

JOINT MEETING
OF THE
NONPRESCRIPTION DRUGS ADVISORY COMMITTEE
AND THE
DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

8:30 a.m.

Wednesday, July 16, 1997

Versailles Ballrooms I and II
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland 20814

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RONALD TRANCIK, PH.D.
MICHAEL VALENTINO
DAVID WHITING, M.D.

ALSO PRESENT:

DOUGLAS McCONNAUGHEY
JOHN THOMPSON

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P R O C E E D I N G S

(8:30 a.m.)

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3 DR. D'AGOSTINO: My name is Ralph D'Agostino
4 and I'm the Chairman of the Nonprescription Drugs Advisory
5 Committee.

6 This is a joint meeting of the Nonprescription
7 Drugs Advisory Committee and the Dermatologic and
8 Ophthalmic Drugs Advisory Committee. Our agenda today is
9 on Rogaine 5 percent for men.

10 What I'd like to do now is to ask the members
11 of the advisory committees and the consultants to introduce
12 themselves, speaking into the microphones so that the
13 transcriber can make sure that all the mikes are working.
14 George, why don't you start?

15 DR. BLEWITT: George Blewitt, industry liaison,
16 Nonprescription Drugs Advisory Committee.

17 DR. BRASS: Eric Brass, Harbor-UCLA Medical
18 Center, Nonprescription Drugs.

19 DR. TSCHEN: Eduardo Tschen, University of New
20 Mexico, Department of Dermatology, Albuquerque, New Mexico.

21 DR. MINDEL: Joel Mindel, Departments of

1 Ophthalmology and Pharmacology, Mt. Sinai Medical Center,
2 New York.

3 DR. KODA-KIMBLE: Mary Anne Koda-Kimble,
4 Department of Clinical Pharmacy, University of California
5 at San Francisco, Nonprescription Drugs Advisory Committee.

6 DR. MILLER: Fred Miller, dermatologist,
7 Geisinger Medical Center, Danville, Pennsylvania.

8 DR. LAVIN: Philip Lavin, Boston Biostatistics
9 and Harvard Medical School.

10 MS. HAMILTON: Kathleen Hamilton, consumer rep
11 to the Nonprescription Drugs Advisory Committee.

12 DR. TONG: Good morning. I'm Ted Tong from the
13 University of Arizona, Departments of Pharmacy,
14 Pharmacology, and Toxicology, and I'm a member of the
15 Nonprescription Drugs Advisory Committee.

16 DR. MCKINLEY-GRANT: Lynn McKinley-Grant. I'm
17 with the Department of Dermatology at the Washington
18 Hospital Center and George Washington University and a
19 member of the Nonprescription Drugs Advisory Committee.

20 DR. D'AGOSTINO: Ralph D'Agostino, Boston
21 University.

1 DR. NEAL: Andrea Neal, Executive Secretary to
2 the Nonprescription Drugs Advisory Committee.

3 MS. SLINGLUFF: Beth Slingluff with Carondelet
4 Health Care Services, Tucson, Arizona. I'm with the
5 Nonprescription Drugs Advisory Committee.

6 DR. DRAKE: Lynn Drake from the University of
7 Oklahoma Health Sciences Center, Department of Dermatology
8 and the Department of Dermatology at Massachusetts General
9 Hospital.

10 DR. JOHNSON: Cage Johnson, University of
11 Southern California, Nonprescription Drugs.

12 DR. ROSENBERG: Bill Rosenberg, dermatology at
13 the University of Tennessee from the Dermatology Advisory
14 Committee.

15 DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien,
16 Departments of Dermatology and Internal Medicine at Johns
17 Hopkins University School of Medicine in Baltimore,
18 Maryland, and I'm a consultant to the Dermatologic Advisory
19 Committee.

20 DR. McGRATH: Patricia McGrath, University of
21 Western Ontario, Nonprescription Drugs.

1 DR. WILKIN: Jonathan Wilkin, Director,
2 Division of Dermatologic and Dental Drug Products, FDA.

3 DR. WEINTRAUB: Mike Weintraub, FDA.

4 DR. BOWEN: Debra Bowen, Director, Division of
5 OTC Drug Products.

6 DR. KATZ: Linda Katz, Deputy Director, OTC
7 Drug Products, FDA.

8 DR. D'AGOSTINO: Thank you.

9 We'll now have the meeting statement.

10 DR. HASHIMOTO: Ken Hashimoto, Department of
11 Dermatology, Wayne State University in Detroit.

12 DR. D'AGOSTINO: We'll now have the meeting
13 statement by Andrea Neal.

14 DR. NEAL: The following announcement addresses
15 the issue of conflict of interest with regard to this
16 meeting and is made a part of the record to preclude even
17 the appearance of such at this meeting.

18 Based on the submitted agenda for the meeting
19 and all financial interests reported by the committee
20 participants, it has been determined that all interests in
21 firms regulated by the Center for Drug Evaluation and

1 Research which have been reported by the participants
2 present no potential for an appearance of a conflict of
3 interest at this meeting with the following exception.

4 In accordance with 18 U.S. Code 208(b)(3), full
5 waivers have been granted to Dr. Ralph D'Agostino and Dr.
6 Lynn Drake.

7 A copy of these waiver statements may be
8 obtained by submitting a written request to FDA's Freedom
9 of Information Office, room 12A-30 of the Parklawn
10 Building.

11 In addition, we would like to note for the
12 record that several of our participants have past
13 involvements which we believe should be disclosed so that
14 their comments can be objectively evaluated.

15 Dr. Tschen was previously involved as an
16 investigator in studies involving minoxidil for use in the
17 treatment of androgenetic alopecia.

18 Dr. Philip Lavin's company, Boston
19 Biostatistics Research Foundation, previously provided
20 statistical support regarding a study on the use of SEPA to
21 enhance minoxidil efficacy for androgenetic alopecia.

1 In the event that the discussions involve any
2 other products or firms not already on the agenda for which
3 an FDA participant has a financial interest, the
4 participants are aware of the need to exclude themselves
5 from such involvement and their exclusion will be noted for
6 the record.

7 With respect to all other participants, we ask
8 in the interest of fairness that they address any current
9 or previous financial involvement with any firm whose
10 products they may wish to comment upon.

11 DR. D'AGOSTINO: Thank you.

12 We'll now have opening comments from Dr.
13 Michael Weintraub.

14 DR. WEINTRAUB: Thank you, Dr. D'Agostino.

15 I appreciate the fact that this is the third
16 straight day you've been in hearings, and we really do
17 appreciate this. We hope that today you'll have an
18 educational experience and be able to educate us as well.

19 Some might ask the question why do we have
20 Rogaine again. We've already discussed Rogaine 2 percent
21 many times, and you might think it wouldn't be necessary to

1 discuss Rogaine 5 percent anymore.

2 We in the OTC area have had drugs directed at
3 men, specifically for men, in the past. They were drugs
4 for impotence. They were drugs for benign prostatic
5 hypertrophy, et cetera. But we haven't had a non-specific
6 organ-directed product like Rogaine 5 percent ever for men.
7 It may be even true for women.

8 Actually I shouldn't use the term "men."
9 Yesterday some of us learned that the better term to use is
10 non-women.

11 (Laughter.)

12 DR. WEINTRAUB: That was used by one of the
13 speakers at yesterday's meeting.

14 But anyway, in any case, we are going to ask
15 the question which will be of importance and of interest.
16 Not only did this drug work and was it safe, but also could
17 the company construct a label for use by men and it would
18 not be for use by women.

19 So, those are the broad outlines of the things
20 we would like you to discuss, but as I say, we haven't had
21 anything exactly like this. The reason for having a

1 Nonprescription Drugs Advisory Committee is to have a
2 public forum, and of course, we are very glad to have the
3 Dermatologic Advisory Committee and the Ophthalmic. We
4 have a member from the Ophthalmic Committee as well. The
5 key thing here is to have a public presentation of these
6 data. So, I hope it will be instructive and helpful to us.

7 Thank you.

8 DR. D'AGOSTINO: Thank you.

9 We'll now go into the open public hearing. Two
10 people have identified themselves and desire to make
11 presentations during the open public hearing: Douglas
12 McConnaughey and John Thompson. Douglas and John, you can
13 use either the podium or the mike to make your
14 presentation. Please give your name and affiliation and if
15 there's any support for this meeting.

16 MR. McCONNAUGHEY: Good morning. My name is
17 Douglas McConnaughey. I'm a professional journalist from
18 Boise, Idaho, and I have to say that Pharmacia & Upjohn has
19 covered my time to be here and paid my expenses to
20 Washington today.

21 I experienced severe hair loss over the course

1 of the last seven years. During the last year, I
2 experienced a lot of hair loss, and in fact, the complete
3 back of my head was -- there wasn't any hair and I had a
4 severe receding hair line. The few hairs that were left
5 between those two spots were gray.

6 I'm a single dad. I have a second grade son, a
7 first grade daughter that I'm raising by myself. At the
8 beginning of last year, the school year -- well, first of
9 all, I have to say I live in a very small ranching
10 community outside of Boise. Most of the other fathers at
11 school are a lot younger than I am and haven't experienced
12 any hair loss yet. I noticed how impacting it was to my
13 son at the beginning of the school year when I had him on
14 my shoulders and he said, geez, Dad, it's slick back here.
15 So, I paid attention to that.

16 I host a daily news magazine called P.M. Idaho.
17 We cover home health, hearth, pocketbook issues a lot, and
18 what kind of topics you would normally consider around the
19 water cooler. Of course, Rogaine has been a topic for a
20 lot of people. Does it work? Does it not work? Of
21 course, we have heard all the other claims of other

1 products for years. So, a lot of the people in the public
2 wonder if it really does work.

3 I'm a cynic naturally. I spent 27 years as a
4 newspaper, television, radio, and wire service reporter,
5 and believe you me, I didn't believe it would work.

6 So, we came up with an idea to have an on-air
7 test. Myself, our sports anchor, and our on-air
8 psychologist all agreed to start using Rogaine. That was
9 seven months ago. During that process, we also interviewed
10 some of the clinical assessment staff from Pharmacia &
11 Upjohn.

12 I have to say to you that Rogaine exceeded all
13 of my expectations, and I don't say that lightly. I tell
14 you the three areas that they produced results for me.

15 One, as you can see, the top of my head -- I
16 had significant and excellent hair regrowth, and it's very
17 full.

18 The second area was that my receding hairline
19 came back. It reestablished that hairline and came to the
20 front of my head. It isn't completed yet, but I have hair
21 on the front of my head.

1 And the third area, very surprisingly to me,
2 was that the hair that came back was the hair that I had
3 when I was in my early 20s. It's darker, it's softer, and
4 it's fuller.

5 I promised my audience that I would report back
6 to them factually and honestly as I'm doing to you today,
7 and that's what I told them. I have hair and it's as a
8 result of that.

9 At the end of the school year, I was with my
10 son at a back-to-school night and so he could see all the
11 other dads there. He looked up to me and he said, gee,
12 Dad, you're just like all the other dads. You have hair
13 now.

14 When you consider 2 percent and 5 percent
15 minoxidil for men, I know that one size doesn't fit all and
16 sometimes another dose is what's necessary. Rogaine works
17 for a number of reasons, not the least of which is because
18 it's available and I would recommend that.

19 DR. D'AGOSTINO: Thank you very much.

20 John?

21 MR. THOMPSON: Good morning, Mr. Chairman and

1 members of the committee. My name is John Thompson. I'm
2 from Orange County, California. I'm a construction
3 management consultant.

4 I'd like to take just a moment to thank the
5 committee for the opportunity today to talk briefly about
6 Rogaine and also to Pharmacia & Upjohn for sponsoring my
7 trip here to Washington. My only hope is that my second
8 trip will be longer than 18 hours in duration and it won't
9 be quite as humid.

10 I've been a successful Rogaine program
11 participant for about two years. I first noticed -- and it
12 kind of hit me over the head -- that I was going to be a
13 product of next-generation genetics when I went to visit my
14 father four years ago in Reno, Nevada. He had suffered
15 male pattern baldness as early as age 40, and he was kind
16 of chiding me because at the ripe old age of 37, it was the
17 downhill pull to 40.

18 I brought a couple of photographs which you
19 probably may not be able to see because I'm far away from
20 the table, but my dad here at age 42 on the left began to
21 suffer a receding hairline which began to progress

1 noticeably and dramatically into his 40s and also into his
2 50s. My dad at the ripe old age of 62 currently has
3 substantial male pattern baldness in the front area of his
4 scalp all the way to the middle and back section.

5 DR. D'AGOSTINO: Are the mikes working? I'm
6 sorry, John.

7 MR. THOMPSON: That's all right.

8 (Pause.)

9 MR. THOMPSON: Upon returning from my visit
10 with my dad, I was in denial about, A, getting older and,
11 B, going bald. About a year later, I had a photograph
12 taken which is referenced here. I think probably the
13 doctors in the front row can see it much more clearly. I
14 began to suffer that pain of genetics that I mentioned
15 earlier by hair loss around the temple area and also in the
16 front. The picture also dramatically illustrates that it
17 was receding also where my dad had experienced the same
18 situation, towards the center of my scalp because the part
19 line of my hair was very irregular and it was very unfull.

20 I went to a series of doctors for various
21 consultations to see what options were available to me, and

1 finally I went onto the Rogaine program. My dermatologist
2 told me it would take approximately one year of daily
3 treatments, which I naturally committed to. At the time it
4 was a prescription medication.

5 Three months into the program, I am very happy
6 to say I began to see very positive results. My
7 dermatologist told me that if hair loss was beginning to
8 decline, that there would be less hair in styling products
9 such as my comb and in my styling brush in the morning, and
10 I did notice that.

11 Certainly the most dramatic result, though, was
12 in the fifth month, and that as the telltale signs of very
13 beginning hair growth along the front of the scalp. It was
14 really great because I knew it was working.

15 One of the tests a doctor had told me to do was
16 to take my hand and actually pull the hair back and if you
17 were lucky enough to start experiencing the growth, you'd
18 notice little, little, small, practically hairless -- well,
19 my weren't that hairless -- or colorless -- excuse me, but
20 small little growth lines along the front of the scalp.
21 They were pretty much brown. They weren't really colorless

1 which also was fairly exciting.

2 They were like kids, though. They were going
3 in every different direction and they weren't really doing
4 what I wanted them to do until they grew out actually
5 longer.

6 In fact, this morning when I was applying the
7 Rogaine, I did the test anyway, realizing I'd be testifying
8 before the committee this morning, and I did the test
9 again. They weren't short. They were significantly
10 longer.

11 I'm very satisfied with the results of the
12 minoxidil that I've taken currently to date in the last two
13 years, and I'm hopeful that the committee and the FDA will
14 react favorably towards the 5 percent solution.

15 There's varying results with Rogaine today.
16 Some people plateau, such as myself I believe, with the 2
17 percent. Some people have marginal or negligible results.
18 Some people it takes longer. I would hope that with the 5
19 percent solution, those who have experienced perhaps a
20 longer time line might accelerate, people such as myself
21 who have maybe plateaued in their success might be able to

1 get even greater success.

2 I know today you have a lot of people coming up
3 and discussing Rogaine, people, doctors, scientists, who
4 know a lot more technical information than I do. But
5 speaking strictly as a consumer, I can sum up Rogaine with
6 two words: Rogaine works. Thank you very much.

7 DR. D'AGOSTINO: Thank you very much also.

8 We'll now move on to the next item which is the
9 FDA presentations. We have two presentations from the FDA
10 at this point. Shahla Farr and Roger Goetsch are going to
11 speak on the clinical studies and the spontaneous
12 reporting.

13 What I'd like to suggest is that we let both of
14 the presenters give us the presentation, and then ask some
15 questions after the two presentations.

16 Also, I want to remind the advisory committees
17 that Pharmacia & Upjohn will in fact cover some of this
18 material later on, and I've asked the FDA people to stay
19 for the full morning -- they were planning on it anyway --
20 so that when we ask questions of Upjohn, we will also have
21 the FDA individuals to answer the questions or to give us

1 their insights into the material.

2 Shahla, do you want to begin? This material,
3 your presentation, has also been passed out to the
4 committee members.

5 MS. FARR: Good morning. My name is Shahla
6 Farr. I'm with the Division of Epidemiology and
7 Biostatistics at the FDA, and today I will be presenting to
8 you the efficacy and safety data for the Rogaine 5 topical
9 solution for males and females.

10 Before I begin my presentation, I would like to
11 compliment Upjohn Pharmaceuticals for a superb CANDA
12 submission. In my experience, their CANDA has been one of
13 the most impressive submissions for its thoroughness and
14 ease of use.

15 For the members of the committee and other
16 people who wouldn't know what CANDA is, CANDA stands for
17 computer assisted new drug application. In other words,
18 it's the electronic submission of the NDAs.

19 There are some minor clarifications that I
20 should mention first. Through this presentation, I'll use
21 the words "net growth" or "net loss" to refer to positive

1 or negative changes in the net hair count.

2 In the studies that I will present, the vehicle
3 that was used is that for the 5 percent Rogaine which is a
4 stronger formulation than the 2 percent vehicle.

5 Also, subjects were instructed to apply 1
6 milliliter of the test solution to the affected areas which
7 would be the vertex, which is the back of the head for
8 males, and the front of the scalp for females. They were
9 instructed to use this twice daily, 12 hours apart.

10 Also, 1 centimeter squared of the affected area
11 was under the study.

12 The background. The sponsor's intention was to
13 demonstrate that 5 percent solution is as safe as and
14 superior to the 5 percent vehicle and the 2 percent
15 solution in males and females over a 32 or a 48-week
16 period.

17 The sponsor had conducted four independent,
18 randomized, double-blind vehicle-controlled and multi-
19 center studies, four studies. They had numbers that are
20 pretty long. So, from now on, I just refer to them as to
21 study 1 and study 285 for males, and study 9 and 286 for

1 females.

2 To gain approval for this new formulation, the
3 sponsor must show statistical superiority of Rogaine 5
4 percent to its vehicle and Rogaine 5 percent to Rogaine 2
5 percent using a two-sided 5 percent significance level.

6 The focus of this report will be on patients'
7 net gain in hair count based on a 1 centimeter square area
8 at the end of the treatment period on the evaluable
9 population, which my evaluable population consisted of
10 subjects who had completed the study.

11 My presentation is organized as such. I will
12 be speaking on the male studies first. I will talk about
13 the demographics and baseline characteristics of each
14 study. Then I will go on about the efficacy which is mean
15 change in hair count from baseline at the end of the
16 treatment. At the end I will talk about the safety which
17 is local irritation.

18 For the female studies, I will do the same
19 except in terms of safety, I will also include the
20 hypertrichosis, which is the unwanted hair in females.

21 At the end I will conclude with efficacy and

1 safety conclusions separately.

2 This is the first study, study number 1, which
3 was for males. This study was a single study. The
4 duration was 32 weeks, 345 healthy males. The ratio in
5 each group -- this study compared 5 percent Rogaine with 2
6 percent with the 5 percent vehicle, and the population was
7 divided by the ratio of 2 to 1 to 1, and 321 subjects
8 completed the study.

9 As we can see, all the p values are here.

10 The demographics and baseline characteristics
11 that I looked at were age, race, baseline hair count, years
12 of hair loss, and duration of hair loss category, and all
13 the three arms were comparable relative to the baseline
14 characteristics and demographic conditions.

15 Now, this is the efficacy for the same study,
16 study 1, which as I said was 32 weeks. What I'm showing
17 here, these numbers are the actual hair counts at baseline,
18 at week 16, and week 32. Of course, these are the
19 different treatment arms.

20 The points that are interesting to see in here
21 are the fact that, as I showed before, all three treatments

1 started equally. Statistically there was no difference, as
2 we see in the p value, especially between the 5 percent and
3 2 percent.

4 At week 16, there were some differences
5 actually between the 5 percent and 2 percent, that we could
6 see that the 5 percent subjects were gaining more hair.

7 At week 32, the results were borderline,
8 significant.

9 But all in all, the difference between week 0,
10 which was baseline, to week 16, was highly significant, and
11 again between baseline and week 32, we had highly
12 significant results also.

13 I have the number of the completers in this
14 study. A high number of subjects actually completed in the
15 5 percent Rogaine, 94 percent. In the 2 percent, 92
16 percent of people finished. In the 5 percent vehicle, 93
17 percent of the subjects finished the study.

18 This graph actually demonstrates what I talked
19 about in terms of the hair count. This is for the same
20 study, study 1 for males. This axis shows the number of
21 the hairs and this is the time period. It just shows the

1 trend. The 5 percent Rogaine is the blue line. The green
2 is the 2 percent Rogaine, and the red line is the placebo.
3 The study ended at week 32. So, we will see the trend
4 here.

5 In terms of the safety, 345 subjects who had
6 actually participated in the study were looked at. What we
7 noticed is that in terms of dryness and erythema, we got
8 significant results, which meant that the 5 percent users
9 had more dryness and erythema than the 2 percent users.

10 This is the second male study, study 285. Here
11 six centers were involved, participated in the study.
12 Since FDA requires independent trials for its approval, one
13 center which was in common with the first male study, with
14 study number 1, we had to remove. So, there were 100
15 subjects who were actually removed from the whole study.

16 This study was for 48 weeks duration, and the
17 number of the subjects that actually I analyzed were the
18 393 originally, and I took the 100 out, so 293 subjects.
19 Out of that, 258 actually completed the study.

20 Again, the same parameters in terms of
21 demographics and baseline characteristics were looked at.

1 As we see, all the three arms were actually comparable in
2 terms of the demographics and baseline characteristics.

3 Now, this is the hair count for the study 285.

4 We started from baseline, week 16, week 32, and week 48.

5 Here also we see that at week 32 there was a
6 borderline significant difference between the 5 percent and
7 2 percent. Then the difference again between baseline and
8 week 16 also was borderline significance. But all in all,
9 the final results actually showed statistically significant
10 results when we compared the baseline to week 32 and also
11 from baseline to week 48. There were actually significant
12 results, which meant that subjects who used Rogaine 5
13 percent actually gained more hair than the subjects who
14 used the 2 percent, and the same for week 48.

15 Again, a high percentage of subjects in this
16 study completed the study, 88 percent in the 5 percent
17 Rogaine, 86 percent in the 2 percent, and 91 percent in the
18 5 percent vehicle.

19 This graph also shows the pattern of hair
20 growth, again net hair growth that I talked about. We see
21 that pretty much they started at the same place here, and

1 again the blue line is the 5 percent. The green is the 2
2 percent and the red line is the vehicle. This also shows
3 at 48 weeks the pattern of net hair growth.

4 Now, the safety for this. I looked at them for
5 the whole 393 subjects who participated in the study. For
6 this study, erythema and folliculitis were not collected.

7 Again, here we see that in terms of dryness and
8 itchiness actually, the 5 percent and 2 percent
9 statistically differed. The subjects who used the 5
10 percent suffered more of the dryness and itchiness.

11 What I did at the end, I combined the two male
12 studies and I looked at them as a whole. I compared them 2
13 by 2. Here again we see as a whole dryness is a problem
14 when we compared the 5 percent to 2 percent and 5 percent
15 to its vehicle, and erythema showed again 5 percent was
16 worse than 2 percent. Here itching, like before.

17 Then when I compared the 2 percent Rogaine to
18 the 5 percent vehicle, there were some interesting results
19 here that actually the 5 percent Rogaine -- or I'm sorry --
20 the vehicle was more -- they had more dryness in the
21 vehicle arm than the 2 percent. Dryness and erythema.

