTOR DATTEL: I mean, it's a harmless  
21 thing.

22 DOCTOR LEWIS: It's a harmless thing.

23 ACTING CHAIR BRASS: Doctor Chin, do you  
24 want to comment on this?

25 DOCTOR CHIN: Therefore, speaking for the

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1 FDA and adhering to our usual standards of rigorous,  
2 scientific robustness, the question is, has there been  
3 a head-to-head comparison of wet clothing versus **non-**  
4 wet clothing, and what's the final call on that? Do  
5 we include that statement or don't we include that  
6 statement?

7 ACTING CHAIR BRASS: We will leave it up to  
8 you to decide.

9 Any final comments from the committee?

10 If not, I would like to thank all the  
11 participants, remind NDAC members to complete their  
12 calendar for next year, we want to get the meetings  
13 scheduled, and the meeting stands adjourned.

14 Thank you **all**.

15 (Whereupon, the meeting was concluded at  
16 2:54 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the  
matter of:                   **Meeting**

Before:                       **Food and Drug Administration**

Date:                         **September 11, 1998**

Place:                        **Bethesda, MD**

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.

  
\_\_\_\_\_

<p><b>Look-See Concordance Report</b></p>	<p>72nd [1]183:9</p>	<p>adding [6] 55:4;93:12;168:5; 171:2;183:11;196:10</p>	<p>15:1;17:9;22:9;27:12;39:25; 62:9;85:22,24;87:11;90:2; 128:18;157:21;183:2;192:14</p>
<p>..</p>	<p>- 8 -</p>	<p>addition [10] 15:18;19:7; 53:20;67:10;93:1,14;95:18; 113:25;121:1;167:1</p>	<p>agenda [2] 8:1,13</p>
<p>UNIQUE WORDS: 3,152</p>	<p>8-1/2 [1] 201:-77</p>	<p>Additional [2] 59:2;70:8</p>	<p>agent [5]71:18,24;72:1,6, 14</p>
<p>TOTAL OCCURANCES: 14,892</p>	<p>8:51 [1]5:2</p>	<p>additional [18] 14:10;16:17; 18:11,16;33:6;77:18;93:13; 104:2;109:17;113:13,20; 129:20;131:19;164:1,25; 179:9;184:9;200:3</p>	<p>agents [3]12:6;70:25;73-.5</p>
<p>NOISE WORDS: 365</p>	<p>8th [1]36:12</p>	<p>adequate [1] 19:12</p>	<p>agee [2]79:6;80:4</p>
<p>TOTAL WORDS IN FILE: 39,786</p>	<p>- A -</p>	<p>adequately [3] 22:10;36:19; 60:6</p>	<p>agree [14] 22:6;80:24;96:16, 21;112:14;113:1;144:11; 156:8;173:8,20;175:1; 197:17;205:6,7</p>
<p>SINGLE FILE CONCORDANCE</p>	<p>● n. [4] 5:2;70:12,13;115:5</p>	<p>addreaa[11] 8:19;16:5; 28:12;35:3;59:20,22;127:9; 129:1;132:22;195:9;203:7</p>	<p>agreed [2] 33:3;91:7</p>
<p>CASE SENSITIVE</p>	<p>abdomen [1] 38:20</p>	<p>addresses [2] 7:22;151:16</p>	<p>agreement [4] 76:17;165:10; 174:4;188:7</p>
<p>NOISE WORD LIST(S):</p>	<p>abdominal [11]53:17;55:13; 57:10;64:9;66:15;75:15; 122:1;149:15;152:19;167:7; 169:23</p>	<p>addressing [1] 141:25</p>	<p>agrees [1] 63:8</p>
<p>NOISE.NOI</p>	<p>ability [2] 36:8;144:3</p>	<p>adda [2] 77:18;91:16</p>	<p>aid [1] 196:22</p>
<p>EXCLUDES OCCURRENCES IN FIRST 3 PAGES</p>	<p>able [10] 37:21;38:3;78:21; 98:5,19;107:8;153:16; 155:21;177:10;197:4</p>	<p>adequate [1] 19:12</p>	<p>aiding [1] 163:18</p>
<p>INCLUDES ALL TEXT OCCURRENCES</p>	<p>abnormal [1]76:1</p>	<p>adhering [1] 206:1</p>	<p>al [1]51:16</p>
<p>IGNORES PURE NUMBERS</p>	<p>abscess [1] 119:1</p>	<p>administer [1]135:1</p>	<p>alert [1]120:21</p>
<p>WORD RANGES @ BOTTOM OF PAGE</p>	<p>absent [2] 165:6;201:17</p>	<p>administration [1]67:6</p>	<p>Alerting [1] 125:17</p>
<p>- \$ -</p>	<p>absolutely [4] 80:14;173:8; 177:6;190:11</p>	<p>admirable [1]135:17</p>	<p>ALEXANDER [5]116:14; 152:15,23;153:2,5</p>
<p>\$25,000.00 [1] 85:1</p>	<p>absorbed [1]71:14</p>	<p>admission [1] 182:18</p>	<p>Alexander [7]116:12,15; 126:1;152:14,15;165:5; 190:19</p>
<p>- 1 -</p>	<p>abstract [1]76:13</p>	<p>admonishment [1] 142:8</p>	<p>Allan [1]76:14</p>
<p>1-800 [2] 97:23;191:5</p>	<p>accept [1]191:13</p>	<p>adolescent [4] 54:17;76:5; 79:4;174:20</p>	<p>alleviating [1] 130:4</p>
<p>1-8XX [1] 97:16</p>	<p>acceptable [1] 162:15</p>	<p>adolescents [3] 54:14; 139:25;174:23</p>	<p>allow [8] 31:24;32:3;58:12; 78:22;88:10;162:12;169:16; 190:6</p>
<p>1028 [1] 70:12</p>	<p>acceptance [1]189:23</p>	<p>adopt [1] 162:11</p>	<p>allowed [4] 23:11;49:22; 72:23;95:4</p>
<p>1040 [1] 70:11</p>	<p>accepted [2] 175:18,25</p>	<p>adopted [2] 87:25;88:9</p>	<p>allows [5] 31:18;55:2;95:22; 106:15;119:13</p>
<p>1042 [1] 70:13</p>	<p>access [3] 76:6;98:18; 171:21</p>	<p>Adult [1] 36:14</p>	<p>alluded [1] 71:8</p>
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