1 Now I begin the female studies, study number 9.
2 That was four centers for 48 weeks and 345 females
3 participated. The ratio on that was 2 to 2 to 1. 179
4 actually completed the study. All the three arms were
5 comparable in terms of the demographic and baseline
6 characteristics.

7 Here the same table. I started from baseline
8 and looked at week 16, week 32 and week 48, and then the
9 differences between the different time periods and also
10 from baseline to week 32 and baseline to week 48. There
11 was no statistically significant results when we compared
12 the 5 percent Rogaine to 2 percent Rogaine.

13 There were a very large number of subjects who
14 actually dropped out from the study. As you see here, only
15 54 percent finished. The ones who were in 5 percent
16 Rogaine finished the study, as opposed to 63 percent in the
17 2 percent Rogaine arm, and 68 percent in the vehicle arm.

18 This graph also shows the pattern of net hair
19 count. The blue line again is 5 percent Rogaine. The
20 green line is the 2 percent, and the red is vehicle
21 throughout the 48 weeks.

1 The safety in females. Again dryness was a
2 problem for the 5 percent users and itching. There were a
3 higher number of subjects in the 5 percent group who
4 suffered from itching than the 2 percent.

5 This is the last study for females, study 286.
6 Nine centers participated in the study. The duration was
7 48 weeks. 381 healthy females participated. The ratio was
8 2 to 2 to 1. And 253 completed the study. Again, the
9 baseline characteristics and demographics -- there was no
10 statistical difference between them.

11 The same table as the other studies. Again,
12 here when I compared the 5 percent to 2 percent, there was
13 no statistically significant results shown.

14 In this study, like the other female study, a
15 high number of subjects actually dropped out, and here we
16 have 63 percent completers as opposed to 69 percent as
17 opposed to 68 percent.

18 Now, this graph as before, the blue line is the
19 Rogaine 5 percent. The reason this is looking like this is
20 because at the beginning at baseline, they actually started
21 with a little lower numbers even though it wasn't

1 statistically significant. But as you see, the blue line
2 again is the 5 percent. The green is the 2 percent and the
3 red is vehicle. It shows the pattern in the net hair
4 growth.

5 Finally, the safety issues for this study, we
6 have 381 subjects participated. Again, in this one
7 erythema and folliculitis were not collected for this
8 study, but we see dryness, itchiness, and stingy were
9 statistically significant where the 5 percent subjects
10 suffered more than the 2 percent. Even though
11 hypertrichosis did not show any significance, a few number
12 of subjects suffered in the 5 percent than the 2 percent or
13 the vehicle arm.

14 Now, the conclusions for the efficacy, studies
15 number 1 and 285 statistically support the applicant's
16 claim that 5 percent Rogaine induces net increase in
17 nonvellus hair count in a male population over a 48 or 32-
18 week study period.

19 Studies 9 and 286 for females did not
20 demonstrate any net gain hair count for the 5 percent
21 Rogaine over the 2 percent Rogaine.

1 In terms of safety, male studies 1 and 285
2 indicated that 5 percent Rogaine induces more dryness,
3 erythema, and itching in subjects than the 2 percent
4 Rogaine. In addition, more subjects suffered dryness and
5 erythema in the vehicle treatment arm than the 2 percent
6 Rogaine group.

7 In female studies 9 and 286, they indicated
8 that the 5 percent Rogaine induces more dryness, itching,
9 and stingy in subjects than the 2 percent Rogaine.

10 Thank you. This concludes my speech and our
11 next presenter is Dr. Goetsch from the Division of
12 Pharmacovigilance and Epidemiology.

13 DR. D'AGOSTINO: Thank you.

14 DR. GOETSCH: Thank you very much for the
15 opportunity to speak to the committee. My name is Roger
16 Goetsch. I'm with Pharmacovigilance and Epidemiology.
17 We're going to talk today about post-marketing surveillance
18 of the 2 percent minoxidil.

19 What we did is basically looked at the
20 spontaneous reporting system of the FDA, otherwise known as
21 Med Watch. The difference between what Ms. Farr presented

1 and what I'm going to present is that my population is the
2 whole world or the United States, and it's not a controlled
3 clinical trial.

4 The points I'm going to discuss today on the 2
5 percent. I want to go over basically the limitations of
6 the spontaneous reporting system. I want to look a little
7 bit about the profile that we saw with the overall
8 reporting of the 2 percent, and the main issue that we were
9 looking at is what happened with overdoses on the 2 percent
10 minoxidil, and focusing mainly on serious reports and
11 looking at tachycardia, looking for some kind of systemic
12 effect of the topical minoxidil, and then give my
13 conclusions.

14 Limitations of the spontaneous reporting system
15 is that it is spontaneous. It is voluntary. Anybody can
16 report, anybody can send anything in. We know that we have
17 under-reporting. We also know that as time goes by as the
18 drug is first marketed, the reports will increase and as
19 time goes on, it will then tend to decrease.

20 We know with spontaneous reporting, we have a
21 problem with causality. It's not like a clinical trial

1 where you will follow a patient for X period of time.

2 We also know that we get incomplete reports and
3 variability. We know that some of the fields are not
4 populated. But it's also probably the most useful of
5 signals. It's very inexpensive, and as today, we're going
6 to look at what happened with overdoses of 2 percent to try
7 to get a feeling what may happen in the population with the
8 5 percent solution.

9 In our database -- and this is all minoxidils.
10 This is not any specific company. This is any minoxidil
11 report that we've received from the day that it was
12 marketed to March of this year, and we had over 16,000
13 reports. The gender breakdown was 60 percent male, 40
14 percent female. The average age was a 43-year-old. The
15 range was from 1 year old to 90 years old.

16 To give you an idea where the reports came
17 from, 79 percent came from consumers. The rest came from
18 health professionals.

19 I also threw in the regulatory definition for a
20 Med Watch form, a 15-day which was 6 percent of the
21 reports. This is defined as serious on-label reports.

1 Periodic reports are what is sent to the agency as a non-
2 serious event. Direct reports are what we receive directly
3 to the agency where the company may not have information.

4 Of the 2 percent of the 16,000 reports, we
5 looked at the top 10 adverse events. You have to realize
6 on the report, you can have up to four events. So, there
7 can be a crossover. We found that 26 percent of the people
8 had hair loss, 18 percent had no drug effect, and 18
9 percent the reaction caused the hair loss to even be worse.
10 We had the itching, a problem with application. 9 percent
11 had rash, dry skin, and 6 percent had a blistering, and 5
12 percent had some kind of unspecific hair disorder. You
13 have to realize these are reporting rates. These are not
14 incident rates.

15 So, then we decided let's look at the 2 percent
16 overdose reports, which we got 264 reports out of those
17 16,000 reports. We found that the gender switched a little
18 bit. 52 percent went to female, 47 percent male. The
19 average age pretty much stayed the same. The range was
20 still 2 years old to 84. The reports still consumers were
21 sending in, 89 percent, and 11 of them came from health

1 professionals. These are doctors, pharmacists, nurses,
2 other people.

3 Now, the regulatory changed. We had no direct
4 reports. All of these came in as a 15-day or periodic.

5 Of those 264, we also looked at the top 10
6 adverse events reported and we found the profile was very
7 much the same. 22 percent had an increased hair loss. 18
8 percent said it got worse. 10 percent said it didn't even
9 work. Itching. Now we're getting some systemic effects.
10 We're getting some dizziness and we're also getting some
11 hair that was not supposed to be growing on a certain area,
12 8 percent.

13 Then we focused in at the 5 percent of
14 tachycardia, thinking that we could see what kind of
15 systemic effects may be caused by increasing this dose
16 beyond the 2 percent.

17 So, we looked at the serious reports. There
18 were only 5: 1 fatality, and 3 hospitalizations, and 1 was
19 a foreign life-threatening report. In the next couple of
20 slides I'll briefly give you a detail of what actually
21 happened on those 5 reports.

1 The only fatality report we received was of a
2 32-year-old from Miami, Florida that swallowed five
3 bottles, which would give you 6 grams, and then expired.
4 This was definitely a suicide, fatal overdose. I talked to
5 the physician just last week and he said definitely the
6 patient went into hypotensive crisis and died in the ER.
7 Now, you have to realize they swallowed this. This was not
8 topical.

9 There was a 2-year-old female that was found
10 with an empty Rogaine bottle which would have given 1.2
11 grams that had been full 2 hours earlier. She was taken to
12 the ER, lethargic, increased pulse, decrease in blood
13 pressure, admitted to the ICU with a diagnosis of possible
14 cardiac involvement from the swallowing of minoxidil. She
15 recovered and was discharged the same day.

16 Number 3 is a 2-year-old female that swallowed
17 half a bottle of Rogaine, which would give you 600
18 milligrams. She was taken to the ER, admitted to the
19 hospital for an overnight observation, had no detectable
20 events. Basically the parents found her with the dropper
21 in her mouth and it was kind of concluded that maybe she

1 didn't consume any of the medication at all and it was just
2 a precaution. So, this was a worrisome hospital event that
3 possibly didn't have to happen.

4 Number 4 was a 5-year-old that drank as much as
5 5 mls, which would give you 100 milligrams which would be
6 equal to the 5 percent minoxidil that we're talking about,
7 was admitted to the hospital for an overdose of minoxidil.
8 As the other case, no event was detected and they felt that
9 the child probably never consumed any.

10 We did get one foreign serious report. This
11 came from Venezuela of a 54-year-old probably cardiac
12 patient that was prescribed minoxidil for hair loss. He
13 took over a teaspoonful, 15 to 20 mls. That gives you 300
14 to 400 milligrams of the product. He took it orally by
15 mistake and typically experienced syncope, severe
16 hypotension, atrial fibrillation, EKGs, and acute renal
17 failure. He was also on an ACE inhibitor, and he did
18 recover. It was just life-threatening.

19 So, then we moved on. We wanted to see what
20 kind of systemic effects the overdose cases would show. We
21 identified 14 reports that had a tachycardia that were all

1 described by the consumer of an overdose. The usual dose
2 we're talking about with the 2 percent is 1 ml twice a day
3 which would give you 40 milligrams. The mean dose on all
4 of these 14 were 80 milligrams. The average age was pretty
5 close to the average profile of 40 years old. The age was
6 1 to 1.

7 The onset of this was interesting because it
8 happened at the first dose up to the second day of exposure
9 to this drug, and the tachycardia or the rapid heart beat
10 would last for 1 or 2 days.

11 The minoxidil overdoses that we saw were mostly
12 twice the recommended daily dose. The rapid heart beats
13 were usually seen in a couple days, disappeared when they
14 decreased the dose down to the 2 percent recommended dose.

15 Our problem is this may not be the case if
16 they're given the 5 percent, 100 milligrams, minoxidil.

17 We're probably looking at a very rare
18 subpopulation that may get a systemic absorption to
19 minoxidil. It's very hard to do causality with the SRS,
20 but it's an observation.

21 My conclusion then today after looking at the 2

1 percent minoxidil and the post-marketing safety is we have
2 an awful lot of experience with minoxidil. It has been out
3 there since 1988. Last year it went OTC. It went generic.
4 Most of the adverse events are of the skin, of the hair
5 disorders.

6 Overdose was not from topical; it was from
7 actually being swallowed. So, we're asking the question of
8 safety device.

9 Tachycardia. We've seen 14 cases. This looks
10 like it's very rare. It look like it's a subset of a very
11 small population.

12 Thank you very much.

13 DR. D'AGOSTINO: Thank you.

14 Let's entertain questions now to both of the
15 speakers. Again, remember that some of the questions that
16 you may have concerning the designs of the study and the
17 implementation of the studies the sponsor will make a
18 presentation later and may be the best source for answering
19 those questions. Are there questions? Eric?

20 DR. BRASS: I have two questions. First, when
21 you presented study 285, you indicated that a center was

1 dropped because it participated in both studies. I was
2 unaware that that was argument for independence and whether
3 there was some special consideration that went into the
4 center being dropped. We've seen other studies where
5 centers have participated in multiple --

6 MS. FARR: In my experience that has been one
7 of our requirements. In all the NDAs that I have reviewed,
8 if there were two studies for the same indication and there
9 were some centers in common, one of the centers in the
10 study that had a higher sample size were eliminated.
11 That's one of the requirements of independence, yes, of
12 studies.

13 DR. BRASS: My second question is the wording
14 from the sponsor at various points includes the word
15 "faster" for the 5 percent than the 2 percent. My question
16 is what would you consider a definition of "faster." How
17 would you statistically analyze for that?

18 MS. FARR: That's unfortunately one of the
19 problems we have been having with the sponsor. I don't
20 know on what basis they're claiming that. The studies were
21 not designed to show that, and I have brought it to their

1 attention before a few times. So, I don't know on what
2 basis they are claiming that.

3 DR. D'AGOSTINO: Other questions on this side?
4 Yes.

5 DR. MILLER: The center that was dropped. Do
6 you have the data from that center? I was thinking
7 specifically of the questionnaire data or the evaluation by
8 both investigator and by those people who had received the
9 Rogaine. That was a negative study in that arm, and I
10 would be interested in knowing what they did in the next
11 study. Were they also negative there in their response?

12 MS. FARR: I didn't look at that at all. The
13 way we do our reviews are completely, as far as we can,
14 blinded. I first look and see if in fact the two studies
15 are really independent of each other, and if I see a common
16 investigator, without looking at the results, I drop them.

17 Then another comment that I wanted to make is
18 even though 100 subjects were dropped out, the results were
19 still highly significant. So, I don't think that really
20 affected the results. The results were very strong for the
21 male studies.

1 DR. MILLER: They were strong in that study,
2 but in the first study, that second arm was negative, as I
3 recall. In 001, the counts were significant but the
4 evaluation by the investigator and also by those using the
5 product, that was not a significant study.

6 MS. FARR: Yes. Well, in the review in my
7 presentation, that is basically what I looked at. We
8 mainly went by the hair count and hair change from
9 baseline. So, I did not look at them to see, for example,
10 that center that was dropped out, how they did.

11 DR. D'AGOSTINO: Phil?

12 DR. LAVIN: Yes, Phil Lavin.

13 In your analysis here, you indicate on your
14 backgrounder page adjusting for age, yielded a borderline
15 significance between the 5 percent and 2 percent solutions,
16 p .06. Was that with or without that --

17 MS. FARR: No. They were dropped from the
18 beginning.

19 DR. D'AGOSTINO: Speak into the mike, Phil.

20 DR. LAVIN: Yes. I was just looking for a
21 point of clarification as to whether or not the 5 percent

1 versus the 2 percent analysis which was done for study 285
2 -- she indicated in there that there was a p value of .06
3 for the difference between the 5 percent and the 2 percent.

4 MS. FARR: Yes. As I mentioned, that study was
5 already dropped out. So, they were not analyzed at all in
6 that study.

7 DR. D'AGOSTINO: Mary Anne?

8 DR. KODA-KIMBLE: You noted a difference in
9 completion rate between males and females in the two
10 studies. Do you have any idea why that might have been and
11 did that affect the statistical analysis in any way?

12 MS. FARR: Yes, right. That's a possibility.
13 We actually talked about that also, and I suggested that
14 perhaps the reason that the results didn't come out as good
15 as we expected was because a lot of the women dropped out.
16 I don't know the answer why, as to why they dropped out,
17 but it definitely brought down the number of the sample
18 size and they lost statistical power. So, perhaps that's
19 the reason. I have no answer for that.

20 DR. D'AGOSTINO: You have another question?

21 DR. KODA-KIMBLE: Yes. I had a question about

1 the tachycardia because it was something that I read in the
2 report. Although you say it's rare and this is consistent
3 with the pharmacokinetics and absorption of this drug, it
4 did strike me that most of those cases were in situations
5 where the individuals had doubled the dose. So, now we're
6 talking about a 5 percent solution, and I'd like you to
7 comment.

8 DR. GOETSCH: Exactly. That's one of my
9 concerns also. It was very startling that when they did
10 double the dose, that's when they had the tachycardia, and
11 when they suddenly decreased it back to the normal dose it
12 went away. It would concern me now that you're going to
13 double the dose for them and this will be a health concern.

14 DR. D'AGOSTINO: Any questions on this side of
15 the table? Yes.

16 DR. HASHIMOTO: For the female study, you said
17 the application to the front and for the male study, the
18 vertex. Why the female patient only to the front?

19 MS. FARR: Probably the sponsor can answer that
20 better, but apparently that is more common in females, that
21 they start losing their hair more in front, and in males

1 more in the back of the head, the back of the scalp.

2 DR. HASHIMOTO: The regrowth of hair in the
3 front may be more difficult than the vertex.

4 MS. FARR: Yes. Maybe the sponsor can answer
5 that better.

6 DR. D'AGOSTINO: Yes. We can I think let the
7 sponsor make its presentation.

8 MS. FARR: That was the decision that was made.

9 DR. D'AGOSTINO: I think that's a good point,
10 and the sponsor can address it when they give their
11 presentation.

12 Other comments over here?

13 (No response.)

14 DR. D'AGOSTINO: It's about 9:30. Rather than
15 have the sponsor start their presentation, I think we
16 should take a break now even though it may be early. We'll
17 start immediately at 9:45. That way we'll have plenty of
18 time for the sponsor's presentation and questions.

19 (Recess.)

20 DR. D'AGOSTINO: The next item on the agenda is
21 the presentation by Pharmacia & Upjohn.

1 Before we go on to the presentation by
2 Pharmacia & Upjohn, Andrea Neal has to make a statement.

3 DR. NEAL: I just need to provide an addendum
4 to the conflict of interest statement. In addition to Dr.
5 Tschen having performed a previous investigation of
6 minoxidil, Dr. Lynn Drake would like to disclose that she
7 also did and it was with the vehicle.

8 DR. D'AGOSTINO: Thank you.

9 We are now going to have the presentation from
10 Pharmacia & Upjohn. Michael Valentino will present the
11 agenda for the presentations and introduce the individual
12 speakers. Michael?

13 MR. VALENTINO: Good morning. Thank you, Dr.
14 D'Agostino.

15 Dr. D'Agostino and members of the two
16 committees, Dr. Weintraub and FDA staff members, and ladies
17 and gentlemen, we are sincerely pleased to be here today to
18 review with you our vast database on 5 percent topical
19 minoxidil solution and we are also very anxious to discuss
20 with you the need for this product in the OTC environment
21 and the appropriateness for this product in the OTC

1 environment as well.

2 My name is Michael Valentino and I am President
3 of Pharmacia & Upjohn Consumer Healthcare for North
4 America.

5 What I would like to do this morning is, in my
6 introductory comments, just provide some information about
7 the marketplace that 5 percent topical minoxidil solution
8 is going into so that we have a common understanding. Then
9 also I'd like to spend a little time and frame the main
10 issues that I think we're going to spending most of our
11 time as a group discussing this morning.

12 At that point, I'm going to turn the podium
13 over to Dr. Thomas Cash who is going to spend a little time
14 discussing the psychosocial effects of hair loss on people.
15 He's going to talk a little bit about the stress that these
16 patients endure and what affect these stresses have on
17 their overall well-being.

18 After Dr. Cash, Dr. Ron Trancik is going to
19 come up from Pharmacia & Upjohn's Clinical Department, and
20 he's going to go through a thorough safety and efficacy
21 review, and where appropriate, he's going to be, of course,

1 making comparisons to the 2 percent product.

2 Following Dr. Trancik is going to be Stuart
3 Rose from our Market Research Department. Stuart is going
4 to be discussing the labeling work that has been done in
5 support of this proposition, and he's also going to attempt
6 to give us some insight as to how that label has developed
7 iteratively over time and how we believe now that it is a
8 clear, concise communication to consumers.

9 Then finally, Ron is going to come back up
10 again and discuss the risk/benefit assessment that has been
11 done and also provide some concluding remarks.

12 I think it's appropriate for us to start with,
13 as I said, a common understanding of the market that 5
14 percent topical minoxidil solution is going to go into.
15 Our studies indicate that there are about 40 million men
16 that suffer from androgenetic alopecia. But as we do more
17 market research and learn more about this population, we
18 believe now that there really are only about 6 million to 7
19 million of those men that are sufficiently motivated enough
20 to do something about the problem and take action. So,
21 that is the target audience essentially for this product.

1 Up until this point, these people in the
2 marketplace have had an alternative -- and we think a
3 pretty good one -- to turn to called Rogaine 2 percent.
4 So, it's probably important for us to spend a little bit of
5 time discussing what our experience has been so far with
6 Rogaine 2 percent.

7 We're happy to report, as the committee members
8 might expect, that what we've been able to accomplish is
9 much broader access. In fact, we have a user base now that
10 is five-fold larger than the prescription user base. In
11 specific terms, we had a little over 400,000 users as an
12 Rx, and today we have a user base that's a little over 2
13 million. So, a five-fold increase, but you can see it's
14 still a fairly small overall population of people that are
15 taking advantage of the product.

16 When we talk to these people, one of the things
17 that they tell us is that they appreciate Rogaine, but they
18 really need a product that provides greater efficacy. You
19 and we both know that Rogaine 2 percent has efficacy
20 limitations, and in our dialogue with our users, as we try
21 to learn more, they continually play back the fact that

1 they really need a product that provides much greater
2 efficacy. In some instances, as we know, Rogaine 2 percent
3 does not work at all. In other cases, the efficacy is
4 quite variable. So, the consumers are playing back to us
5 that they need a higher strength product.

6 Additionally, when we talk to non-users, they
7 main reason that they give us for not entering the category
8 is their belief that there is no alternative that provides
9 the efficacy that would entice them to come into the
10 category. When we probe that further, they say to us that
11 if they were convinced that there was a product that
12 provided more efficacy, they certainly would enter the
13 category.

14 I would like to spend a moment and just give a
15 little bit of the recent regulatory history as a baseline
16 of understanding.

17 Last December we received an approvable letter
18 from the FDA for the 5 percent as an Rx product. At that
19 point, we had the FDA's agreement that this product was
20 safe and effective and produced a risk/benefit ratio that
21 was certainly acceptable. I think as far as efficacy is

1 concerned, it's not one of the things that we as a group
2 today are going to be spending most of our time focusing
3 on.

4 You may be wondering why we submitted the 5
5 percent as an Rx when in fact we had the 2 percent product
6 as an OTC. In fact, what has happened here is an issue of
7 timing. We did not have the 2 percent product officially
8 approved at the time when we needed to submit the 5
9 percent, and so that's why that difference exists. When we
10 did get the approvable letter for 5 percent, we filed an
11 OTC NDA for the male indication, as has been indicated so
12 far.

13 I do want to point out that we are working with
14 the FDA right now aggressively and are pursuing additional
15 clinical trials with women, and we have a very good
16 expectation that at some point we're going to be in a
17 position to have that product approved for women as well.

18 So, the main issues that I think are going to
19 turn out to be the focus of our discussion this morning
20 are: Is this product safe in an OTC setting for men, and
21 what happens, what is the consequence if women use the

1 product inappropriately? We're going to be, of course,
2 addressing both of those issues in detail.

3 We believe very strongly that all the criteria
4 for OTC consideration has been more than met by the 5
5 percent submission. When you talk about efficacy, as I
6 said, from our point of view, efficacy is not so much an
7 issue because the agency has already agreed that the
8 product is effective. But in specific terms, the data
9 indicate that 46 percent more hair is grown and the results
10 can be seen sooner, and we'll get into that discussion in
11 detail.

12 We also believe that we're in quite an enviable
13 position because we have a product that is more effective
14 and essentially the safety profile is comparable to the 2
15 percent product, whether in the Rx environment or the OTC
16 environment. So, there is a superior risk/benefit ratio
17 here to be considered.

18 We believe quite strongly that acceptable
19 labeling has been developed and there will be a thorough
20 discussion of that labeling in a few minutes.

21 So, I would like to conclude my opening remarks

1 with just a couple of comments. We believe quite strongly
2 that the 5 percent should be approved for OTC availability.
3 Ladies and gentlemen, we're quite proud of this drug. It
4 is literally a part of our company. We have studied it and
5 worked with it for nearly 20 years. We worked side by side
6 with the FDA studying and working with it. We think it is
7 a very well understood compound.

8 We believe that the drug has a strong benefit-
9 to-risk ratio for men.

10 We also believe that labeling appropriately
11 advises men of the differences between the 2 percent and
12 the 5 percent product, and importantly, we believe that
13 we've written labeling that appropriately deters women from
14 use of the product.

15 So, finally, it is our view that the OTC
16 status, as a result of our 2 percent experience, will
17 dramatically expand usage as we all hope when we consider
18 propositions like this, and that there is a very real need
19 for this product in the marketplace and this need can now
20 be addressed with a product that is even more effective
21 than what has been available and in fact is quite

1 effective.

2 So, what I'd like to do at this point is turn
3 the podium over to Dr. Cash who is going to discuss the
4 psychosocial effects of hair loss in men. Dr. Cash?

5 DR. CASH: Thank you and good morning. It's a
6 pleasure to be here today to share with you a pertinent
7 facet of my professional life's work.

8 For 25 years now, my program of scientific
9 research has concerned the psychology of physical
10 appearance, including over 100 published scientific
11 articles and three books. My research has examined the
12 psychosocial effects of a range of physical attributes and
13 conditions, including studies of beauty, obesity, eating
14 disorders, acne, as well as androgenetic alopecia.

15 As a clinical psychologist, I've also developed
16 and evaluated a psychotherapeutic treatment program to help
17 person's whose lives are diminished by their despair and
18 discontent with their physical appearance.

19 The human condition is inherently one of
20 embodiment and the functioning and appearance of the human
21 body are, of course, indeed life-shaping. This is true

1 both in terms of others' reactions to our physical
2 appearance as we interact with our social world and in
3 terms of how we perceive and react to our own conditions of
4 embodiment.

5 The psychology of physical appearance
6 incorporates both of these two perspectives. The outside
7 view concerns the interpersonal effects of human
8 appearance, including the occurrence of social prejudice
9 and discrimination. The inside view pertains to our
10 subjective attitudes and feelings about our own looks,
11 experiences which psychologists call body image.

12 Scientific research on the psychosocial effects
13 of androgenetic alopecia reveals that both views are
14 negatively affected by hair loss. Experimental studies
15 have verified the existence of uncomplimentary social
16 stereotypes of baldness. In initial impressions, people
17 unconsciously perceive the appearance and personalities of
18 men with visible hair loss less favorably than men with a
19 full head of hair.

20 Although there are certainly more severe social
21 prejudices in our society, still the social meaning of hair

1 loss can lead balding men to feel apprehension and the
2 conviction that they're losing more than the hair on their
3 heads.

4 According to two controlled scientific
5 investigations that I published in 1992 and 1993 in the
6 Journal of the American Academy of Dermatology, stress,
7 distress and compromised well-being come with androgenetic
8 alopecia for either gender. Rare is the person who is
9 indifferent to the onset of hair loss.

10 In my 1992 study, there were three groups of
11 randomly sampled men: 63 with modestly visible
12 androgenetic hair loss, 40 with more extensive hair loss,
13 and 42 non-balding controls. None had received any medical
14 or surgical treatment for hair loss.

15 Compared to men with more modest alopecia,
16 those with more extensive hair loss reported a more adverse
17 impact. For example, of the 70 possible effects listed on
18 our hair loss effects questionnaire, men with modest
19 balding reported a significant impact on 60 percent of
20 these events, and men with extensive balding reported such
21 an impact on 79 percent of the items.

1 As this slide shows, this high loss group
2 experienced significantly more negative socio-emotional
3 effects of their hair loss, more worry and preoccupation
4 about it, and somewhat stronger behavioral efforts to
5 conceal, compensate, and cope with the hair loss.
6 Specifically, substantial percentages of men expressed
7 desires for more hair, reported peer teasing about their
8 hair loss, feelings of self-consciousness and worry about
9 their physical appearance, concerns about aging, and so
10 forth.

11 These data confirm that androgenetic alopecia
12 is an unwelcome, stressful experience for most men. In
13 fact, when the non-balding controls were asked to imagine
14 their reaction, should they begin to have gradual pattern
15 balding, a mere 8 percent said that they would not be
16 bothered by it.

17 To determine whether the stress of alopecia
18 might impair men's psychosocial functioning, balding and
19 non-balding men were compared further on body image and
20 adjustment. Our results indicated that it is improbable
21 that androgenetic alopecia damages functioning in most men.

1 Group differences in psychological adjustment
2 were not significant except that balding men clearly had
3 more negative body image attitudes, less satisfaction with
4 their hair, as you can see here, and also with their
5 overall physical appearance. In other words, hair loss
6 impaired body image beyond a focal discontent on hair.

7 Our correlations in the study did reveal that
8 the men who were most upset by hair loss had less adaptive
9 functioning, and as this slide conveys, those most
10 distressed by their hair loss were men who regarded their
11 balding as socially noticeable, those who expected it to
12 progress, younger men with an earlier hair loss onset, and
13 single men who were not dating.

14 Well, then in 1993 with dermatologists Vera
15 Price and Ron Savin, we studied a clinical population,
16 newly referred patients with androgenetic alopecia, 96
17 women and 60 men. We included a female control group in
18 this study of 56 non-alopecia patients seeking treatment
19 for cutaneous conditions that were not publicly visible.

20 We found that alopecia was a profoundly
21 distressing experience for women whose body image and

1 psychological adjustment were much less favorable relative
2 to the female controls, and again we found that hair loss
3 was quite troubling to men. Over one-fourth of the men
4 reported being very or extremely upset by their alopecia.

5 The next slide describes some of the
6 psychosocial effects that these male patients attributed to
7 their hair loss. For example, the vast majority of these
8 men felt helpless, frustrated, and worried by the
9 condition. They believed that it substantially diminished
10 their looks and that they had to endure social teasing
11 about their hair loss.

12 Furthermore, a comparison of men's reactions in
13 our two studies clearly reveals that distress was higher in
14 a treatment seeking sample than in a random sample of
15 balding men. Understandably, it is their psychological
16 discomfort that in great part motivates patients to seek
17 effective treatments and remedies for their alopecia and
18 associated anguish.

19 Our studies further reveal, as this slide
20 indicates, that left to their own coping resources, people
21 with androgenetic alopecia often seek information and

1 selective social support, struggle to manage their
2 disruptive negative thoughts and feelings, try to conceal
3 their hair loss with altered hair styling or by taking
4 cover under hats or caps. They may also spend more time
5 and effort on their appearance in other ways to try to
6 compensate for their condition. For example, balding men
7 may grow a beard, work out more, or wear nicely looking
8 clothes.

9 The search for ways to reverse the course of
10 hair loss is a search to restore one's sense of physical
11 acceptability and well-being. Safe and effective solutions
12 to the strife that accompanies androgenetic alopecia are
13 valuable to those who are affected. The losses at stake
14 and the gains to be had, of course, do pertain to hair, but
15 more importantly, the losses and gains are also felt in the
16 quality of embodied life.

17 I thank you for your attention and now let me
18 turn the podium over to Dr. Ron Trancik, Pharmacia &
19 Upjohn.

20 DR. TRANCIK: Thank you, Tom.

21 Good morning. My name is Ron Trancik. I am in

1 the Clinical Research Department of the Consumer Healthcare
2 Division at Pharmacia & Upjohn where I am the principal
3 monitor for Rogaine. I have over 20 years of
4 pharmaceutical industry experience in the clinical
5 development of dermatologic products.

6 Over the next 15 minutes, I will present to you
7 an overview of the safety and efficacy data that we have
8 generated over the last several years with Rogaine Extra
9 Strength for Men. For brevity in this presentation,
10 Rogaine Extra Strength for Men will often be referred to as
11 Rogaine 5 percent. In many cases there will be direct
12 comparisons to the existing Rogaine OTC product which will
13 be referred to as Rogaine 2 percent.

14 These comparisons will show that Rogaine Extra
15 Strength for Men has comparable safety and superior
16 efficacy to the existing Rogaine OTC product. We believe
17 that our data strongly support the direct OTC approval of
18 Rogaine Extra Strength for Men.

19 The safety of Rogaine Extra Strength for Men
20 will be based on the following.

21 First, pharmacokinetic studies have been

1 conducted to support the wide margin of safety of Rogaine.

2 I will also present safety data generated in
3 our well-controlled clinical trials which contained over
4 2,000 patients, but I will focus mainly on the male data.

5 Thirdly, we do have commercial marketing
6 experience with Regaine 5 percent worldwide. I point out
7 that Regaine is the name of the product in countries
8 outside of North America where it is referred to as
9 Rogaine.

10 Lastly, I would like to share with you our
11 pharmacovigilance data generated with Rogaine 2 percent as
12 a prescription product compared to Rogaine 2 percent U.S.
13 experience as an OTC product.

14 Superior efficacy has been demonstrated with
15 Rogaine 5 percent in clinical studies conducted in over 700
16 males and support the enhanced efficacy of 5 percent over
17 Rogaine 2 percent.

18 Based on the experience we have gained with
19 Rogaine 5 percent, we will conclude that there is
20 comparable safety and superior efficacy of Rogaine Extra
21 Strength for Men as compared to Rogaine 2 percent, and that

1 the data support the direct OTC approval of Rogaine Extra
2 Strength for Men.

3 Before I get into the safety and efficacy data,
4 I want to present an overview of the history of minoxidil
5 in the U.S. Minoxidil has been around for a number of
6 years and was initially approved as the antihypertensive
7 drug Loniten.

8 Following Loniten is a list of major events
9 which have been realized in the U.S. utilizing minoxidil in
10 a topical dosage form in Rogaine products which are used to
11 treat androgenetic alopecia, or hereditary hair loss. The
12 original Rx product was approved in males in 1988, followed
13 by approval in 1991 in females.

14 More recent history with the 5 percent product
15 has involved meetings with the FDA, culminating in an NDA
16 submission of the 5 percent product as an Rx drug. This
17 occurred in December of 1995.

18 Rogaine was then approved as an OTC product in
19 February 1996.

20 In December of 1996, we received an approvable
21 letter for Rogaine 5 percent as an Rx product for use in

1 males only.

2 Following another meeting with the FDA where we
3 discussed the direct OTC approval of Rogaine 5 percent, we
4 resubmitted the NDA as a direct OTC product in February of
5 1997.

6 Lastly, we are here today at the request of the
7 FDA to discuss specific labeling issues relating to the
8 direct OTC approval of Rogaine 5 percent.

9 Another very important message on this slide is
10 that Rogaine has a long history of product usage both as a
11 prescription and an OTC product. The safety of minoxidil,
12 the active ingredient in Rogaine, has been studied
13 extensively and has been well-established when applied
14 topically. The FDA and other regulatory agencies worldwide
15 have reviewed and approved over 100 Rogaine/Regaine
16 submissions.

17 Next I would like to review the marketing
18 experience for the 2 percent and 5 percent products. The 2
19 percent solution is approved in 90 countries around the
20 world. In 20 of those countries, it is available as a
21 nonprescription product.

1 With respect to Regaine 5 percent, we now have
2 19 countries where the product has been approved for up to
3 4 years in both males and females. It is marketed in 14
4 countries with two of the 14 countries, the product being
5 available as a pharmacy only nonprescription product.
6 Those countries are Denmark and New Zealand.

7 We also have 12 prescription approvals pending,
8 along with 2 direct OTC approvals pending, including the
9 submission here in the U.S. and a recent submission in the
10 United Kingdom.

11 Next I would like to review the safety of
12 Rogaine 5 percent. Comparable safety to Rogaine 2 percent
13 has been established by pharmacokinetic studies, clinical
14 studies, and commercial marketing experience. I will
15 discuss each of these areas separately over the next
16 several minutes.

17 Based on our pharmacokinetic studies, the
18 absorption from Rogaine 5 percent is low, representing
19 about 1.7 percent of the applied topical dose. We have
20 also over the years studied many factors which might
21 influence the absorption of minoxidil, including sunburn,

1 occlusion, and the concomitant use of minoxidil with other
2 drugs such as Retin A. This drug has a well-defined
3 pharmacokinetic profile.

4 Most importantly, we have established a minimum
5 effect level where hemodynamic changes first occur.
6 Between 20 and 30 nanograms per milliliter is the minoxidil
7 serum level at which just measurable hemodynamic effects
8 are observed. For example, at approximately 20 nanograms
9 per milliliter, we see about a 5 beat per minute increase
10 in heart rate in untreated hypertensives, a change not
11 unlike events which occur in daily life.

12 Even at levels close to and exceeding 80
13 nanograms per milliliter, a serum minoxidil level greater
14 than 70 times the level achieved with topical minoxidil
15 only an increase of 10 to 15 beats per minute in heart rate
16 was observed.

17 In addition, patients were monitored in our
18 long-term clinical trials and we have found that serum
19 minoxidil levels in these clinical trial patients translate
20 on an average to 0.6 nanograms per milliliter for patients
21 treated with Rogaine 2 percent and 1.2 nanograms per

1 milliliter in patients using the 5 percent product. 1.2
2 nanograms per milliliter is a mean of over 2,000 minoxidil
3 serum level samples generated in 670 male and female
4 patients treated with Rogaine 5 percent. The highest level
5 observed was 19.1 nanograms per milliliter in this patient
6 population.

7 The 0.6 and 1.2 nanograms per milliliter levels
8 are well below the 20 nanograms per milliliter minimal
9 effect level for observed minor hemodynamic changes and
10 establishes a margin of safety greater than an order of
11 magnitude when Rogaine is used topically for the treatment
12 of common hair loss.

13 The safety of Rogaine 5 percent was also
14 established in four well-controlled clinical trials. Two
15 of these studies in males, namely protocols 001 and 0285
16 were considered definitive studies. There were 827 males
17 enrolled in these four studies with 371 of those patients
18 treated with Rogaine 5 percent.

19 Relative risk estimates were calculated for all
20 body systems. Medical events generated in these four male
21 and female clinical trials can be distilled down to the

1 dermatologic body system as shown on this slide. Out of
2 the 16 body systems monitored in both our male and female
3 studies, only within the dermatologic body system was a
4 statistically significant dose-response observed; that is,
5 the risk of dermatologic medical events was greater with 5
6 percent, than 2 percent, than placebo.

7 While there is a statistically significant
8 relative risk difference between 5 and 2 percent
9 treatments, the events within the dermatologic category are
10 relatively minor, such as itching, dryness, and are
11 reversible. None of the events in the Rogaine 5 percent
12 treatment group were considered serious in the male
13 population.

14 As you can see on this slide, if you analyze
15 just the male data, there is no longer a statistically
16 significant difference between the Rogaine 5 percent and
17 Rogaine 2 percent.

18 Next I would like to focus on treatment
19 discontinuations due to medical events. As seen on this
20 slide, the preponderance of discontinuations was due to
21 dermatologic medical events with over half of the

1 discontinuations falling in that category as compared to
2 all other medical events.

3 If we further examined the dermatologic medical
4 event discontinuations by gender, we can again see that the
5 majority of the discontinuations was in females, with less
6 than one-third of the discontinuations due to medical
7 events in the male population.

8 More specifically, if we look at medical events
9 within the dermatologic body system, you can see that the
10 male population contributed to half of the discontinuations
11 due to pruritus or itching, whereas in the case of
12 hypertrichosis, there were no males who discontinued due to
13 this event.

14 Hypertrichosis is defined as growth of hair on
15 areas of the body where it doesn't usually grow. With
16 topical minoxidil, it is generally on the face, primarily
17 above the lateral eyebrows, temples, and along the sides of
18 the face. Also with topical minoxidil, it is often fine
19 hair, or peach fuzz, but it is not course mustache or
20 beard-type hair. It is an unwanted cosmetic effect but is
21 infrequent and reversible.

1 In our well-controlled female studies, which
2 included 301 females treated with Rogaine 5 percent, we had
3 20 medical event reports of hypertrichosis, which
4 represents 7 percent of the female study population. Of
5 these, 7 patients chose to discontinue treatment due to the
6 side effect. 13, or approximately two-thirds, of those
7 females with hypertrichosis chose to continue using Rogaine
8 5 percent.

9 As you will see later in Mr. Rose's
10 presentation of our intent-to-heed labeling studies, this
11 resulted in adding a warning to the Rogaine Extra Strength
12 for Men label: "May cause unwanted facial hair in women."

13 A review of the 7 patients who discontinued our
14 clinical studies due to hypertrichosis revealed that the
15 unwanted hair was primarily on the face, more specifically
16 along the cheeks and forehead, and ranged from vellus hair,
17 or peach fuzz, to one case reported as severe facial hair.

18 This condition, which is reversible in 4 months
19 and even in some patients will disappear with continued use
20 of Rogaine 5 percent, can be minimized by careful
21 application of the product, washing hands following

1 application, and allowing the solution to dry before going
2 to bed.

3 From a clinical perspective, we have
4 consultants in the audience who can speak to their clinical
5 experiences with Rogaine as it relates to hypertrichosis,
6 if you are interested.

7 Also during the course of our well-controlled
8 clinical trials, we monitored local tolerance of patients
9 using the product. These data were collected by elicited
10 check-box responses in the case report forms to determine
11 if the patient was experiencing signs and symptoms of skin
12 intolerance such as itching, erythema, and dryness. The
13 majority of these reactions, as I think you saw on the
14 slides shown by Shahla Farr, were mild and patients were
15 able to continue use of the product.

16 In males we found that Rogaine 5 percent was
17 approximately equal to placebo, both of which were greater
18 than Rogaine 2 percent. We feel this is due primarily to
19 skin reactions to propylene glycol in the formulation.
20 Levels of propylene glycol in Rogaine 5 percent and placebo
21 solutions are equal and both contain more than propylene

1 glycol in Rogaine 2 percent.

2 An assessment of the local tolerance data
3 conducted by the FDA, as you saw presented by Dr. Farr,
4 concluded that Rogaine 5 percent induces more dryness,
5 erythema, and itching than Rogaine 2 percent. This
6 conclusion, as it relates to the use of the product in
7 males, is that local intolerance to Rogaine 5 percent has
8 been addressed in the labeling with the phrase that with
9 Rogaine Extra Strength for Men "Increased scalp irritation
10 may occur."

11 Next I would like to move on to the commercial
12 marketing experience that we have with Rogaine 5 percent.
13 As I mentioned earlier, we are marketing a product for both
14 males and females in 14 countries, in 2 countries as a
15 nonprescription product. Based on our worldwide
16 pharmacovigilance database, we have 37 users reporting 69
17 medical events, with the most frequent being dermatologic,
18 on the order of 60 percent. Of the 69 medical events, 34
19 events were in males, 19 in females, and in 16 of the
20 events, the gender was unknown. None were considered
21 serious.

1 In addition, we have 15 users reporting 38
2 medical events with extemporaneously compounded minoxidil
3 formulations.

4 Based on our pharmacovigilance monitoring, we
5 conclude that there are no new signals emerging as it
6 relates to the toxicologic profile of Rogaine 5 percent.
7 This information has been compared to our commercial
8 marketing experience database with Rogaine 2 percent and is
9 consistent with that database with again the most frequent
10 events reported within the dermatologic category.

11 Next I would like to draw your attention to the
12 medical event profiles comparing Rogaine 2 percent as an Rx
13 product versus its use as an OTC product since it was
14 launched in early 1996.

15 This slide shows the top four categories which
16 represent over 80 percent of all reports. As you can see,
17 over the last 8 years, again the majority of the events are
18 within the dermatologic category. The two most common
19 reported events within the miscellaneous category are lack
20 of efficacy and product complaints. Neurologic events are
21 primarily headaches and dizziness. Cardiovascular events

1 include rapid heart beat and increased blood pressure.

2 Most importantly, if you compare the
3 percentages in these two columns, you can see that the
4 medical event profiles are remarkably similar regarding the
5 use of Rogaine 2 percent as an OTC product as compared to
6 its prescription usage.

7 The conclusion is that the use of Rogaine 2
8 percent in an OTC environment has not changed the safety
9 profile of the product.

10 In summary, the comparable safety of Rogaine 5
11 percent to Rogaine 2 percent has been established by
12 pharmacokinetic and well-controlled clinical studies along
13 with a commercial marketing experience of Rogaine 5 percent
14 outside the U.S. and a comparison of the Rogaine 2 percent
15 prescription versus OTC pharmacovigilance databases
16 generated within the U.S. We feel that the established
17 safety of Rogaine 5 percent supports the direct OTC
18 approval.

19 Next I would like to move on to a brief
20 discussion of the efficacy data generated in males with
21 Rogaine 5 percent.

1 Two definitive studies were conducted with a
2 total enrollment of almost 700 patients. This slide
3 summarizes the primary and secondary endpoints which were
4 collected in the most recent male definitive study.

5 I will not go into a lot of detail here, but
6 just focus your attention on the 5 percent versus 2 percent
7 column. S refers to a statistically significant
8 difference, whereas NS is not statistically significant.
9 You can see that based on our primary efficacy endpoints,
10 which included key questions which were part of a
11 comprehensive questionnaire, along with the objective
12 endpoint of nonvellus hair counts, there were statistically
13 significant differences between Rogaine 5 percent and 2
14 percent. We were able to clearly demonstrate superiority
15 of Rogaine 5 percent versus Rogaine 2 percent using our
16 primary clinical endpoints.

17 In addition, we were able to demonstrate a dose
18 response based on hair count results in both of our
19 definitive studies in males, namely protocol 001 and 0285,
20 showing that Rogaine 5 was superior to Rogaine 2 percent
21 with both better than placebo.

1 Superior efficacy in males then is demonstrated
2 both by magnitude of effect and time to response.

3 Regarding magnitude of effect, we realized a 46 percent
4 increase in hair counts at week 48 with Rogaine 5 percent
5 as compared to Rogaine 2 percent.

6 In addition and again using hair count data, we
7 demonstrated that the response to Rogaine 5 percent at week
8 8 was equivalent to the response achieved with Rogaine 2
9 percent at week 16, thus demonstrated a more rapid onset of
10 hair growth response.

11 These results, namely superior efficacy and
12 comparable safety of Rogaine 5 percent to Rogaine 2
13 percent, led to an approvable letter from the FDA for
14 Rogaine 5 percent as a male-only prescription product.

15 In addition, we feel the safety and efficacy
16 data support the OTC approval of Rogaine Extra Strength for
17 Men.

18 Thank you.

19 Next I would like to introduce Mr. Stuart Rose
20 who is the Director of our Marketing Research Department.
21 Mr. Rose will take you through an overview of our intent-

1 to-heed labeling studies.

2 Again, thank you.

3 MR. ROSE: Thank you, Ron.

4 Consumer-based research conducted for Rogaine 5
5 percent pertains to labeling and has been framed around two
6 central issues raised by the FDA. The completed label
7 testing was gender-specific and focused on the
8 comprehension of the proposed labeling among men, as well
9 as women's intent to heed the label warnings against
10 product use.

11 Specifically, the FDA has posed the following
12 questions for the joint committee today as it pertains to
13 labeling.

14 First, based upon the committee's review of the
15 proposed labeling and the data from the male label
16 comprehension test, will men be able to appropriately
17 choose between Rogaine Extra Strength for Men and Rogaine
18 Regular Strength for Men?

19 Second, based upon the committee's review of
20 the proposed labeling and the data from the female intent-
21 to-heed studies, will women appropriately avoid Rogaine

1 December 1996 and June of this year.

2 Upon recruitment, qualified participants in
3 each of the four studies were invited to a central location
4 within the shopping mall to complete the interview. Common
5 to each study, respondents were provided with a brief
6 description of the hair regrowth treatment category and
7 given the opportunity to read a test label, after which
8 they were asked a series of questions about the label they
9 had just read. The actual questions and the version of the
10 label that was tested varied from study to study, and these
11 differences will be pointed out as we talk about each of
12 the specific label tests.

13 Now let's take a look at the label
14 comprehension tests completed among men.

15 The objective of this study was to determine
16 the extent to which the test label can adequately direct
17 men in selecting between Rogaine Extra Strength for Men and
18 Rogaine Regular Strength for Men in making an appropriate
19 benefit/risk assessment. Specifically Pharmacia & Upjohn
20 and the FDA wanted to make sure that men understand that
21 Rogaine Extra Strength is more effective at growing hair

1 while acknowledging that the product has an increased
2 chance of minor scalp irritation versus Rogaine Regular
3 Strength.

4 In terms of test design, qualified male
5 respondents were given the opportunity to read the Rogaine
6 Extra Strength for Men carton label as if they would look
7 at it as if they came across it in a store environment.
8 They were then asked to complete a brief, self-
9 administered, multiple choice questionnaire.

10 After completing that questionnaire,
11 respondents were told to re-read the Rogaine Extra Strength
12 for Men carton label completely both front and back.
13 Afterward, participants were asked to fill out the same
14 brief, self-administered, questionnaire again to assess
15 depth of comprehension following a forced and complete read
16 of the carton label.

17 Prior to the label testing, discussions with
18 the FDA led to several enhancements. Specifically, we
19 incorporated more prominently positioned bolded bullet
20 points into the use and warnings sections of the back panel
21 label. As we can see in this slide, back panel label copy

1 presents the key benefits of Rogaine Extra Strength versus
2 Rogaine Regular Strength which are more hair growth and
3 hair growth experienced sooner.

4 This is directly followed by the next bolded
5 bullet point which presents the risk that Rogaine Extra
6 Strength may increase scalp irritation.

7 Further below on the back panel in the warnings
8 section, a bolded copy statement appears. "Increased scalp
9 irritation may occur with Rogaine Extra Strength. If scalp
10 irritation is experienced, consider switching to Rogaine
11 Regular Strength. If scalp irritation continues, stop use
12 and see a doctor."

13 Before we look at the results, it's important
14 to acknowledge that labeling plays a different role in
15 different settings. In a store where a consumer may not
16 have read the entire label, it's important that the
17 consumer understand what the product does. However, how to
18 use the product or what to do if a side effect may occur
19 are more appropriate following a more comprehensive and
20 thorough read of the label which may occur once at home.

21 Now let's take a look at the results.

1 The Rogaine Extra Strength for Men label
2 clearly communicates that the product is more effective
3 than Rogaine Regular Strength for Men. As we can see,
4 approximately 3 out of 4 non-users and users alike
5 understand that Rogaine Extra Strength grows more hair and
6 grows hair sooner than Rogaine Regular Strength after
7 reading the label as if they came across it in a store
8 environment.

9 After completing a reading of the front and
10 back carton label completely, 8 out of 10 correctly
11 understand both of these enhanced efficacy benefits
12 associated with the product.

13 It's important to note that this is more of a
14 true read of actual label comprehension than at the store
15 level read where the respondent may not have read the
16 entire label. In fact, there's a significant increase in
17 comprehension of both enhanced efficacy communication
18 objectives from the store level read to the complete read
19 among the non-user group who may be less familiar with the
20 product and its use.

21 Now I would like to turn our attention to male

1 comprehension of the possible risk of minor scalp
2 irritation, as well as understanding of the appropriate
3 course of action to be taken should this minor and easily
4 remedied side effect occur.

5 In both groups, just over half of the men
6 understood the increased likelihood of scalp irritation
7 associated with the product after only reading the carton
8 label at a store read. However, this comprehension greatly
9 improves to 7 out of 10 following the complete read of the
10 carton label which would certainly occur if any side effect
11 were encountered in using the product.

12 Please remember that none of these men were
13 using the product or experiencing the side effect at the
14 time that this test was conducted.

15 Looking at the bottom of the chart, it's
16 important to note that approximately 7 out of 10 in each
17 group also understood the need to switch to Rogaine Regular
18 Strength if scalp irritation occurs. This is true across
19 both groups at both the store level and complete carton
20 level readings.

21 In conclusion, the Rogaine Extra Strength for

1 Men label communicates the important messages about the
2 product in terms of a correct benefit/risk assessment. In
3 terms of efficacy benefit, men clearly understand that
4 Rogaine Extra Strength for Men grows more hair and grows
5 hair sooner than Rogaine Regular Strength.

6 In terms of the risk assessment, men understand
7 that Rogaine Extra Strength is more likely to cause scalp
8 irritation than Regular Strength and that the user should
9 switch to Regular Strength if scalp irritation is
10 experienced. This understanding improves considerably
11 following a more comprehensive, complete read performed by
12 study participants. We feel that this understanding will
13 assist men in correctly and knowledgeably choosing between
14 Rogaine Regular Strength and Rogaine Extra Strength.

15 However, although we were satisfied with these
16 label comprehension scores, we have further strengthened
17 the label based on this learning.

18 As you can see in this slide, we have expanded
19 considerably the discussion of scalp irritation in the use
20 section and have provided better direction to men regarding
21 switching to Rogaine Regular Strength versus stopping use

1 of the product and seeing a doctor. In fact, this
2 paragraph also appears again below in the warnings section.

3 Now let's turn our attention to women's intent
4 to heed the label warning against product use.

5 In preliminary discussions with the FDA
6 regarding an OTC approval of Rogaine 5 percent, a concern
7 was raised by the FDA regarding the number of women who
8 would use the stronger product given absence of a female
9 offering. Accordingly, we developed labeling to strongly
10 discourage female use of the product.

11 I'd like to point out that the product was
12 initially labeled Rogaine Maximum Strength for Men that
13 you'll see in this test stimulus.

14 As you can see here, in the initially proposed
15 labeling, in addition to the "for Men" designation in the
16 actual name of the product, there was prominent black
17 window/white type mention on the front panel boxed, "not
18 for use by women." This boxed warning appeared yet again
19 on the back panel, along with a half a dozen other mentions
20 specifying male-only usage. Our goal was to make this
21 information as clear and as simple as possible.

1 We then commissioned an intent-to-heed study
2 among women to evaluate this label and to specifically
3 address the FDA's issue. The overall purpose of this study
4 was to provide reassurance that very few women would in
5 fact, use Rogaine Maximum Strength for Men based on the
6 label warnings.

7 More specifically, the objective was to
8 estimate the proportion of women who, upon examination of
9 the proposed label, would incorrectly select Rogaine
10 Maximum Strength for Men for their own personal use. It's
11 important to note that this proportion might also include
12 women who may choose to accept the risk of a minor unwanted
13 cosmetic effect for the potential benefit of growth.

14 In terms of methodology, qualified female
15 respondents were informed about the possible availability
16 of a Rogaine Maximum Strength for Men product, exposed to a
17 mock shelf set as seen here, however with the actual carton
18 labels. Participants were then asked to choose which
19 product they would select for their own personal use.

20 Respondents were then handed the Rogaine
21 Maximum Strength for Men carton label and asked to

1 completely read the front and the back of the box.
2 Participants were then asked if this product would be
3 appropriate for their own personal use regardless of
4 whether or not they had selected it in the initial
5 behavioral component of the study.

6 Now let's take a look at the results.

7 As we can see in this bar chart illustrating
8 respondent responses to the question, an overwhelming
9 majority of women made a correct choice. Specifically, 95
10 percent of non-users and 85 percent of users correctly
11 chose a product labeled for women. Only one-half of 1
12 percent of the broad audience of non-users and only 3
13 percent of the narrower audience of current Rogaine and/or
14 minoxidil-based product users selected Rogaine Maximum
15 Strength for Men in this important behavioral component of
16 the test.

17 It's interesting to note that no more selected
18 Rogaine Maximum Strength for Men than any of the other 2
19 percent male offerings in spite of the availability of the
20 stronger product.

21 Respondents were then asked, based upon the

1 label you have just read, is this product appropriate for
2 your own use? As we can see, an overwhelming majority of
3 women made the correct decision. 86 percent of non-users
4 and 80 percent of users correctly indicated that Rogaine
5 Maximum Strength for Men was inappropriate for their own
6 personal use.

7 Contrastingly, 10 percent of non-users and 17
8 percent of users attitudinally indicated that Rogaine
9 Maximum Strength for Men was appropriate for their personal
10 use even though almost all of these women did not select
11 the product in the more important behavioral part of the
12 test.

13 In conclusion, we believe that the results of
14 this intent-to-heed study of the test label indicate that
15 the actual number of women who would select Rogaine Maximum
16 Strength for Men is in fact very small and therefore
17 appropriately discourages female use.

18 Although we felt the study adequately
19 demonstrated that intended use of a product labeled Rogaine
20 Maximum Strength for Men would be very low, we continued to
21 work with the FDA to address the issue. Accordingly,

1 Pharmacia & Upjohn and the FDA collectively agreed that it
2 should be possible to improve upon the results by
3 strengthening the label warnings further. We also mutually
4 agreed to rename the product Rogaine Extra Strength for
5 Men, and it was decided to retest the revised label among
6 women using an alternate test design.

7 Let's take a moment to look at the improvements
8 that were made to the label. In addition to changing the
9 product name from Maximum Strength to Extra Strength, the
10 label was strengthened to more clearly discourage women
11 from using the product. Specifically, the front panel
12 warning, "not for use by women," was placed in a white
13 window with black type which is much intrusive than the
14 black window with white type.

15 Additionally, the FDA requested that the "for
16 Men" designation on the front panel be enlarged
17 dramatically with "Extra Strength" and "for Men" copy
18 points being made both the same type size and the same
19 color.

20 Moreover, a prominent yellow window with a red
21 framed warning box reiterating "not for use by women"

1 including the language "Does not work better in women than
2 Rogaine for Women. May cause unwanted facial hair in
3 women" was incorporated on the back panel.

4 Additionally, the pregnancy warning was removed
5 from the originally proposed label at the FDA's suggestion
6 so as not to give any impression that women could use this
7 product.

8 Recognizing that there exists no standardized
9 approach to label comprehension or intent-to-heed study
10 testing, discussions with the FDA led to an alternate test
11 design versus that used in the initial intent-to-heed
12 study. The primary difference in this test design was that
13 women would be asked to read only the Rogaine Extra
14 Strength for Men label without the benefit of understanding
15 the other current minoxidil product choices that exist in
16 the hair regrowth treatment category.

17 Respondents were then asked if they would buy
18 the Rogaine Extra Strength for Men for their own personal
19 use. Participants were then instructed to thoroughly read
20 the front and back panel of the label and specifically
21 asked or probed for if the product was for men only, for

1 women only, or for both men and women.

2 Let's look at the results.

3 After only reading the Rogaine Extra Strength
4 for Men carton label at the store read level, this test
5 design indicated that 63 percent of non-users and 60
6 percent of users would not purchase the product for their
7 own personal use. However, despite considerable
8 strengthening of the label warnings against female use,
9 using this methodology, 34 percent of non-users and 37
10 percent of users responded to the question that they would
11 purchase the product.

12 However, after being asked to read the entire
13 package label at the complete read level, which is a more
14 true read of label comprehension, 81 percent of the non-
15 users and 75 percent of the users correctly understood that
16 the product is for men only.

17 We have tested two versions of our proposed
18 Extra Strength for Men labeling under two alternate
19 methodologies, which has resulted in a range of responses.
20 We believe one particular test design most realistically
21 addresses the issue at hand, however. We strongly believe

1 that the initial test design reflects a real world, retail
2 store shelf environment by providing consumers with the
3 actual array of minoxidil products available and allowing
4 for a choice that an interested consumer would actually
5 make in the real world.

6 As shown here, the earlier test of the original
7 label wording in a choice-based situation showed that only
8 3 percent of users and one-half of 1 percent of non-users
9 would select the Rogaine Extra Strength product. However,
10 in the absence of any choice and with what we and the FDA
11 have deemed as judgmentally stronger labeling, one-third of
12 women said they would buy Rogaine Extra Strength for Men.

13 There are two reasons we believe explain this
14 difference in result. The primary reason is that this test
15 design does not relate to the real world as the earlier
16 test design did. In the real world, women have options in
17 this product category which greatly guide their product
18 selection.

19 A second reason concerns the research
20 situation. The second test design creates a context effect
21 or experimental demand bias. For example, when asked if

1 they would buy something or not, people are likely to sense
2 the hoped-for answer is yes. This is a well-known tendency
3 for many people to be agreeable and provide what they
4 believe to be the hoped-for answer whether it is correct or
5 not.

6 Let's take just a moment to put this finding in
7 context. It's estimated that only 250,000 women have
8 purchased the current 2 percent Rogaine for Women product
9 since it has been available as an OTC. If this data set
10 were correct, based on the second intent-to-heed study
11 result, there would be 8 million women, or a 32-fold
12 increase in the number of women who would be using the
13 product. Clearly this outcome is preposterous and there is
14 some dissonance in this data set.

15 We conclude that this absolute magnitude of
16 women saying that they will buy Rogaine Extra Strength for
17 Men in the second study is grossly overstated and is due to
18 the absence of availability of other minoxidil product
19 choices which exist in the real world and does not reflect
20 that environment.

21 Another factor explaining this unrealistic

1 outcome is the yea-saying tendencies, of consumers wanting
2 to provide the hoped-for answer without a choice and to
3 please the interviewer.

4 In order to better understand the difference in
5 these data sets and to provide additional insights into the
6 methodology, we decided to conduct a supplemental control
7 arm of the second intent-to-heed study. I'd like to point
8 out that although this study has been submitted to the FDA,
9 it does not appear in your briefing documents as they had
10 not at that time had adequate time to review the study.

11 The protocol is identical to the second intent-
12 to-heed study with one exception and that exception is the
13 stimulus which will serve as the control. The current
14 Rogaine for Men 2 percent product was used as a control
15 because it is similar to the Rogaine Extra Strength for Men
16 product but does not have the label warnings against female
17 use.

18 Essentially two outcomes are possible. If
19 Rogaine Extra Strength is attractive to women, a higher
20 proportion will ignore the warnings and should select
21 Rogaine Extra Strength for Men rather than Rogaine for Men.

1 If it is a yea-saying effect, a higher percentage should
2 choose Rogaine for Men since it does not have the warnings.

3 As we can see, a considerably higher percentage
4 of women indicated that they would buy Rogaine for Men, the
5 2 percent offering, than said would buy the Rogaine Extra
6 Strength for Men, indicating that the labeling is in fact
7 working to deter usage among women and that a powerful yea-
8 saying tendency is at work.

9 We can speculate there might be other reasons
10 as well. For example, some of the women might be aware
11 that both Rogaine for Women 2 percent and Rogaine for Men 2
12 percent are in fact the same product. Yet, even given no
13 choice and in the face of higher efficacy, women did pay
14 attention to the warning. We believe this supports the
15 validity of the first choice-based test design.

16 In conclusion, we believe the carton label for
17 Rogaine Extra Strength for Men has been successfully tested
18 among both women and men. This learning has allowed for
19 strengthening of the label with important wording and
20 package graphic changes which have in turn been retested
21 providing acceptable levels of comprehension.

1 The Rogaine Extra Strength for Men label
2 effectively communicates to men the important messages
3 about the product's benefit/risk assessment of greater
4 effectiveness with a possible increased chance of minor
5 scalp irritation.

6 In addition, women are clearly being informed
7 that the product is not intended for their own personal use
8 and we feel confident that the overwhelming majority will
9 heed the warning and not opt to use Rogaine Extra Strength
10 for Men.

11 It's important to remember that we're talking
12 about an unwanted cosmetic effect that is minor and
13 reversible and that would occur among only a very small
14 number of women among an already small group of women who
15 would incorrectly opt to use the product.

16 Based on the test design that we believe is
17 most reflective of a real world, choice-based situation, we
18 feel that this label testing learning addresses the
19 question put forth to the committees this morning and
20 supports OTC approval of a male-only Rogaine Extra Strength
21 product.

1 The cartons that are on the table in front of
2 you represent the proposed labeling appearing on page 59 of
3 your briefing document, and this is the proposed carton for
4 Rogaine Extra Strength for Men and reflects the total
5 learning derived from our label testing and the FDA's
6 input.

7 This slide presents the most significant
8 modifications incorporated into the carton label. We have
9 expanded the discussion of scalp irritation in the use
10 section to provide better direction to men regarding
11 switching to Rogaine Regular Strength versus stopping and
12 seeing a doctor. This discussion appears yet again in the
13 warnings section of the back panel. The warning against
14 use if you are female has been added as bullet which is
15 visually linked with the already very prominent yellow red-
16 framed window warning, and the pregnancy warning has been
17 removed so as not to give any impression that women could
18 use Rogaine Extra Strength for Men.

19 Again, we believe that these changes provide
20 assurances that men will use the product appropriately in
21 comparison to Rogaine Regular Strength for Men and that

1 women are adequately warned that they should use Rogaine
2 for Women.

3 Thank you.

4 At this time I'll now turn the presentation
5 back over to Ron Trancik who will provide you with a
6 benefit/risk assessment of Rogaine Extra Strength for Men.

7 MR. VALENTINO: Mr. Chairman, by my watch we're
8 at about an hour now. We believe we have about 5 more
9 minutes.

10 DR. D'AGOSTINO: Go right ahead.

11 DR. TRANCIK: Thank you, Stuart.

12 Like all marketed drugs, in spite of clear and
13 unambiguous labeling, there will always be some off-label
14 use. I will quote Dr. Randy Juhl, former chairperson of
15 the Nonprescription Drugs Advisory Committee, who indicated
16 at the November 17, 1995 meeting where Rogaine OTC was
17 discussed. "The question we have to ask is not can it be
18 labeled so that nobody uses it wrong, but what happens when
19 people do use it wrong."

20 We have shown based on our extensive clinical
21 and commercial marketing experiences with Rogaine 5 percent

1 that there are no significant medical consequences
2 associated with the use of this product in the female
3 population other than an increase in dermatologic events
4 and occurrence of hypertrichosis. This unwanted effect,
5 which is cosmetic in nature and reversible, occurs in a
6 small number of female users.

7 Keep in mind that only 7 patients out of 301
8 females in our well-controlled clinical studies who were
9 treated with Rogaine 5 percent chose to discontinue use of
10 the product due to hypertrichosis. 13, or almost two-
11 thirds, of the women with hypertrichosis chose to continue
12 using Rogaine 5 percent.

13 I also remind you that Rogaine 5 percent is
14 approved in 19 countries outside the U.S. for both males
15 and females.

16 In addition, working with the FDA, we will
17 continue to pursue the approval of Rogaine 5 percent in
18 females.

19 We believe that the enhanced benefit/risk in
20 males is supported by our data.

21 The safety of Rogaine Extra Strength for Men is

1 comparable to the existing Rogaine 2 percent OTC product
2 and the efficacy is superior both in terms of magnitude of
3 response and in achieving a more rapid response.

4 This, coupled with the social and psychological
5 factors associated with hair loss in men, strongly support
6 the approval of Rogaine Extra Strength for Men as a direct
7 OTC product.

8 In conclusion, we have labeling studies which
9 have shown that women, when given a choice, will avoid
10 using Rogaine Extra Strength for Men.

11 Also we have shown that men can choose between
12 Rogaine Extra Strength for Men and Rogaine Regular
13 Strength.

14 The safety and efficacy Rogaine Extra Strength
15 for Men has been established based on our clinical trial
16 data and our commercial marketing experience with both
17 Rogaine 5 percent and Rogaine 2 percent as an Rx and OTC
18 product.

19 In conclusion, we strongly believe that Rogaine
20 Extra Strength for Men is an appropriate product for direct
21 OTC approval.

1 Thank you for your attention.

2 At this point, Mr. Chairman, I realize that
3 there were several questions that were raised in the FDA
4 presentation that were not directly addressed in our
5 presentations, and we can do that now or we can do it
6 later, at your wish, whatever you desire.

7 DR. D'AGOSTINO: It might be appropriate for
8 you to do them now if you have them listed rather than try
9 to have people remind themselves of the questions.

10 DR. TRANCIK: Okay. The first question had to
11 do with the use of the product in the frontal area in
12 females. I think there may have been just a slight amount
13 of confusion. The protocol calls for application of the
14 solution to the frontal parietal areas of the scalp which
15 really is the top of the scalp. The instructions which
16 were given to the females were to apply product not to the
17 bitemporal frontal hairline but to the top of the scalp.

18 Next I'd just like to make a comment on the
19 dropping of one center from the database in the male study.
20 I point out two things.

21 Number one is that doing that, the results and

1 the conclusions of the data generated in males do not
2 change. The product is effective. The 5 percent is better
3 than 2, and the safety profiles do not change. So, the
4 conclusions are essentially identical.

5 But to address your question, Dr. Miller, with
6 respect to the one study, the one center. That was
7 Funicella's center that conducted the 001 study. You are
8 correct that in that study we did not show a difference in
9 treatment groups using the categorical question that was
10 used in that study. We did show a difference in hair
11 counts, but during that study, we used a four-point
12 categorical scale. This was back in the old days, so to
13 speak. Whereas now we are using a much more comprehensive
14 questionnaire which utilizes visual analog scales, and I
15 won't get into the details of that. But the fact that that
16 center was dropped out -- the 025 center -- has nothing
17 really to do with the fact that they didn't show a
18 difference in the 001 study.

19 Next there was a question as it relates to the
20 dropouts in the female studies and the reasons for
21 dropouts. I think we have a transparency or two that we

1 can show.

2 I apologize for the messiness of the slide, but
3 this a table right out of our technical reports. This is
4 from the first female study referred to as the 009 study.
5 On this slide you can see the various categories as it
6 relates to reasons patients discontinued the study, medical
7 events for the 5 percent treatment group, about 12 percent;
8 and 7 percent for 2 percent; and 5 percent for placebo.
9 Then collectively for, as we refer to it, administrative
10 reasons, patient request withdrawal, lot to follow-up, et
11 cetera, 39 versus 34 versus 14 in the placebo, and then the
12 last category is lack of efficacy and you can see that
13 there was one patient in the placebo group that dropped out
14 due to lack of efficacy.

15 This is a problem we've had with our studies.
16 In the female studies, we've had somewhat more difficulty
17 maintaining patients in the protocols.

18 In the next one, it's the 286 study again in
19 females, and you can see again -- I won't go through these
20 in detail, but here are the reasons again for dropouts in
21 those studies.

1 Next if you could put up slide C5822-15. A
2 question as it relates to the response to 5 percent
3 occurring faster than the 2 percent. These are based on
4 data generated in our 0285 male study. As I had mentioned
5 in my presentation, we looked at the response at week 8 and
6 compared it to the response at week 16. As you can see, we
7 had an increase of 30 hairs with respect to patients who
8 were treated with Rogaine 5 percent at week 8, and we had
9 the same level of response for patients treated with 2
10 percent at week 16, and that forms the basis of our
11 statement that the results are seen sooner.

12 Next I would like to call up Dr. Bob Schirmer
13 who is going to address some of the questions that may have
14 been raised as a result of Dr. Goetsch's presentation
15 regarding his spontaneous reporting system.

16 DR. SCHIRMER: Hello. My name is Bob Schirmer.
17 I'm an internist and I'm representing the pharmacovigilance
18 group or surveillance and epidemiology at Pharmacia &
19 Upjohn.

20 DR. D'AGOSTINO: I'm not sure you can be heard.

21 DR. SCHIRMER: My name is Robert Schirmer. I'm

1 an internist. I'm representing the epidemiology and
2 surveillance group at Pharmacia & Upjohn.

3 You heard Dr. Goetsch suggest that there was a
4 signal, that there's an occurrence of tachycardia
5 associated with dermal overdose of minoxidil topical
6 solution 2 percent.

7 As Dr. Goetsch pointed out, the purpose of the
8 spontaneous reporting system is to generate signals of
9 potential drug-related problems not recognized during
10 premarket testing. Part of the issue there is how do you
11 generate a signal. That has to do with the caveats that
12 accompany the spontaneous reporting system.

13 It's important to remember for spontaneous
14 reports that for any given report, there's no certainty
15 that the suspect drug caused the reaction, that accumulated
16 case reports cannot be used to calculate incidence or
17 estimates of drug risk, and that accumulated case reports
18 must be interpreted as reporting rates not occurrence rates
19 or incidence rates.

20 So, I'd like to share with you how I looked at
21 the issue of is there a risk for specific adverse events

1 and particularly tachycardia or increase in heart rate
2 associated with dermal overdose. If I can have the next
3 slide.

4 This slide will show you the distribution of
5 medical events for dermal overdose for Rogaine 2 percent
6 compared to Rogaine at 2 mls per day or where the dose is
7 unknown. The right-most column refers to the dictionary
8 body system, and we're interested in the cardiovascular
9 body system and particularly increase in heart rate. The
10 middle column refers to dermal overdose which is defined as
11 use of Rogaine 2 percent in excess of 2 mls daily. There
12 are in our database 657 patients with 1,034 events. The
13 far right column represents the remainder of the Rogaine 2
14 percent experience where it's known that they used 2 mls
15 per day or less or the dose is not provided, again a very
16 large number of reports, 22,940.

17 The point here is that increase in heart rate
18 represents 2 percent of the events in the dermal overdose
19 group and 1 percent of the events in the recommended dose
20 group. I did not interpret that as a signal of an increase
21 in risk associated with dermal overdose.

1 If I could have the next slide please. In the
2 Pharmacia & Upjohn system, there are 20 spontaneous reports
3 coded as increase in heart rate out of the total of 657
4 reports of dermal overdose. One point to make is that
5 these are all consumers with the exception of one nursing
6 student. The latency, defined as the time from the start
7 of drug to the onset of the first event -- and as you
8 noticed, patients generally report a couple of events. The
9 median there was 7 days. The daily dose that these
10 patients were using was around 4 mls. Dechallenge
11 information was provided by 8 consumers and 6 of those
12 reported that their symptoms went away when they stopped
13 the drug. In 2 of them, they said it didn't. Rechallenge
14 information was provided in 3, and in 2 patients they said
15 that their events recurred when they restarted the drug.

16 Documented pulse, heart rate information was
17 provided only in one report. In that case, the consumer
18 reported that their heart rate went from 70 beats per
19 minute to 80 beats per minute while on the drug.

20 As indicated, we know a lot about minoxidil.
21 It's a vasodilator and the physiological responses to

1 vasodilation are increase in heart rate, salt and water
2 retention, and decrease in blood pressure. Of these
3 patients who had an increase in heart rate, only two of
4 them reported concomitant increase in weight or edema.
5 None of them reported concomitant decrease in blood
6 pressure. None of these 20 patients sought health care
7 advice beyond calling our 800 number. They did not go to
8 see their physician, and there were no hospitalizations or
9 deaths.

10 My interpretation of this is that if there is
11 an increase in heart rate occurring as the result of
12 systemic absorption of this product, that it is not a
13 significant public health problem and does not require
14 people to see their physician.

15 Are there questions?

16 DR. D'AGOSTINO: Mary Anne, are you satisfied
17 with that?

18 DR. KODA-KIMBLE: 5 percent Regaine is
19 available worldwide outside of North America.

20 DR. SCHIRMER: Yes.

21 DR. KODA-KIMBLE: I just wondering, what are

1 the surveillance mechanisms in other countries? What is
2 the likelihood of getting reports in those countries?

3 DR. SCHIRMER: As Dr. Trancik mentioned, among
4 the countries where the product is available is New
5 Zealand. New Zealand is actually our major reporter. I
6 think New Zealand has a fairly sophisticated spontaneous
7 reporting system, but it's a very small population. So, as
8 mentioned, we only have 37 reports from outside the U.S. in
9 the 4 years that it has been available.

10 DR. D'AGOSTINO: Why don't we put the lights
11 back on and then open up the discussion to the full
12 committees. Eric and then Joel.

13 DR. BRASS: I have a number of questions
14 related to the safety issue and then one about efficacy.

15 First, your label indicates that if somebody
16 uses the 5 percent product and has dermatologic problems,
17 that you suggest they switch to the 2 percent product. Do
18 you have data on what the natural history of the
19 dermatologic complaints are if you, rather than stopping
20 completely, use the 2 percent on an already injured scalp?

21 DR. TRANCIK: The data we have, of course, are

1 comparisons of patients who have used 5 percent versus 2
2 percent, and the incidence is greater, as you saw, based on
3 the medical event data that I showed and also based on the
4 local intolerance data showed by Dr. Farr.

5 We believe that the reactions are caused
6 primarily to the propylene glycol in the formulation and
7 not the minoxidil. Since the levels of propylene glycol
8 are substantially lower in 2 percent than in 5 percent, we
9 believe that if a patient experiences some scalp irritation
10 with 5 percent that's intolerable, that we can have them
11 use the 2 percent. Then we also label the product to
12 indicate that if they experience irritation or cutaneous
13 intolerance to the 2 percent product, then they discontinue
14 use.

15 DR. BRASS: I understand it, but is it not
16 conceivable that once a reaction has been initiated, that
17 it might be sustained by the lower level, though not
18 initiated by the lower level?

19 DR. TRANCIK: Well, if it is sustained by the
20 lower level, then they would just discontinue use.

21 DR. BRASS: I understand, but what I'm getting

1 at is a specific decision has been made to recommend lower
2 dose rather than discontinuation, and I was looking for
3 data to support that.

4 My second set of questions has to do with the
5 pharmacokinetic data. What was the timing of the drawing
6 of the blood level with respect to administration of the
7 product?

8 DR. TRANCIK: As you were asking the question,
9 I see that our pharmacokineticist, Jim Ferry was standing
10 up. So, I'll direct that question to him.

11 DR. D'AGOSTINO: May I ask also when
12 individuals from the sponsor come to the podium, please
13 identify yourself so the transcriber can get the
14 appropriate name?

15 DR. FERRY: Yes. Thank you for reminding me.
16 My name is Jim Ferry and I'm a research scientist and
17 Associate Director of Pharmacokinetics for Pharmacia &
18 Upjohn.

19 Blood samples in the clinical trials for hair
20 growth were taken at the time that hair growth measurements
21 were taken, so these would have been taken at week 8, if a

1 week 8 visit, 16, 32, and 48 weeks.

2 DR. BRASS: What about in relationship to the
3 timing of the dose that day of the drug?

4 DR. FERRY: We did not specify that because the
5 history of information that we have on the pharmacokinetics
6 of this drug is that the profile is flat for the duration
7 of that interval and I can show you a plot if you'd like to
8 see that. So, we felt at any time relative to the dose
9 that that sample was taken would be representative of the
10 concentration profile for that patient for that day.

11 DR. BRASS: Can you give us any information as
12 to whether there was any effect of the dermal irritation on
13 the blood levels? Did patients who had skin reactions tend
14 to have higher blood concentrations?

15 DR. FERRY: No, they did not. Irritation was
16 not consistently associated with higher blood levels. That
17 really makes sense in our pharmacokinetic database because
18 we showed that it takes a substantial trauma to the stratum
19 corneum to increase serum concentrations.

20 DR. BRASS: What percentage of the patients had
21 blood concentrations above 10 nanograms per ml?

1 DR. FERRY: There were over 2,000 samples,
2 because patients had multiple visits. We had 13
3 observations above 10 nanograms per ml, and because we had
4 multiple observations, we were able to determine whether or
5 not patients had consistent evidence of sustained
6 absorption because we were also interested in identifying
7 subsets of the population which might be identified as high
8 absorbers. This in fact is not the case. The observations
9 of high absorptions occur at a single point in time. As we
10 summarized in our NDA, we believe that given the large
11 number of samples that we take, that these are probably
12 representing either aberrational analytical findings,
13 contamination of the samples, or perhaps sporadic increases
14 in absorption for that particular visit.

15 DR. BRASS: Thank you.

16 Were heart rates objectively measured during
17 the course of the clinical trial?

18 DR. FERRY: I'm going to pass that on to Ron
19 Trancik because I'm not sure how heart rates were measured.

20 DR. TRANCIK: Yes. Patients were monitored at
21 follow-up visits for heart rates and blood pressure.

1 DR. BRASS: Can you tell us what percentage of
2 the patients experienced an increase in heart rate above 5
3 beats per minute from their baseline?

4 DR. TRANCIK: We have that information but it
5 would take some digging to get that out of some volumes we
6 have here. I can't give you that answer right off the top.

7 DR. FERRY: I can tell you that one analysis
8 that was conducted was to look for whether or not there
9 were outliers in heart rate in all groups of patients,
10 including placebo patients, and there were no more
11 incidences of heart rate increases in the 5 percent or 2
12 percent populations than there were in the placebo
13 populations.

14 DR. BRASS: I'd be interested in seeing that
15 data later, including what your threshold was for
16 determining that increased heart rate.

17 Then finally coming back to this rate of onset
18 question. Am I correct that the rate of onset, that
19 comparison you showed us for sooner, was not prospectively
20 defined as either a primary or secondary outcome variable?

21 DR. TRANCIK: That's correct.

1 DR. BRASS: Were any statistics applied to that
2 analysis? Were those same statistics applied to the other
3 001 study?

4 DR. TRANCIK: We looked at the data in the 001
5 study and the same conclusions could be drawn. The hair
6 count numbers didn't match up just like 30/30 as they did
7 in the 0285 study, but as far as the statistical handling
8 of that, I'd like to ask Kerry if he could make a comment,
9 our statistician.

10 MR. BARKER: I'm Kerry Barker from the
11 Department of Biostatistics.

12 We didn't do any formal statistical test.
13 However, we did approach a confidence interval around that
14 difference between the Rogaine 5 percent at week 8 and the
15 Rogaine 2 percent at week 16. The confidence interval, if
16 you used the entire database for study 285, was about plus
17 or minus 1.6. So, that's how confident we were in terms of
18 how much that difference was. If you exclude that one
19 investigator, that goes up to about plus or minus 1.8. But
20 that was done after the study. We just did a confidence
21 interval to see --

1 DR. BRASS: I'm sorry. What was the confidence
2 interval around?

3 MR. BARKER: Around the difference between the
4 response for Rogaine 5 percent at week 8 and the Rogaine 2
5 percent at week 16.

6 DR. BRASS: I see.
7 What was that same analysis on 001?

8 MR. BARKER: Well, 001 we didn't have a week 8
9 value. We only did that for the first study 285.

10 DR. D'AGOSTINO: It might be nice after lunch
11 to have a slide, overhead sheet presented or prepared that
12 actually does that for whatever data you have.

13 Joel, do you have a question?

14 DR. MINDEL: I have several. I wanted to first
15 ask a preliminary question before I made my comment.

16 What were the specific vehicle differences
17 between the 2 percent and the 5 percent?

18 DR. TRANCIK: There's a slide that shows the
19 composition of the formulations of the 2 percent and 5
20 percent. While they're digging out that slide, the vehicle
21 I referred to as placebo in my presentation. Dr. Farr

1 referred to it more correctly as the vehicle. The vehicle
2 used in all of our studies was the 5 percent vehicle which
3 contained more propylene glycol than the 2 percent product.

4 DR. MINDEL: And the alcohol content was the
5 same?

6 DR. TRANCIK: The alcohol was dropped
7 commensurately as the propylene glycol level was increased.
8 The formulation was optimized initially for the 2 percent
9 product to be very close to a saturated solution which is
10 thermodynamically the most favorable state you want to be
11 in in terms of delivering drug through the skin. So, when
12 we increased the concentration of minoxidil from 20
13 milligrams to 50 milligrams, we increased the percent of
14 propylene glycol in the formulation from 20 to 50.

15 DR. MINDEL: Now I'll make my comment. The
16 data are consistent with the use of an effective drug at a
17 toxic dose. First you get a more rapid onset of action,
18 followed by progressive loss of hair. Looking specifically
19 at that 285 study, you have the more rapid onset, and then
20 progressively the hair count decreases towards baseline.
21 This is true not only in this study but the other studies.

1 It may be that it goes below baseline if carried out far
2 enough.

3 So, compounding this is that the initial
4 vehicle study also shows some increase followed by
5 progressive decrease in hair count with time.

6 The question is, is it the toxicity of the drug
7 we're seeing or the toxicity of the vehicle that we're
8 seeing across these studies?

9 I'd like also Ms. Farr to make a comment as to
10 whether my observation is correct.

11 DR. D'AGOSTINO: Does the sponsor want to
12 respond first?

13 DR. TRANCIK: First of all, I think toxicity --
14 that's a very strong word. I don't agree that it relates
15 to the toxicity of the drug or the vehicle. I think what
16 it relates to is the phenomenon -- this in part relates to
17 the cycling phenomenon of hair upon initiation of Rogaine
18 therapy or minoxidil therapy.

19 We do have studies out to 2 years using another
20 methodology which we could get into, if you'd like, that
21 show in fact that there is a flattening of the response

1 over time.

2 What happens when minoxidil is applied is that
3 minoxidil shifts hairs from the resting or telogen phase to
4 the anagen or growing phase. In fact, in some patients you
5 even see a slight increase in hair shedding upon initiation
6 of therapy, but what is happening is you are recruiting
7 those follicles that are in the miniaturization process
8 that are going from nice, long pigmented hairs down to
9 eventually vellus hairs, or peach fuzz, into reversing that
10 miniaturization process. So, you get a burst of growth and
11 then you get a flattening of growth. I think the
12 diminution that we see at times in the response over time
13 is due in part to the cycling of hair and that you now have
14 a cohort of hairs that are growing in the same phase.

15 There is a recent publication in the British
16 Journal of Dermatology that shows that there's a clear
17 cycling phenomenon or seasonal phenomenon as it relates to
18 hair growth.

19 I'll just stop there because I could continue
20 for a while.

21 DR. D'AGOSTINO: Ms. Farr, do you want to

1 comment?

2 MS. FARR: Well, actually I don't have anything
3 more to add, but I would want to maybe show the table and
4 the graph for study 285 again. Maybe you wanted to look at
5 it a little more.

6 All I can say is that we just can see the
7 trend. Here I'm showing baseline and then week 16 and week
8 32, week 48. Then here I'm showing the differences between
9 the different measurements. Here from baseline to week 16,
10 we see a high increase in net hair count, and then the
11 difference between week 16 to week 32, there's a negative
12 4, negative increase. Then from week 32 to week 48, also a
13 higher negative increase.

14 But we have based our analysis or our approval
15 solely on the differences from baseline to week 32 or week
16 48, and in both cases you will see a statistically
17 significant result.

18 Yes, we had that issue with the sponsor
19 withdrawn. We have discussed that issue, the fact that --
20 let me show you the graph now.

21 As you mentioned, you see that here everybody

1 starts together and then you see the curve changes and
2 starts declining. Even here at week 48, they're
3 overlapping. We have discussed this issue, and we asked
4 them if in fact they wanted to do other studies, maybe it
5 would be better if they do it for a longer period of time
6 so we can see what happens actually after, let's say, 52
7 weeks or longer. But I think this graph is pretty self-
8 explanatory.

9 DR. D'AGOSTINO: Joel, did you want to comment?

10 DR. MINDEL: No. This is one study. There are
11 several studies. Is this consistent across all the
12 studies?

13 MS. FARR: Yes, as I showed with the graphs
14 before.

15 DR. MINDEL: Men and women.

16 MS. FARR: Yes.

17 DR. MINDEL: All four studies.

18 MS. FARR: That's correct.

19 DR. MINDEL: And I believe that this is
20 consistent with a toxic effect. It's consistent with, not
21 proof of, a toxic effect from an effective drug.

1 DR. D'AGOSTINO: We will pick that up later on.

2 Phil has a comment.

3 DR. TRANCIK: I would like to hear your
4 definition of toxicity.

5 DR. D'AGOSTINO: I think that we could pick
6 that up later on. I think the point is made in terms of
7 what is happening and the committee I think can --

8 DR. LAVIN: I know there was some mention of
9 extension data for one or two of the studies. I'd be
10 interested in seeing what some extension data would look
11 like out to 2 years or 3 years.

12 My second point I'd like to raise, I'd be
13 interested in sort of looking at the real world situation.
14 We have now all of these 2 percent users out there who are
15 potentially going to be switching over to 5 percent. I'd
16 be wondering if there are any data on what happened to 2
17 percent people who switched over to 5 percent.

18 From the data that the FDA and the sponsor both
19 showed, we saw a gain of plus 9 hair counts for the
20 difference in study 001 and a gain of plus 7 in hair counts
21 in 285. That's going to be very hard to see, but I'd be

1 interested in using the patient as their own control to see
2 if that kind of a difference was larger when patients on 2
3 percent were allowed to take 5 percent. So, I think those
4 are key data that have not been seen this morning.

5 DR. D'AGOSTINO: I do want to remind the
6 committee that the questions we're ultimately going to look
7 at are dealing with the safety and effectiveness as agreed
8 on already. We can't necessarily shift our criteria of
9 effectiveness, and we do also want to make sure that the
10 safety issues are very, very much before our eyes.

11 DR. MINDEL: I'm raising the issue of safety of
12 the hair.

13 DR. D'AGOSTINO: You certainly are, and I just
14 want to make that clear that that's what we are talking
15 about here.

16 DR. MINDEL: Safety of the hair.

17 DR. D'AGOSTINO: Right.

18 DR. TRANCIK: Am I allowed to just make a quick
19 response?

20 DR. D'AGOSTINO: Certainly, please.

21 DR. TRANCIK: Could you put up slide D58227?

1 This is a study that I referred to earlier. I just
2 mentioned it. This is a 2-year study that was conducted
3 using a different methodology, and I won't go into the
4 details of that.

5 But just quickly, our standard methodology in
6 our definitive trials has been typically counting hairs.
7 This is weighing hairs. This is a 2-year study which shows
8 5 percent versus 2 percent versus placebo, and there was
9 also an untreated group as well. I think you can see, as I
10 pointed out earlier, a burst of growth up to about week 16
11 or 20 and then a flattening of response.

12 As far as the long-term studies that we
13 conducted in the continuation portion of our definitive
14 studies, those were conducted primarily for safety reasons.
15 We did not do hair counts on those. We stopped hair counts
16 at week 48 and just continued patients on just to monitor
17 safety over time, long-term safety.

18 Then also to address the one question that
19 you're specifically asking and that is the patient being
20 his own control. We do not have data on patients that have
21 used 2 percent and failed and then switched them to 5

1 percent or even patients who have responded to 2 percent as
2 to what would happen with 5 percent. All we can do is
3 compare populations that used the two different
4 formulations.

5 DR. LAVIN: Yes. I think from a consumer point
6 of view and from a statistical point of view, I'd be really
7 interested in seeing what would happen to people who switch
8 from 2 percent to 5 percent because it's a natural thing.
9 If two-thirds of the population aren't getting a benefit
10 with 2 percent, the natural thing might be for them to try
11 the 5 percent product, and it would nice to have data to be
12 able to show them that there was some promise.

13 DR. TRANCIK: Of course, we anticipate that.
14 The key issue is increasing the level of minoxidil. From
15 the standpoint of an OTC product, the question is one of
16 safety and efficacy but safety first. I think we've shown
17 that the safety of the 5 percent product is certainly
18 comparable to the safety of the 2 percent product with the
19 possible exception of some skin intolerance.

20 DR. D'AGOSTINO: Lynn, do you have a comment?

21 DR. MCKINLEY-GRANT: I have a couple of

1 questions related to the hypertrichosis. When is the onset
2 of it? How long does it last? I know that it is
3 reversible, but does it reverse when they went to 2 percent
4 solution?

5 DR. TRANCIK: What I'd like to do, as I
6 mentioned in my presentation, if there is more in-depth
7 discussion than I presented which was primarily
8 presentation of our databases, our well-controlled clinical
9 study databases, I would like to have two of our
10 consultants get up and just give you a little 5-minute talk
11 about hypertrichosis. I'm sure they'll be able to answer
12 your questions. Thank you.

13 First is Dr. Vera Price from San Francisco.

14 DR. D'AGOSTINO: I'm sure the committee has a
15 lot of questions. I hope there aren't two 5-minute talks
16 that you're going to launch into.

17 DR. PRICE: I'm Vera Price. I'm a professor of
18 dermatology at the University of California, San Francisco.
19 I've been in clinical practice for over 20 years and have
20 many patients who have been using Rogaine, and I've also
21 been involved in clinical trials using Rogaine for Upjohn

1 since the early 1980s.

2 As far as defining hypertrichosis, it's as Ron
3 Trancik told you. This is hair growing where it doesn't
4 usually grow.

5 In the case of minoxidil-induced
6 hypertrichosis, it's usually above the lateral brows, on
7 the sides of the eyes, sometimes across the malar region,
8 and down the sides of the cheeks, and perhaps along the
9 hairline. It is not the coarse mustache, beard-type hair
10 that we sometimes think of as hirsutism.

11 This hair with minoxidil ranges from being fuzz
12 to fine, 3 to 5 millimeters in length. It is pigmented. I
13 won't say the women like it. They don't like it, but in my
14 studies I had no dropouts actually with the 5 percent
15 because the women liked the increased hair on their heads.
16 So, they were willing to put up with the hair on the sides
17 of their face because they liked the increased coverage of
18 their scalp.

19 As far as when it occurs, it varies. It's
20 frequently early, in the first months of use, but it can
21 take as long as several months before they see it. The

1 important thing is that with continued use in the studies,
2 the hair almost always, if it doesn't go away completely by
3 the end of a year, it's much less, and that was
4 interesting. In the studies the women who continued the
5 use of 5 percent minoxidil who had hypertrichosis, the
6 small, say, 5 percent in my studies of women, who developed
7 it, it tended to disappear by the end of a year or greatly
8 reduce. Of course, if they stop usage, it goes away in
9 several months.

10 DR. D'AGOSTINO: Lynn, do you have any further
11 comments on that?

12 DR. MCKINLEY-GRANT: No, that's it.

13 MS. HAMILTON: I had an additional question.
14 Is the unwanted facial hair loss a result of
15 discontinuation of the product or is there a treatment that
16 might be utilized beyond just discontinuing use of the
17 product?

18 Also the earlier presentation suggested that it
19 took 4 months. Can I assume that to reverse the unwanted
20 facial hair, it takes 4 months if somebody either enters
21 into a treatment or discontinues use of the product?

1 DR. THOMAS: Good morning. I'm Lorna Thomas.
2 I'm a dermatologist in private practice in Detroit.
3 Although my practice setting and my geographic area are
4 different from Dr. Price's, my observations are very
5 similar with respect to hypertrichosis in females using
6 Rogaine.

7 Basically it is seldom seen. It is not
8 serious. It does tend to diminish with time. It does not
9 really require any treatment because either it resolves
10 spontaneously if you just leave it alone, or in some cases,
11 because it's not thick, coarse hair, women will choose to
12 bleach it a little bit so that it's less obvious.

13 For example, this is a patient of mine. She's
14 a 55-year-old black woman who has been using Rogaine for
15 about 10 months. I think you can see that she has a little
16 hair here above the brow and just follow along with me as
17 we work our way toward the hairline. This is
18 hypertrichosis. This is her normal hairline. She's doing
19 beautifully on Rogaine. She's getting good growth out in
20 this area and throughout the head, but this was the extra
21 hair that developed.

1 Now, she's pretty representative of what you
2 see. They get this hair right along here, sometimes also
3 on the cheekbone. She also has a little bit right in this
4 area here along the sides of the face, and that's basically
5 it.

6 She has chosen to do nothing about this other
7 than bleach the hair down right around here by that earring
8 because she is so delighted with what's happening up in
9 here. This woman's father was totally bald, and she began
10 losing her hair some 25 years ago and she was very
11 concerned about that, not so much about this.

12 DR. D'AGOSTINO: That was very helpful,
13 actually both of those.

14 DR. THOMAS: Here's another picture. You can
15 see hopefully. This is hard to capture down here because
16 this is really kind of a peach fuzz consistency so it
17 doesn't show up very well in a photograph.

18 Also, I'd like to point out that even this
19 right here is relatively fine, soft kind of downy hair.
20 It's not the same as this hair out here, this terminal
21 hair, and it certainly isn't anything like coarse beard

1 hair, as Dr. price pointed out. It's just a little fine
2 hair.

3 She's really quite representative of what you
4 see.

5 DR. D'AGOSTINO: I don't think we need any more
6 overheads please or slides.

7 Ted, do you have a comment?

8 DR. TONG: Dr. Thomas, I have a question.
9 We've heard that this is a product that's going to be
10 targeted for men. You've shown us a patient here who has
11 been successful with the 5 percent. What advice would you
12 give her once this product comes on the market and she
13 goes --

14 DR. THOMAS: No. This patient is using 2
15 percent.

16 DR. TONG: She's using 2 percent.

17 DR. THOMAS: Yes.

18 DR. TONG: I thought it was the 5 percent. My
19 question was, what do you say to your women patients who
20 come in and ask for advice about a 5 percent product? You
21 would say, stay with the 2 percent?

1 DR. THOMAS: If they're doing well with their
2 scalp hair, absolutely, yes.

3 DR. D'AGOSTINO: Kathleen?

4 MS. HAMILTON: If the photograph that we saw
5 was with 2 percent use, could you describe what differences
6 might appear with 5 percent use by a woman?

7 DR. PRICE: Yes. We did see more incidence of
8 hypertrichosis, as you've seen it here, with the 5 percent
9 over 2 percent. In my studies, about 5 percent of the
10 women on 5 percent solution and about 2-3 percent using 2
11 percent solution. As far as the amount, I think those
12 women who are predisposed -- the way it looks is about the
13 same, but you will see it a little more frequently in those
14 using the 5 percent solution.

15 MS. HAMILTON: And is the time period to
16 reverse that condition the same, or does it take longer?

17 DR. PRICE: I would tell all women that it's
18 going to take them somewhere between 4 to 6 months and it
19 could be 8 months to reverse. But I do advise them not to
20 do any hair removal because this will go away by itself
21 when they stop the medication.

1 DR. D'AGOSTINO: Lynn?

2 DR. MCKINLEY-GRANT: Dr. Price, this is just a
3 quick question, but did you actually see more hair growth
4 on the top of the head with 5 percent than 2 percent in
5 your studies in women?

6 DR. PRICE: In my studies I absolutely saw more
7 hair with the 5 percent than with the 2 percent. It was a
8 clear difference.

9 DR. D'AGOSTINO: Beth and then Lynn.

10 MS. SLINGLUFF: The suggested explanation for
11 the reason that the female studies did not reach
12 statistical significance was because of the dropout rate
13 and therefore the loss of sample size.

14 Two questions. Are there any other hypotheses
15 that the sponsor would like to put forward as a possible
16 explanation for that?

17 And secondly, I believe I understood the
18 sponsor to say that there are currently other female
19 studies underway. When are those slated for completion?

20 DR. TRANCIK: I'll answer the last one first.
21 I didn't say they were underway. We're in the process of

1 initiating them. We've had a couple of discussions with
2 the FDA, and as Dr. Farr indicated, they have encouraged us
3 to -- let me just say we've discussed the terms of these
4 studies and the salient features of these studies, and I
5 think we've come to full agreement now on the protocol.
6 We're planning to initiate these studies in females in the
7 very near future. As I mentioned, we will continue to
8 pursue approval of a 5 percent product in the female
9 population.

10 Your first question was?

11 MS. SLINGLUFF: Do you have any other potential
12 explanation for why you were unable to achieve statistical
13 significance?

14 DR. TRANCIK: We were unable to show efficacy
15 in females? Again, I think it was very well pointed out by
16 Dr. Farr. It relates to the power of the studies.

17 I should point out that we had in the female
18 definitive study, we had a treatment by interaction effect
19 at one of the centers. There were 2 patients that were
20 outliers, so to speak. It's interesting when you drop
21 those 2 patients from the analysis of the hair count data,

1 you do show statistically significant difference between 5
2 and 2 percent. So, I think the power of the study and the
3 outlier or the treatment by interaction effect are two
4 reasons.

5 In our new studies, of course, we've increased
6 the power and we're taking measures to ensure that we
7 minimize the dropout rate in those studies.

8 DR. D'AGOSTINO: Lynn?

9 DR. DRAKE: I would like to ask a question of
10 Dr. Cash, if I may. The data you presented was interesting
11 to me. Was this an actual quality of life study? Was it a
12 validated questionnaire? Was it a survey?

13 Number two, I got the impression the
14 information you were presenting were on patients who were
15 experiencing hair loss. Have you done similar work on
16 patients who have had a response to hair growth efforts?

17 DR. CASH: Yes. The two studies that were done
18 involved two different types of questionnaires. In the
19 first study, we were validating a hair loss effects
20 questionnaire which we then subsequently used. But in
21 addition to that, we included items or included measures

1 that had been standardized and validated in other research
2 on psychosocial functioning.

3 But in terms of quality of life data with
4 treated patients, I don't have those data. I mean, I
5 haven't conducted those studies, but I know that there has
6 been some look at quality of life in our research by your
7 group.

8 DR. D'AGOSTINO: Let them respond.

9 MS. COHEN: I thought they had.

10 DR. D'AGOSTINO: Do you have a response or some
11 information?

12 You might want to ask your question, Susan,
13 while they're putting that -- do you have it?

14 DR. CASH: We could spend a lot of time talking
15 about the questionnaire that was developed that we used in
16 the two most recent definitive studies. I won't do that.
17 All I'll say is that, as I mentioned when I responded to
18 Dr. Miller, that in the earlier studies, we used just a
19 simple question as it relates to hair growth response, a
20 four-point categorical scale.

21 Then -- historically, this was several years

1 ago -- in discussions with the FDA, we developed a very
2 comprehensive questionnaire which addressed hair growth
3 response in a number of different categories. This was
4 essentially a questionnaire which was designed to address
5 issues such as, what does an increase of 30 hairs per
6 square centimeter mean to the patient.

7 So, we designed, along with statisticians and
8 psychologists and users and dermatologists, a very
9 comprehensive questionnaire. It was divided essentially
10 into four categories: hair growth response, global benefit
11 to response, styling as it relates to patients who style
12 their hair, quality of life. I'm showing the male data
13 because we are supposed to be speaking about males today.

14 This table doesn't have any statistical
15 analyses on it, but I can tell you that in many of these
16 incidences, using the visual analog questions that were a
17 part of this questionnaire -- this column shows you the
18 dose-related effect, that is, 5 percent better than 2
19 percent better than placebo. Now, not all of these were
20 statistically significantly different, but I think you can
21 see a very strong trend here in terms of an effect of 5

1 percent over 2 percent better than placebo. As a part of
2 that questionnaire, Dr. Drake, we did have a category which
3 addressed a number of issues as it relates to quality of
4 life.

5 DR. D'AGOSTINO: Is that all right?

6 DR. DRAKE: Thank you.

7 DR. D'AGOSTINO: Susan?

8 MS. COHEN: I found what Dr. Cash said very
9 interesting. I know nothing about the people that he
10 questioned, and I'm looking around the room and I see a lot
11 of productive people, but they might not have a lot of
12 hair. So, I need to know a lot more than that.

13 In terms of your box, which is interesting, I
14 think you tried very hard to do the best you could. Could
15 you not consider "not for use by women and children" and
16 have it right up there so they can actually see it?

17 My next question could be, since you're talking
18 about chest pains and rapid heart beat, faintness or
19 dizziness, should someone with heart disease be using the
20 product?

21 The other thing is "do not apply on other parts

1 of the body." I think that also should be enlarge too.

2 DR. D'AGOSTINO: Could you make you sure you
3 speak into the mike?

4 MS. COHEN: Yes. I just thought it could be
5 enlarged. "Do not apply on other parts of the body."

6 I guess I want to ask, are you going to come
7 back next year and want 7 percent?

8 DR. D'AGOSTINO: I'd like to hear the answer to
9 the last question first.

10 (Laughter.)

11 MS. COHEN: Me too.

12 And my other question would be, although it
13 isn't within our parameters, is this going to be more
14 expensive to the consumer because they're getting 5 percent
15 instead of 2 percent?

16 MR. ROSE: Yes. I'd like to direct that
17 question to Richard Spangler, Director of Marketing.

18 MR. SPANGLER: My name is Richard Spangler.
19 I'm the Director of Marketing for Rogaine. In terms of
20 your pricing issue, we plan to launch the Rogaine Extra
21 Strength for Men at the current pricing that you have that

1 is out there for the 2 percent product. It will be
2 launched at the current pricing of the 2 percent product
3 that we have out there today.

4 MS. COHEN: That's usually the beginning, yes,
5 until people use it. Right.

6 But the other things about the markings on the
7 box, if it's possible to put "not for use by women and
8 children." I know it would be a lot of redesign but the
9 other is kind of lost down in there, and I thought maybe
10 you could emphasize it that way.

11 DR. TRANCIK: I think the last item on the
12 agenda as I saw it was any suggested labeling changes, and
13 I think we will be continuing to work with the FDA to
14 address any suggestions that might come up.

15 DR. D'AGOSTINO: It is appropriate also for you
16 to respond to particular questions from the advisory
17 committee, though. Do you have a thought on what is being
18 suggested?

19 DR. TRANCIK: Pardon?

20 MS. COHEN: Maybe you haven't had a chance to
21 think about it yet. That's okay.

1 DR. D'AGOSTINO: Okay, we will get back to it.

2 MS. COHEN: Yes, but heart disease. I'd like
3 to know if someone is taking medications of any kind, is
4 there any contraindication?

5 DR. TRANCIK: No, there is not. I think based
6 on the presentation you heard earlier, the safety is
7 comparable to the 2 percent other than some skin problems.
8 As far as concomitant use with other heart medications and
9 any cardiovascular effects as it relates to the higher
10 concentration of minoxidil in the product, they're simply
11 not manifested.

12 MS. COHEN: But has that been looked at?

13 DR. TRANCIK: We will retain the labeling that
14 we have now that says if you experience dizziness,
15 increased heart rate, discontinue use and see your
16 physician. So, in that sense, we're capturing the same
17 labeling that we have in the 2 percent product.

18 MS. COHEN: But did you in fact have people who
19 were on heart medicine using Rogaine and did you follow
20 them?

21 DR. TRANCIK: Yes.

1 MS. COHEN: Okay, and what were the results?

2 DR. TRANCIK: The results were there was no
3 reason to not continue them to use the product. There's no
4 reason to put that on the labeling based on our experience
5 both in our clinical studies and also based on our
6 spontaneous reporting systems.

7 DR. D'AGOSTINO: Mary Anne, do you have a
8 comment?

9 DR. KODA-KIMBLE: Yes. I have several
10 questions. The first relates to marketing out of the
11 United States. I'd like to know on what basis the drug is
12 marketed to both males and females in other countries and
13 why the drug is limited to pharmacy sales only in Denmark
14 and New Zealand where it is available over the counter?

15 DR. TRANCIK: The approval of the product in
16 countries outside the U.S., of course, are based on our
17 submissions that are made in those countries. In fact, the
18 original submissions I believe -- and Ray can correct me if
19 I'm wrong -- to both New Zealand and Denmark were as an Rx
20 product, and following review of the submission and
21 discussion with those regulatory agencies, they suggested

1 to make it available as a nonprescription product. They
2 didn't see any reason not to.

3 Does that answer your question?

4 DR. KODA-KIMBLE: You did have evidence in the
5 other countries that it was effective in males and females,
6 5 percent Regaine?

7 DR. TRANCIK: Yes. Yes, we had evidence. In
8 fact, we have seven well-controlled studies in total with
9 both males and females. We do have evidence that it's
10 effective, yes. Some of the regulatory agents deemed it to
11 be appropriate for use in both males and females.

12 DR. KODA-KIMBLE: And then I want to return to
13 Dr. Brass' questions. Specifically I'm curious about the
14 nature of the dermatitis, its pathogenesis, whether it is a
15 hypersensitivity reaction, whether some of them could be
16 hypersensitivity, or whether it is irritation.

17 DR. TRANCIK: In many of the patients who
18 experienced -- well, routinely if we discontinue a patient
19 due to a skin reaction, they're patch tested. We do
20 diagnostic patch testing to try to determine the nature of
21 the reaction and I can tell you the majority of them are an

1 irritant contact dermatitis. When you break down the
2 formulation and patch test the individuals to the
3 individual components of the formulations, the majority of
4 those reactions are due to the propylene glycol.
5 Occasionally we see an allergic contact dermatitis, but
6 that is very rare.

7 DR. KODA-KIMBLE: In the inactive ingredients,
8 you indicate the percent alcohol but don't indicate the
9 percent propylene glycol. Even though it's an inactive
10 ingredient in one sense, it certainly seems to be
11 contributing to the irritation. It might be important to
12 indicate the percent propylene glycol.

13 Then my next-to-the-last question relates to
14 the rate issue because I think there may be a definitional
15 issue here. I'd like to see that data. First of all, I
16 don't think it was in our submissions. I might be in
17 error, but I don't recall seeing the 8-week data points.

18 DR. TRANCIK: In the briefing document -- and I
19 don't know the page, but there is a paragraph in there that
20 talks about the response --

21 DR. KODA-KIMBLE: A paragraph.

1 DR. TRANCIK: There is a table that I showed
2 you I don't believe was in that document.

3 DR. KODA-KIMBLE: If you could, over the lunch
4 break, prepare a graph which shows not number of hairs but
5 percent of maximum response at 8 weeks, 16 weeks, and 32
6 weeks for the 2 percent and 5 percent, I would be
7 interested in the data presented in that way. I'm not
8 convinced that it's faster but that there may be an
9 absolute increase in response related to the concentration
10 of the product. So, I'd be interested in that data
11 presented in that way after the break.

12 DR. TRANCIK: Well, we will see what we can do.

13 DR. KODA-KIMBLE: Then finally, I'd like some
14 explanation. I read the document related to the mechanism
15 of hypertrichosis and essentially my concern is that it is
16 related to absorption of the product as opposed to contact
17 of various parts of the face to the pillow and that sort of
18 thing. Did I recall that there is some hypertrichosis that
19 can occur on the chest, or was I mistaken about that? I
20 thought I read it.

21 DR. TRANCIK: I don't think we reported any

1 cases of hypertrichosis on the chest. I think our
2 interpretation of the wealth of data that we have both with
3 2 percent and 5 percent historically over the years is that
4 it is primarily due to translocation of the drug. There
5 are patients who have high serum minoxidil levels who do
6 not get hypertrichosis. I'm not going to totally exclude
7 that as an explanation, but I would say that the majority
8 of the cases are due to translocation.

9 DR. D'AGOSTINO: Are there any questions? Yes.

10 DR. SIMMONS-O'BRIEN: As part of the entry
11 criteria for the participants, were there questions
12 regarding hair styling and grooming techniques,
13 preparations already used on the scalp that are
14 nonprescription, chemicals used, how often chemicals used
15 for the men and the women?

16 Then my question is if that was the case for
17 those who subsequently developed any irritant reactions, do
18 you have any statistics or data on those participants as to
19 what -- if you didn't, what their styling/grooming
20 techniques were or chemical products possibly used on the
21 hair concomitantly while being a part of the study?

1 DR. TRANCIK: The only thing that we did in our
2 patient selection criteria was request that they use a mild
3 shampoo and that they continue their normal hair hygiene
4 routines and not make any dramatic changes in what they
5 would normally do. We did not capture the names of each
6 product that was used as it relates to hair care.

7 DR. SIMMONS-O'BRIEN: Well, I guess were there
8 any participants or people who wanted to participate? Were
9 they rejected or eliminated from the study because of their
10 use of chemicals on the scalp?

11 DR. TRANCIK: No, there were not. No. If they
12 were using chemicals on it -- they rejected if they were
13 using drugs on their scalp for treating psoriasis of the
14 scalp or tinea capitis or something else like that. They
15 had to have a normal scalp, so to speak.

16 DR. D'AGOSTINO: Yes.

17 DR. ROSENBERG: Since this is an Rx to OTC
18 issue, the agency having ruled on the safety and
19 effectiveness of the product, I want to try and focus on
20 the Rx to OTC aspect of it. I'll admit at the outset I
21 have a strong bias. For many products, the consumer, left

1 with his or her own devices, will come to a better
2 conclusion than with the recipient of prescriptions in
3 terms of whether they are really satisfied or they work or
4 not.

5 So, I was particularly interested in your
6 presentation showing how the number of users and sales went
7 up after the 2 percent product was changed from
8 prescription to over-the-counter, and I wanted to ask a
9 couple of questions.

10 To what degree is it recruitment of new users?
11 To what degree is it people who have continued rather than
12 stopped because they didn't want to go get prescriptions
13 renewed? How many of the new users stay with it and how
14 did that compare with prescription users? Any elaboration
15 on that brief mention that you gave on the OTC market as
16 we've seen it with 2 percent?

17 MR. ROSE: Well, I'd like to clarify the 5
18 percent product has not been available as a prescription
19 product. This is a direct OTC approval we're seeking
20 today.

21 DR. ROSENBERG: I thought it had received

1 approval.

2 MR. ROSE: An approvable letter.

3 DR. ROSENBERG: Approvable letter, I see.

4 Okay. All right. I'm sorry.

5 Well, let's go back to the questions, though,
6 about the change in use of 2 percent product after the
7 change in classification.

8 MR. ROSE: Well, we do know that we greatly
9 expanded the user base. We had just under 500,000 users in
10 toto of the prescription product. After the product had
11 been made available OTC, no longer existing on the Rx side,
12 we increased the user base five-fold, to just 2.3 million
13 users, the vast majority of those users being men.

14 DR. ROSENBERG: So, you're not talking about
15 numbers of units sold. You're talking about numbers of
16 persons who use it?

17 MR. ROSE: I'm talking about number of people
18 using the product.

19 DR. ROSENBERG: Do you have any post-marketing
20 data on how many stay with it and how much is word of mouth
21 and anything like that? How many are recruited by friends

1 and so forth? I won't belabor this.

2 MR. ROSE: I think there is a small percentage
3 of consumers that are referred to the product by word of
4 mouth, but perhaps I could have Richard Spangler more
5 directly address the question as Director of Marketing for
6 the product.

7 MR. SPANGLER: Our experience is telling us
8 that, of course, once they become aware of Rogaine being
9 available over the counter, they do talk to their friends
10 or to their doctors or to their hair stylists about the
11 product before they make the purchase decision. So, they
12 do tend to go to someone to get better educated about the
13 product before they make the initial purchase, as well as
14 looking at our labeling, calling our 800 service, our
15 Internet web site. So, we try to provide them a lot of
16 vehicles to learn as much as possible about the product and
17 it looks like they are taking advantage of that before they
18 make the very first purchase.

19 In terms of satisfaction, we haven't seen
20 really any changes since the Rx history. It seems like the
21 loyalty towards the category is the same as it was a

1 prescription product. About just as many people stay with
2 the brand since it has been over the counter as prior to Rx
3 experience. Satisfaction as well seems to be about the
4 same.

5 Even expectations of what they can get out of
6 Rogaine seems to be about the same. We haven't seen a
7 dramatic change in all of a sudden thinking they're going
8 to get so much more just because it's available over the
9 counter. It has been pretty consistent since it was
10 launched as an Rx product.

11 DR. D'AGOSTINO: One quick question from
12 anyone? Yes?

13 DR. MILLER: Let me ask a question about the
14 questionnaires. As I understood what you had presented and
15 what I read, the initial questionnaire dealt with their
16 just looking at the carton and there was a significant
17 number of women who said they would take the Extra
18 Strength. Then when they read it carefully, the number was
19 very significant that said, yes, this is for men only. Is
20 that correct?

21 MR. ROSE: Which study are you referring to?

1 DR. MILLER: The two questionnaires that you
2 had specifically asking women which product would they use,
3 which product would they select, and then the second one
4 was after they had read the data or had read it carefully,
5 there was a significant number of women who said, yes, this
6 one is for men only.

7 But the question was not asked, now that you
8 understand this is for men only, would you use the product?
9 It would seem to me that would help us to answer this
10 question which we're going to later address, and I don't
11 think you asked that, did you?

12 MR. ROSE: No. The sequence of the questions
13 was -- you had correctly stated that before. We first
14 asked them to select in a choice environment which product
15 they would select based on a store read in the first study,
16 followed by the appropriateness question.

17 In the second study, we asked them directly if
18 they would buy the product in an absence of choice followed
19 by a re-reading of the label and specifically asking if
20 they understood this was for men only, women only, or both.
21 As I alluded to in my presentation, over 80 percent of the

1 women correctly understood that this product was for men
2 only.

3 DR. MILLER: But you did not ask them then,
4 even though it's for men only, would you use it if you want
5 to grow hair?

6 MR. ROSE: No, sir, not in that order.

7 DR. D'AGOSTINO: It's around noon and a number
8 of people do have to check out. We will have the sponsor
9 here this afternoon, obviously. We want to go back and ask
10 questions. There have been a couple of issues that have
11 been raised, the safety, the faster acting, which we've
12 asked the sponsor to try to put some overhead sheets
13 together at the lunch break. Hopefully they'll be able to
14 do that and again we can get back to them.

15 We can reconvene at 1 o'clock please.

16 (Whereupon, at 12:00 p.m., the meeting was
17 recessed, to reconvene at 1:00 p.m., this same day.)

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1 AFTERNOON SESSION

2 (1:00 p.m.)

3 DR. D'AGOSTINO: This afternoon I'd like to
4 suggest for the agenda that we have the FDA presentations
5 as scheduled. We have the charge to the committee by Dr.
6 Bowen, and then as we go through the questions, if we
7 desire the sponsor to give us the work they've done during
8 the lunch hour, at that time we will get them at the time
9 of the appropriate question.

10 So, let's now go to the FDA presentations from
11 the Over-the-Counter Division and the Drug Marketing
12 Division. Steve will make the first presentation.

13 DR. AURECCHIA: Thank you, Dr. D'Agostino. I'm
14 Steve Aurecchia from the OTC Drug Division.

15 We have two presentations this afternoon: mine
16 and Dr. Karen Lechter's from the Division of drug Marketing
17 and Advertising.

18 I would like to touch briefly on three areas:
19 the first, a few general concerns in the regulatory
20 treatment of OTC drugs; second, the efficacy and safety
21 data on the 5 percent Rogaine product, which you've heard

1 described in detail this morning; and third, I'd like to
2 just raise a few considerations pertaining to labeling in
3 general and labeling of the Rogaine products in particular.
4 Dr. Lechter will follow with a detailed discussion with the
5 labeling studies that you've heard presented.

6 As you've heard, the present application is a
7 resubmission of the initial 5 percent Rogaine prescription
8 application. The indication has been changed to men only
9 and the product is now intended for OTC marketing.

10 In terms of OTC status, there are several
11 general criteria that are applicable. For new drugs, the
12 efficacy standard is the same for both prescription and OTC
13 drugs. Marketing claims must be supported by adequate and
14 well-controlled trials. As with prescription drugs, safety
15 is measured in the context of efficacy and of the condition
16 being treated, but generally speaking, OTC drugs should
17 have a favorable safety profile.

18 OTC products should also be relatively free of
19 important interactions: food interactions, drug
20 interactions, or disease interactions.

21 Use of OTC drugs should not require

1 professional supervision either for purposes of diagnosis
2 or for monitoring treatment or for side effects.

3 Finally, OTC products must have adequate
4 consumer labeling. In other words, labeling must be
5 written and presented in a manner that is understandable to
6 ordinary consumers.

7 You've heard the efficacy data for the 5
8 percent product reviewed in detail this morning. I want to
9 make just one point. There are two labeling claims.
10 Number one, Rogaine 5 percent grows more hair than Rogaine
11 2 percent, and secondly, Rogaine 5 percent grows hair
12 faster than the 2 percent product.

13 The first claim is supported by data from the
14 two pivotal male trials. With respect to the second claim,
15 however, neither of those trials was designed as a time to
16 response study, and this particular claim derives from a
17 post hoc comparison of hair count data within the male
18 studies at selected time points.

19 As to the safety of the topical 5 percent
20 solution, I think there are three principal sources of
21 information that contribute to our understanding of the

1 safety profile of this product: first, the data from
2 controlled trials in both men and women; secondly,
3 comparative pharmacokinetic studies; and thirdly, and
4 perhaps to a lesser extent, some foreign marketing
5 experience with the 5 percent product.

6 As you heard this morning, the predominant
7 clinical adverse events with 5 percent Rogaine were
8 dermatologic in nature. These occurred in a dose-dependent
9 manner and with the primary cause of discontinuations in
10 both men and women. Dermatologic adverse events were of
11 two general types: dermatitis-like and hypertrichosis.
12 Dermatitis-like events occurred in both men and women. In
13 men this was manifested especially by dryness and itching.
14 Hypertrichosis as a medical event was reported only in
15 women. There were 23 such cases and 8 of these I believe
16 discontinued because of this.

17 The absence of systemic hemodynamic effects in
18 the 5 percent cohort in the control studies is reassuring,
19 given that minoxidil is a very potent vasodilator when
20 administered systemically.

21 Drs. Lipicky and Hung from the Cardio-Renal

1 Division have reviewed the vital sign data from the
2 electronic submission for the safety population. This is
3 presented on the next slide.

4 This is the safety population of 1,562 patients
5 I believe, and this shows mean and median changes from
6 baseline for pulse, diastolic and systolic blood pressure
7 for each of the treatment cohorts. As you can see, there
8 was no change from baseline in pulse across the treatment
9 groups, no tachycardia, nor were there any meaningful
10 changes in either diastolic blood pressure or systolic
11 blood pressure between the three treatment groups.

12 If you look at the plots of these data points,
13 there are no outliers in the 5 percent cohort. If you plot
14 the distribution for change from baseline for each
15 treatment group, the curves do not shift adversely with
16 respect to the 5 percent treatment cohort. I believe these
17 graphs were included in your briefing package.

18 Vital sign data were also tabulated for the
19 dropouts from these trials with adverse events that might
20 have been of a hemodynamic nature or syncope. There were
21 31 such cases and no pattern or correlation was seen with

1 their data or with changes in vital signs for these
2 individuals.

3 Pharmacokinetic studies also contribute to our
4 understanding of the safety profile of 5 percent Rogaine.
5 Total serum minoxidil levels were done in each patient in
6 both the pivotal male trials. I selected the data from
7 study 0285 which I think is representative, and this is
8 shown here.

9 This is a plot of mean serum minoxidil
10 concentrations over time in nanograms per ml. There were
11 comparable percentages of patients at each time point with
12 measurements. The placebo group is shown in green, 2
13 percent in yellow, and the 5 percent is in red, which
14 doesn't show up very well. The levels, as you can see,
15 were low and did not accumulate over time. At weeks 28 and
16 40, the mean level for the 2 percent group was about 0.7
17 nanograms per ml, and it was about twice that at those time
18 points for the 5 percent cohort, or 1.7 nanograms per ml.

19 The maximum value achieved by any patient at a
20 single time point in the study for the 2 percent group is
21 shown here, and that was about 8.1 nanograms per ml, and in

1 the 5 percent cohort, it was about 16.5 which is shown
2 there.

3 You heard earlier that a serum minoxidil level
4 of about 22 nanograms per ml appears to be the threshold at
5 which hemodynamic changes just begin to occur. This value
6 is derived from a previous study, a double-blind, vehicle-
7 controlled, multiple-dose, steady state infusion study that
8 achieved minoxidil concentrations over a wide range, with
9 about 4 to 80 nanograms per ml. So, that threshold
10 relative to the means levels seen in the 5 percent group
11 gives us about a 12-fold difference. So, in this view,
12 there is roughly a 12-fold margin of safety.

13 The third element I mentioned relative to
14 safety was the foreign marketing experience to date, and
15 this was presented this morning. As you heard, marketing
16 has now been initiated in 14 countries, in 12 of these as a
17 prescription product and in 2 as an OTC product. That's
18 Denmark and New Zealand. Not all of these countries have a
19 mechanism for collecting and analyzing spontaneous adverse
20 event reports, so I think this information needs to be
21 interpreted somewhat cautiously, and I would also keep in

1 mind the general limitations of spontaneous reporting that
2 have been referred to earlier with respect to
3 ascertainment, under-reporting, lack of an accurate
4 estimate of the population at risk.

5 But with these caveats, there have been some 69
6 events reported in 37 patients. None were serious and all
7 were dermatologic in nature, and this is certainly
8 consistent with the data from the controlled trials.

9 With respect to OTC marketing, the remaining
10 regulatory element and one that is distinct from
11 prescription drugs is consumer labeling. The product's
12 use, directions for use, warnings, and side effects must be
13 communicated in a way that is complete, accurate, and
14 understandable by the average consumer, including
15 individuals of low comprehension, and that is language from
16 the regulations. And to the greatest extent possible,
17 labeling should be assessed under customary conditions of
18 purchase and use.

19 With respect to Rogaine, our concerns are
20 gender-specific. We currently have a 2 percent product
21 marketed for men and women. Addition of a 5 percent

1 product for men only will set a precedent in which men will
2 need to choose appropriately between the 2 percent and 5
3 percent products for men, and women need to be deterred
4 from inappropriately choosing the 5 percent product for
5 men.

6 The results of four label testing studies have
7 been presented earlier. The male study suggests that
8 consumers may understand the greater efficacy of the 5
9 percent product, but a substantial percentage of men may
10 not appreciate the greater likelihood of scalp irritation.

11 With respect to inappropriate selection of the
12 5 percent men-only product by women, results from the
13 female studies I don't think are altogether reassuring, and
14 Dr. Lechter will discuss this with you in detail.

15 In conclusion then, I think Rogaine 5 percent
16 for men is an appropriate product to consider for OTC
17 marketing. Androgenetic alopecia is readily recognized by
18 the consumer. The treatment is observable and side effects
19 do not appear to be serious and are reversible. The
20 clinical safety data with Rogaine 5 percent are favorable,
21 and it does appear that systemic hemodynamic effects are

1 unlikely given the extent of percutaneous absorption of
2 minoxidil observed in kinetic measurements with the 5
3 percent product.

4 We are not clear, however, whether the proposed
5 men-only labeling will be adequate in deterring women from
6 inappropriately using the 5 percent product, nor is it
7 clear whether the proposed product labeling is adequate in
8 terms of directing men to choose appropriately between the
9 2 percent and 5 percent products.

10 I'll stop there and I'll ask Karen Lechter to
11 take it from here. Thank you.

12 DR. LECHTER: Good afternoon. I'm Karen
13 Lechter with the Division of Drug Advertising, Marketing,
14 and Communications.

15 Four label studies were conducted in
16 conjunction with this application, as you've heard already.
17 Three of these studies were with women. One of them was
18 for men. The first two women studies dealt with the label
19 for the 5 percent product that you're considering today,
20 and one of them dealt with the 2 percent product. The 5
21 percent women's product studies dealt with what product

1 they would select from among five different products and
2 whether the product is appropriate for them to use. The 5
3 percent and the 2 percent studies dealt with whether they
4 would purchase the product whose label they were looking at
5 and who should use the product. The men's study dealt with
6 label comprehension issues.

7 All of the participants were persons who had
8 thinning hair or hair loss. All of the studies included
9 both non-users of minoxidil products and persons who had
10 previously purchased over-the-counter minoxidil products.

11 In phase I of the first study with women, women
12 were shown a display of five cartons of minoxidil products.
13 One of these was the 5 percent minoxidil product for men.
14 The other four were men and women's products, two of them
15 were Rogaine brand and two were store brand.

16 Participants were told to assume they were
17 interested in purchasing one of the products for their own
18 use and they were free to examine the product. They were
19 asked to select one of the products and explain why they
20 chose it.

21 The results showed that out of the 305

1 participants, only 4 chose the Rogaine 5 percent product
2 for men, which for that label was called Rogaine Maximum
3 Strength for Men. Nine others chose other men's minoxidil
4 products. The sponsor has interpreted these results to
5 suggest that very few women would choose the 5 percent
6 product for their own use.

7 However, this methodology does not tell us that
8 women will not use the product. All it tells us that in
9 one instance in which there were choices of four other
10 products, two of which were labeled for women, almost all
11 the women did not choose the 5 percent product and few
12 chose the other men's products. However, it does not tell
13 us whether they would choose the men's product under other
14 situations, such as if they had used the 2 percent product
15 without success or if they were responding to advertising
16 for the product, if they had few other choices available to
17 them in the stores in which they were shopping, or for
18 other reasons. So, this part of the study does not tell us
19 they won't choose it. It tells us that in one situation
20 they did not choose it to any great extent.

21 Phase II of the study. Participants were given

1 the 5 percent product label and told to read it completely
2 and then they were asked to say whether the product was
3 appropriate for their own personal use. Over 12 and a half
4 percent of the participants answered that the Rogaine 5
5 percent product for men was appropriate for their own
6 personal use. Of these, 17.2 percent were minoxidil users
7 and 10 percent of the non-users gave this response.

8 This phase of the study required participants
9 to examine the label rather carefully, which is not
10 necessarily what they would do in a normal purchase
11 situation. It's possible that without a careful reading,
12 more women would feel that this product was appropriate for
13 their use.

14 This study then demonstrates that most women
15 who read the tested package carefully understand it as
16 inappropriate for them. However, there is still a
17 substantial percentage who say they could use it,
18 especially previous minoxidil users.

19 Taken as a whole, the two phases of the study
20 do not demonstrate convincingly that women who saw the
21 tested label would not buy the 5 percent product in

1 substantial numbers.

2 Partly as a result of this study, the sponsor
3 redesigned the label to add the strength and warnings that
4 you heard about this morning to include guidance for men
5 about the 2 percent and 5 percent products and to provide
6 additional warnings for women who might contemplate using
7 the product.

8 In the second study, participants were shown a
9 display board showing the fronts of four different
10 minoxidil cartons, the ones that I had mentioned earlier.
11 They were not shown at this point the 5 percent product.
12 They were then read a category description telling them
13 that there are several different products on the market for
14 hair regrowth. They were then shown the Extra Strength for
15 Men package and were asked to examine it as if they were in
16 a store. This is referred to as the store read. They were
17 asked if they would buy the product for their own personal
18 use.

19 Next they were asked to read the entire label
20 completely. This is referred to as the complete read, and
21 they were asked whether they would say the product was for

1 men only, women only, or both men and women.

2 For the question as to whether they would
3 choose to purchase the product, 35 percent said they would,
4 34 percent of the non-users and 37 percent of the users.

5 Among the non-users, 65 percent with less than a high
6 school education said that they would purchase the product.

7 When the participants answered whether the
8 product should be used by men only, women only, or both men
9 and women, about 20 percent said both: 18 percent of the
10 non-users and 25 percent of the users.

11 Responses that the product was for men only
12 differed based on whether or not the respondents had
13 previously said they would purchase the product for their
14 own use. Those who said they would purchase the product
15 were less likely to say it was only for men. Among the
16 non-users who said that they would purchase the product, 37
17 percent said it was for both men and women. This compares
18 with 8 percent of persons who previously said that they
19 would not purchase the product. Among the users who
20 previously said they would purchase the product, 51 percent
21 said it was for both men and women, compared to 10 percent

1 who previously said they would not purchase the product.

2 The sponsor has stated in the written materials
3 submitted to us that the high proportion of women who said
4 they would buy the product is an artifact of the study
5 design and does not indicate what would happen in the
6 marketplace. The sponsor has hypothesized that there are
7 demand characteristics in the test situation, including the
8 yea-saying bias, and in the written materials, they
9 mentioned the Hawthorne effect which made it likely that
10 some participants would try to please the interviewer by
11 saying they would purchase this product and would behave
12 unnaturally in a test situation.

13 In another explanation of the results, the
14 sponsor has hypothesized that women who had said they would
15 purchase the product were later reluctant to say it was
16 only for men because that would be inconsistent with their
17 prior decision to purchase the product.

18 However, it is equally plausible that these
19 women truly believed that both men and women could use the
20 product and that is why they said they could purchase it
21 and that is why they said that both sexes could use it.

1 We may not agree with the labels that the
2 sponsor has attached to some of the biases that they claim
3 were operational here, but we do understand their argument
4 that something other than the label may have caused these
5 results. There are numerous potential sources for bias
6 that could affect the outcomes of research in social
7 sciences.

8 For that reason, the methodologies of studies
9 must be very carefully crafted to avoid or reduce them.
10 These are several types of biases that are well known.
11 They emanate from the questions themselves or from the
12 situation or from other sources such as the personalities
13 of the participants. The ones in yellow are ones that the
14 sponsor has mentioned in the materials that may have
15 affected the results in these studies.

16 However, the only data we have is that 35
17 percent of the women said they would purchase this product
18 for their own use and 20 percent said it was for both
19 sexes. We do not know what the results would have been had
20 there been no biases, and we don't even know whether there
21 really any biases in this situation. These results are

1 entirely consistent with the proposition that some women
2 will use the product and believe that both men and women
3 can use it.

4 The sponsor's explanation that the results were
5 due to the test situation and were not a true measure of
6 what women would do cannot be supported by the results we
7 have today. The sponsor's claims of experimental bias are
8 speculative.

9 The third study with women, the results for
10 which you do not have in your materials because they were
11 submitted to us too late for us to do a written review, was
12 the same as the study I just described, except the label
13 that they looked at in this study was the 2 percent label
14 for the Regular Strength Rogaine for Men.

15 The results of this study showed that 50
16 percent overall, 45 percent of non-users and 61 percent of
17 users, said they would buy the regular Rogaine for men. 42
18 percent overall said it was for both men and women. 38
19 percent of non-users said this and 52 percent of users.

20 The sponsor has compared these results with
21 those of the previous study using the 5 percent product,

1 trying to make this last study with the regular Rogaine the
2 control arm for the previous study.

3 However, this comparison is statistically
4 inappropriate. For several reasons the comparison is
5 unacceptable. It is inappropriate to compare these data
6 because they are not two arms of a randomized study
7 population. The comparison is methodologically
8 inappropriate.

9 We can only speculate about what the results of
10 the two trials mean. It could mean that due to the
11 labeling for Rogaine Extra Strength for Men, women are more
12 willing to use the regular product than the stronger
13 product, or it could mean that intervening events between
14 the two studies affected the responses differently in the
15 second study, or that there were baseline differences in
16 the two populations, or that artifacts in the test
17 situations differed. We do not know because the
18 participants were not randomly assigned to these two arms.
19 We cannot assume, as the sponsor does, that the differences
20 demonstrate biasing effects of the study situation or even
21 that more participants would use the Regular Strength than

1 the Extra Strength.

2 The most obvious conclusion we can draw is that
3 the warnings on the Extra Strength label probably deterred
4 some women from using it, but there might still be many who
5 would use it.

6 The apparent differences in these results
7 generate hypotheses that must be tested, but we can't
8 speculate as to what the results mean in comparison to each
9 other.

10 Thus, the results of the third study tell us
11 that high numbers of women, 50 percent, are likely to
12 purchase the regular product. 42 percent believe it is
13 appropriate for both sexes. The results do not demonstrate
14 that the results of the second study with the Extra
15 Strength product are due to bias in the test situation, and
16 there's no evidence what bias-free results would look like
17 if there were no bias.

18 The results are consistent with the proposition
19 that many women may choose to use the regular Rogaine and
20 believe it can be used by both sexes.

21 Thus, the sponsor has failed to demonstrate

1 convincingly that women will understand they should not use
2 this product. If the product is approved, the warnings for
3 women should be strengthened above those that were in the
4 tested label.

5 The purpose of the study for men was to
6 determine the extent to which men understand that the
7 product is more effective at growing hair than the 2
8 percent product and that the 5 percent product has a
9 greater likelihood of irritating the scalp. The study used
10 the same label as was used in the second women's study,
11 which is the improved Extra Strength label for men. As you
12 were told before, this has increased information about the
13 differences between the 2 and 5 percent products and
14 additional warnings for women.

15 After some preliminary presentations about
16 minoxidil products, the men were given the Rogaine Extra
17 Strength for Men package and were asked to examine it as if
18 they were in the store. This again is called the store
19 read. They were asked to fill out a short questionnaire
20 themselves. Next, they were asked to read the label
21 entirely. This is the complete read. And they were asked

1 to answer another questionnaire that was identical to the
2 first one.

3 There were seven questions asked after each
4 reading. These were simple yes/no and multiple choice
5 questions. The form of the yes/no questions violated some
6 basic practices of good questionnaire design that could
7 have avoided some of the biases that I mentioned earlier.
8 All of the yes/no questions were leading and all of them
9 required yes responses. This may have biased the results
10 in a direction that indicated higher comprehension. None
11 of the questions required the participants to apply the
12 information on the label or to use their memories.

13 For example, here's one question requiring a
14 yes response. Does Rogaine Extra Strength for Men grow
15 more hair than Regular Strength for Men? Yes/no. A better
16 way to ask this question to avoid the tendency to say yes
17 would be an open-ended question such as the following.
18 What are the differences, if any, in the effects of Rogaine
19 Extra Strength for Men and Rogaine Regular Strength for
20 Men? This question could have been more specific and said,
21 what are the differences in the benefits, if any? If a

1 close-ended question were preferred, a multiple choice
2 question or a checklist could have been used that would not
3 suggest what the correct response was.

4 Here's another example. The question was, if
5 you were using Rogaine Extra Strength for Men, should you
6 switch to Rogaine Regular Strength for Men if you
7 experience scalp irritation? Yes or no. A less biased
8 alternative would be, what, if anything, should you do if
9 you experience scalp irritation while using Rogaine Extra
10 Strength for Men? Again, this could have been an open-
11 ended question or one that involved multiple choice or a
12 checklist or an even more sophisticated question could have
13 presented a scenario to the participants to try to apply
14 the knowledge on the label to a hypothetical situation.

15 Unfortunately, four of the seven questions in
16 this questionnaire were of this type which could have
17 increased the apparent number of correct responses. The
18 issue here is whether this study with all its shortcomings
19 adequately demonstrates whether potential male consumers
20 can use the product safely and effectively. We should
21 examine these results and see what conclusions we can draw

1 from them.

2 This first slide shows the results for the type
3 of information one would expect potential purchasers to
4 look for in the store, and for that reason I think the
5 store read columns, the yellow columns, are most
6 appropriate to look at here. If we do not discount the
7 results because of the potential bias, it appears that
8 participants understood the purpose of the product and that
9 it produces better results than the Regular Strength
10 product. They said it would grow more hair, 74 and 77
11 percent, and even more in the complete read. It grows
12 faster at 72 and 76 percent; more in the complete read.

13 However, they didn't seem to understand very
14 well that they would incur possibly more irritation. This
15 is only in the low 50s, and remember this is a yes/no
16 question where by chance they would answer 50 percent
17 correctly.

18 They did seem to understand well that the
19 product is for men only.

20 Thus, they were more aware of the benefits of
21 the product than the risks, and they understood the

1 communication objective of the increased efficacy
2 moderately well. They understood the information about
3 scalp irritation less well.

4 This slide shows the results for issues that
5 they're more likely to look at at home, and therefore the
6 complete read, the ones in white, might be more appropriate
7 to look at here.

8 Surprisingly, they didn't score particularly
9 high on the dosing frequency and especially among the users
10 who presumably had been using this or a similar product
11 twice a day already.

12 Based on these particular questions, they also
13 understood moderately well that if there's irritation, they
14 should switch to the Regular Strength product.

15 Based on these results, the tested label should
16 be strengthened with regard to dosing frequency, risks, and
17 how to handle irritation. Perhaps it should also be
18 improved with regard to benefits.

19 The study does not directly address the issue
20 of whether men will appropriately self-select the 2 percent
21 or 5 percent product when they're in the store.

1 These results are presented in the best
2 possible light without discounting for possible biases. It
3 is highly likely that lower scores would have occurred had
4 the questionnaire been different than the one that we saw.

5 To recap the women's studies, the results are
6 consistent with the proposition that some women will use
7 the 5 percent product. We have no evidence of biases that
8 affected the results, and if biases operated, we don't know
9 what the results would have been. For this reason, if this
10 product is approved, the labeling should be strengthened
11 for women.

12 I thank you for your attention.

13 DR. D'AGOSTINO: Thank you.

14 Both of the speakers have set the stage quite
15 nicely for the questions that we have.

16 I'd like to ask Dr. Bowen now to give the
17 charge to the committee and then we can go into our
18 discussion.

19 DR. BOWEN: Thanks, Ralph.

20 I'm not so sure you need a charge. You seemed
21 to be charging ahead earlier in the discussion.

1 I think what we want to know, in your opinion,
2 is this product safe and effective for direct OTC marketing
3 to male consumers, and if you vote yes, what we want are
4 your labeling recommendations for optimally communicating
5 that women should not use the product and for optimally
6 communicating to men as to whether and when to select 2
7 percent versus 5 percent.

8 Thanks.

9 DR. D'AGOSTINO: Thank you.

10 DR. MINDEL: Excuse me. The question was if we
11 consider it safe and effective?

12 DR. BOWEN: Then we would like your labeling
13 recommendations.

14 DR. MINDEL: That is if we consider it safe.

15 DR. BOWEN: Yes.

16 DR. D'AGOSTINO: The layout of the questions --
17 and these are available in the agenda that was on the table
18 outside -- has four questions. The first one deals with
19 the women appropriately avoiding Rogaine Extra Strength.
20 I'll read them and then we'll go back to them.

21 It says, based on your review of the proposed

1 labeling and data from the female intention-to-heed
2 studies, will women appropriately avoid Rogaine Extra
3 Strength for Men?

4 Now, that question, the way it's stated here,
5 doesn't say, well, so what if they use it. It asks us
6 specifically will they avoid using it, and I think that we
7 want to keep that in mind. We can enlarge this as we go,
8 but that's the way it's stated.

9 The second question is, based on your review of
10 the proposed labeling and the data from the male label
11 comprehension studies, will men be able to appropriately
12 choose between the Rogaine Extra Strength for Men and the
13 Rogaine Regular Strength for Men?

14 So, we have two questions that deal with the
15 comprehension.

16 The third question then asks us about the
17 safety and effectiveness for the OTC use, not for the Rx
18 use, but for the OTC use in this target population, and
19 that means for men. That would imply, as Dr. Bowen has
20 just said, that the labeling may need to be redesigned or
21 there may be comments about the labeling. If we say yes to

1 that, that would emphasize the Extra Strength versus the
2 Regular Strength and also the women are not to take it.

3 I'd like to open the discussion in terms of
4 focusing on the questions and we can raise other issues
5 that we had this morning as they relate to particular
6 questions.

7 So, if it's all right with the committees,
8 let's go to question number 1. It says, based on your
9 review of the proposed labeling and data from the female
10 intention-to-heed studies, will women appropriately avoid
11 Rogaine Extra Strength for Men?

12 I'd like to ask Beth if she would begin
13 actually the discussion on that. There have been a number
14 of times in the past where we've had questions on
15 comprehension and we've always turned to Beth, and this
16 would be a good time to turn again to lead the discussion.

17 MS. SLINGLUFF: Thank you, Mr. Chairman.

18 (Laughter.)

19 MS. SLINGLUFF: I don't think there's any
20 question that there are going to be women who are going to
21 pick up this product and attempt to use it. I think the

1 labeling studies and the comprehension studies tell us
2 that, and I also think that all of our own experience in
3 dealing with women who have hair loss and are feeling
4 pretty traumatized by that would at least give anecdotal
5 evidence in our own practices that's what women will do.

6 Now, as you've already stated, it's really not
7 our concern here or this question does not deal with the
8 issue of what happens if women use it anyway. However, we
9 have also heard from the sponsor that there is certainly
10 consideration for studies to be done with women in the
11 future. I can envision coming back here in eight months
12 and having those studies presented.

13 Mike, could you just wait till I'm off the
14 committee before we do that, though?

15 (Laughter.)

16 MS. SLINGLUFF: I certainly am not willing to
17 disagree with Dr. Lechter's assessment. I think that she's
18 done a fine one here. I think there's some evidence that
19 some women get the point that they're not supposed to use
20 this. It's not for them. I think there are some definite
21 labeling problems.

1 Do I think women are going to buy it over the
2 counter? Absolutely.

3 DR. D'AGOSTINO: Eric?

4 DR. BRASS: I'm concerned that we are setting
5 moving targets on this label comprehension stuff. We have
6 reviewed labels where there are warnings where failure to
7 heed would pose substantial health risks, even potentially
8 fatal health risks, and we have never seen an adequate
9 label comprehension study for any of those. I agree
10 completely with everything Dr. Lechter said, and I would
11 just compare that to the evaluation of the label
12 comprehension study we had yesterday which I think the
13 issues would have been much more serious.

14 I think the critical word here is
15 "appropriately" avoid. I agree with Beth that people are
16 going to buy it, but I think they're going to know what
17 they're doing to a pretty reasonable extent when they do
18 so. I think health care professionals are going advise
19 women to buy this product.

20 So, I think in the context of appropriately
21 avoid in the context of the risk-to-benefit ratio, I'm

1 comfortable that the sponsor has made a good faith attempt
2 to provide the consumer the information necessary to make
3 that decision.

4 DR. D'AGOSTINO: Is that the right
5 interpretation of the word "appropriate"? One
6 interpretation of "appropriate" is that there's no risk.
7 Another interpretation of "appropriate" is that the label
8 says don't buy it, it's not for you, without an implication
9 of risk.

10 What is it that the committee should actually
11 be looking at? Can anybody from the FDA offer us insight
12 on that?

13 DR. BOWEN: I think the interpretation that
14 women would appropriately avoid this particular product is
15 the right one.

16 DR. D'AGOSTINO: I'm not sure you answered my
17 question.

18 (Laughter.)

19 DR. BOWEN: Well, you phrased it two different
20 ways. You said, will avoid always using the product, and I
21 interpreted your "appropriate" as the way Dr. Brass stated.

1 DR. D'AGOSTINO: So, there's a safety
2 implication?

3 DR. BOWEN: I think it's a risk/benefit for all
4 of these products.

5 MS. COHEN: Ralph, can I ask Karen a question?
6 Karen, when you had the box and you did your tests and you
7 asked questions, did you happen to ask them when they
8 looked -- did they have this particular label?

9 DR. LECHTER: The FDA did not conduct any
10 studies. We just reviewed the studies that the sponsor
11 did, so you might want to direct that question to the
12 sponsor.

13 MS. COHEN: Yes, because I'd be curious to know
14 if they found a woman who might use it, did they read the
15 label? Did you find out what their reaction was to the
16 label? And when you showed it to them and it said not for
17 use by women, oh, I didn't see it. I need to know what
18 actually happened when they looked at the label.

19 MR. ROSE: Actually, Mrs. Cohen, that is not
20 the stimulus that the consumer saw in the test. That
21 package right there demonstrates the learning from all the

1 label testing that was done, and there have been
2 considerable strengthening of all aspects of the label and
3 what you see in front of you.

4 MS. COHEN: So, this is a composite I take it.

5 MR. ROSE: Exactly, based on the learning. We
6 have taken to heart that learning and we have further
7 strengthened the labeling across a number of different --
8 in terms of both men and women to help better assist men to
9 choose between the 2 and the 5 percent product, as well as
10 that the label successfully deters women from purchasing
11 the product.

12 MS. COHEN: As we all know, human beings, what
13 they are, you can do the best you can but sometimes there's
14 a point upon which you just can't improve.

15 Would it make any difference -- I'm asking a
16 question. I don't know the answer. Would it make any
17 difference if this were put up here so that when they get
18 it -- because when it's on the shelf sometimes, you don't
19 see what's down here. You see what's up here. Would it
20 make a difference where you placed that?

21 DR. D'AGOSTINO: I think we have to answer the

1 question based on what we have. We can go back and say
2 they could have done it better and make suggestions on
3 that, but it's not clear we know the answer to the question
4 as it's stated now with the data we have trying to infer
5 and extrapolate what we would have known or we could know
6 if they made changes. I think it's an appropriate question
7 to ask but not under the --

8 MR. ROSE: But we do feel that these are all
9 major improvements that have been made to the label. It
10 has been further strengthen across all of the dimensions
11 based on the learning from testing. Really, that's why we
12 do the testing, to learn for betterment of the label.

13 MS. COHEN: I understand.

14 DR. D'AGOSTINO: Let me also say that, given
15 Dr. Bowen's response to Eric's comment, I think that there
16 may be members of the committees who will find it hard to
17 lump the two concepts together, namely that the label says
18 or the box says, don't use it, and Beth's comments saying
19 that a lot of women will buy it. Then there's the second
20 level which is Eric saying that if they do buy it, is it a
21 problem?

1 Given that we have those two possibilities, I'd
2 like to suggest that we do split it out, that we first ask
3 the question without the implication of safety, and that we
4 can fall back on the intent-to-heed studies and what they
5 show us and what we think they show us. Then we can answer
6 the second question. Would that be appropriate for us?

7 DR. BOWEN: I think that's fine if you need to
8 split it that way. Obviously, whenever we ask these
9 questions, they are related to safety and efficacy and the
10 risk/benefit in the OTC population.

11 DR. D'AGOSTINO: Right. Yes, I understand
12 that. I think that the way the intent-to-heed studies went
13 that the implication of the safety may not be driven home
14 and we should answer that question.

15 So, I'd like to say, first of all, let's
16 address the question simply as given the intention-to-heed
17 studies that we have and our interpretation of them, do we
18 think that women will avoid Rogaine Extra Strength for Men.

19 Yes?

20 MS. HAMILTON: It occurs to me that there's an
21 unspoken assumption in the discussion that we've been

1 having, as well as the way the question is phrased. The
2 assumption is that the decision to be made by a woman will
3 be mostly based on information provided by the sponsor or
4 mostly based on information provided in the label or that
5 the decision will even be based on comprehension of that
6 information.

7 I just want to suggest that I think that
8 marketing to women, especially in the sort of
9 cosmetic/pharmacy area, has really undergone an enormous
10 political/cultural kind of shift in the last few years. I
11 think that women make decisions especially based on
12 pharmacy/cosmetic kinds of products based on lots of
13 information and lots of input that goes well beyond
14 information provided in good faith on the label and by the
15 sponsor, and that we need to keep that in mind.

16 Rogaine is being specifically marketed to
17 women. I'm familiar with television advertising that has
18 been widely distributed in the last several weeks or
19 months.

20 But I'm also aware of marketing regarding
21 deodorant products, for example, that specifically suggest

1 to women just because we say this product is for men only
2 doesn't mean you're not tough enough to use it. I think
3 that those kinds of messages are being communicated to
4 women and we have to balance that kind of input that women
5 are getting with the weight that they're going to give it
6 against possibly very excellent, very, very complete
7 information provided on the label.

8 I do think women will use the product anyway,
9 and I do think there needs to be some additional
10 information provided to them so that they fully understand
11 the potential for the side effects which I do not think are
12 minimal.

13 DR. D'AGOSTINO: Are there other comments on
14 this?

15 What I'm suggesting is that we split this into
16 just a first question, will they avoid purchasing it, and
17 then will they avoid the appropriateness. I'm going to ask
18 Eric at that point again to elaborate on that.

19 But as simply a first question, will they buy
20 it? Let's put it in the positive. Will women buy the
21 product? And I'm asking if there's any further discussion

1 on that. Yes?

2 DR. SIMMONS-O'BRIEN: Dr. D'Agostino, I propose
3 if it's possible to actually change the wording of the
4 question to will the majority of women appropriately avoid.

5 DR. D'AGOSTINO: I don't even know if we need
6 to talk about majority of women because they're not showing
7 over 50 percent in any of these studies, but the percent
8 that they are showing could have been substantial. So, I
9 think we're looking at it as is there a substantial number
10 that will purchase it. There will always be some percent
11 that will buy it, but is there a substantial number that
12 will purchase it?

13 Yes?

14 DR. MCKINLEY-GRANT: I think hair loss in women
15 is probably very traumatic. Their studies were in men, but
16 I think in women it's truly a very traumatic experience.
17 It occurs early and they frequently seek help about it.

18 So, I think that they will purchase it, I think
19 particularly the women using 2 percent Rogaine who are
20 looking for another solution to use. We've heard evidence
21 that the 5 percent does work better and gives more hair

1 growth in women also. So, my answer would be yes to this.

2 We have a lot of evidence that the 5 percent
3 works in women. I know that means us coming back again to
4 go over this, but I would really encourage getting those
5 studies done because I think there will be a lot of women
6 who are going to use it.

7 DR. D'AGOSTINO: Thank you.

8 Are there other questions?

9 (No response.)

10 DR. D'AGOSTINO: What we want to do is again
11 now see if there's any sentiment in the committee on the
12 question that simply says will a substantial number of
13 women purchase Rogaine Extra Strength for Men, pure and
14 simple. Is that clear enough? Let's vote on that. All
15 those who say yes, please raise your hand.

16 (A show of hands.)

17 DR. D'AGOSTINO: All those who think it's no,
18 please raise your hand.

19 (A show of hands.)

20 DR. D'AGOSTINO: Any abstentions?

21 (No response.)

1 DR. D'AGOSTINO: What is the vote on that?

2 It's 16 yeases, 2 noes.

3 Now, I'd like to go and put back the word
4 "appropriately" where we interpret it in the risk/benefit
5 manner. I'll start off, but I'll ask the committee to
6 change it as they feel appropriate. What we're basically
7 asking is will women purchase this and -- that's a good
8 question. I'm not sure. Would women appropriately avoid?
9 It means that those who should avoid it, will they avoid it
10 is the only way that I can interpret this. Those who will
11 end up with some sort of adverse effect, will they in fact
12 be purchasing this.

13 What I'd like to do is throw out to the
14 committees that we now phrase this question -- leave it as
15 it's written here, but understand and try to interpret what
16 we mean and how we put the risk/benefit in so that when we
17 come to vote, we understand what we mean.

18 Eric is the one who raised the risk/benefit.
19 So, why don't you give us your interpretation.

20 DR. BRASS: Well, I guess the way I would
21 rephrase the question is given that we've already voted

1 that the majority of us think women will be exposed to the
2 product, whether or not we feel that poses a safety concern
3 to the population. I think there is little doubt that the
4 women who are exposed to it will suffer a significant rate
5 of contact dermatitis or whatever the appropriate
6 diagnostic phrase is, and I think that will be, on the data
7 available to us, unnecessary.

8 On the other hand, I do not think it is of such
9 a safety concern that individual consumers shouldn't be
10 allowed to make that decision with a variety of inputs,
11 including the potential -- I think there will be situations
12 where individual women who failed 2 percent will go to 5
13 percent. I see no way to avoid that but I don't think the
14 risk is --

15 DR. D'AGOSTINO: Are we saying, though, we
16 believe there's going to be more dryness, more itching --

17 DR. BRASS: Yes.

18 DR. D'AGOSTINO: -- and with safety beyond
19 those conditions that we're concerned about?

20 DR. BRASS: Well, no, I don't want to pretend
21 like I'm minimizing the impact of those adverse events on

1 individuals who suffer them. I think those are going to be
2 real consequences to this decision, but I think on the
3 overall balance, I'm not uncomfortable with that because I
4 do think they're going to be recognizable and reversible.

5 DR. D'AGOSTINO: I'm not sure we have a way of
6 phrasing that easily.

7 Are there other inputs?

8 DR. ROSENBERG: Yes.

9 DR. D'AGOSTINO: Yes, please.

10 DR. ROSENBERG: I'd like to overall associate
11 myself absolutely with Dr. Brass' point of view and say I
12 think he's very correct.

13 If I could go beyond that, though, and get back
14 to what Mrs. Cohen said, I think we ought to consider the
15 alternatives. I think it's absolutely clear in my mind
16 that the alternative to this is to have it as an Rx product
17 only, and I would assure the people here that the
18 dermatologists and other physicians will be much more
19 likely to write the 5 percent prescription for women than
20 women will be likely to read that box and decide to take a
21 chance on it.

1 (Laughter.)

2 DR. D'AGOSTINO: We will come to question 3,
3 which will then in fact raise that, is it appropriate for
4 OTC?

5 DR. ROSENBERG: I don't mean to make fun of the
6 profession. The labeling, of course, is strictly regulated
7 by the information that meets the requirements for
8 acceptance as admissible data by FDA, but there are other
9 scientific papers. There was an international conference
10 on hair in Belgium last year that some of us were at.
11 There were a number of papers there from abroad showing 5
12 percent being more effective than 2 percent. Those of us
13 that read those papers I think are prepared to write that
14 prescription.

15 DR. D'AGOSTINO: Are there other inputs to
16 this?

17 I'm still not sure what the statement is -- I'm
18 sorry.

19 DR. DRAKE: I too just wanted to support Dr.
20 Brass. I think that we're never going to have a zero risk
21 on any over-the-counter product. My background is not

1 only dermatology, but emergency medicine, and I can assure
2 you that people take all kinds of things they're not
3 supposed to take in spite of the best efforts of everybody
4 to see that they don't.

5 I think we have to say, wait a minute. If
6 things are adequately labeled, do we want to say that the
7 consumers don't have the right to make that choice? Are we
8 depriving access to something for the majority because a
9 minority don't want to read or follow the directions?

10 I would just ask the committee to think about
11 it because I've actually grappled with this question on
12 other issues in the past, and I don't think there's a magic
13 answer for it, but I don't think we'll ever see a zero risk
14 population when it comes to people doing things that they
15 should or should not do. That's why I like Dr. Brass'
16 point of is it appropriate and what's the benefit versus
17 the risk, and I'm comfortable with his position.

18 DR. D'AGOSTINO: Having done the first part, if
19 we leave the question now stated exactly as it was
20 originally stated but we interpret appropriately that this
21 risk/benefit faction that we understand that we're saying

1 that will they appropriately avoid it. Will they have an
2 appropriate or good risk/benefit if they happen to use it?
3 Is that an interpretation --

4 DR. BRASS: I think that's fine. I'm willing
5 to make it even more unambiguous. I'm willing to pose the
6 question, does the availability of this product to women in
7 the marketplace pose a health risk? Yes or no. An
8 acceptable health risk.

9 DR. D'AGOSTINO: An acceptable risk. Could you
10 say it one more time so we make sure we get it all?

11 DR. BRASS: Does the availability of this
12 product to women in the marketplace pose an acceptable
13 health risk?

14 DR. D'AGOSTINO: With the understanding that
15 we're assuming that women will in fact purchase it.

16 DR. BRASS: That's correct.

17 DR. D'AGOSTINO: Any further elaboration on
18 that?

19 DR. JOHNSON: Over here.

20 DR. D'AGOSTINO: I'm sorry. Yes, Cage? I
21 didn't see you.

1 DR. JOHNSON: That's okay.

2 I agree very much with what Dr. Brass has said.
3 I think the risk to the health of the patient is really the
4 systemic absorption and inadvertent hypotension and
5 tachycardia occurring. I'm uncomfortable because I can't
6 estimate that risk in my own mind. I look at this table of
7 14 subjects reported, 6 of whom are taking doses at around
8 the level of the 5 percent. I don't know how to put that
9 into context, but I see Eric maybe can help me.

10 DR. BRASS: I raised that concern this morning,
11 and over the break, I had a chance to review the FDA report
12 generated by Dr. Lipicky's group which included the blood
13 pressure and heart rate measurements for all the subjects
14 in 001 and 285, including a scattergram of the individual
15 points and a 99 percentile cutoff for heart rate responses.
16 It's clear that within the limitations of a 1,500 patient
17 database that any kind of systemic cardiovascular response
18 must be extremely rare. It's clearly much less than 1
19 percent.

20 DR. JOHNSON: My concern is you take the small
21 sample size and now we translate this into several million

1 people using it. I think we're going to see more
2 tachycardia. I just don't have a clear idea of how much
3 more tachycardia and whether it is going to pose a
4 significant life-threatening heart disease risk to the
5 over-the-counter population.

6 DR. D'AGOSTINO: Well, that's going to also be
7 men.

8 DR. JOHNSON: As a non-woman, I hope I didn't
9 specify the gender.

10 (Laughter.)

11 DR. D'AGOSTINO: Well, the question is that we
12 have to hit that at least three times in this discussion.

13 Yes.

14 DR. TONG: As we're all trying to frame in our
15 own mind how to respond to this question, I'll go back to
16 the first part of this question, "based on your review of
17 the labeling." I'm looking at the labeling here and it
18 says "not for use by women," and I heard Dr. Rosenberg just
19 comment about some studies. Because the next sentence here
20 says, "does not work better in women than Rogaine for
21 Women." I'm not sure that's a correct statement here.

1 DR. ROSENBERG: My understanding is in terms of
2 the data that FDA have, that is correct. But as I say,
3 there are other papers. Do you turn in the whole file,
4 everything anybody writes from abroad to FDA in these kinds
5 of things? I don't know. I don't what FDA has.

6 DR. D'AGOSTINO: At this point the data for the
7 women, as has been presented to us, did not show an effect.

8 DR. TONG: Because I was thinking of perhaps
9 moving "may cause unwanted facial hair" and some of the
10 other non-life-threatening but still significant effects
11 closer to "not for use by women." The real issue here is
12 we're concerned about the effects and not whether it works
13 better for men for some reason and not others for women.

14 DR. D'AGOSTINO: The question, though, the way
15 this one is, no matter how you interpret it, is will women
16 purchase it and will there be a potential risk by their
17 purchasing it. Basing that on the data we have before us
18 and the intent-to-heed studies, we have to look at the
19 intention-to-heed study which does say that a substantial
20 number will purchase it, and then we have to look at the
21 safety data on the women to ask the question whether or not

1 we think that's going to pose a health problem.

2 Eric did produce a statement and I can't read
3 Andrea's writing.

4 DR. NEAL: Does the availability of this
5 product to women in the marketplace pose an acceptable
6 health risk? Is that correct, Eric?

7 DR. BRASS: Yes. I can inverse it to make it
8 unacceptable. Whatever way makes sense to the committee is
9 okay by me.

10 DR. D'AGOSTINO: As it's stated with
11 "acceptable health risk," meaning that it's not dangerous.

12 DR. BRASS: That's correct. A yes vote would
13 mean it would be okay to do.

14 DR. D'AGOSTINO: It would be okay?

15 Any further comments on that?

16 (No response.)

17 DR. D'AGOSTINO: All those voting yes, saying
18 that it basically won't present a major health risk, please
19 raise your hand.

20 (A show of hands.)

21 DR. D'AGOSTINO: All those opposed, please

1 raise your hand.

2 (No response.)

3 DR. D'AGOSTINO: Any abstentions?

4 (A show of hands.)

5 DR. D'AGOSTINO: Two abstentions.

6 The vote is 16 yes and 2 abstentions.

7 Does that help the FDA?

8 The second question now focuses on the men.

9 Again, it says based on your review of the proposed
10 labeling and the data from the male label comprehension
11 study, will men be able to appropriately choose between
12 Rogaine Extra Strength for Men and Rogaine Regular Strength
13 for Men? Regular versus the Extra Strength.

14 We do have data that says that it's more
15 effective in the Extra Strength versus the Regular
16 Strength. Now, we're asking the question will in fact men
17 be able to choose between the two.

18 MS. SLINGLUFF: I don't think that men are
19 provided with anything on this box that suggests that they
20 shouldn't use this unless they're having a problem. This
21 says that it will grow hair faster, it will grow more hair,

1 and what man, faced with that choice, isn't going to pick
2 this box versus the 2 percent? So, the only reason on the
3 current labeling that would suggest that a man should
4 purchase the 2 percent would be if he's having scalp
5 irritation sufficient with this that he needs to
6 discontinue it. So, my answer --

7 DR. BRASS: Is there anything wrong with that
8 logic?

9 MS. SLINGLUFF: I don't think there's anything
10 wrong with that logic, but the labeling really does not
11 direct a man to buy either product except in that one
12 specific situation.

13 MS. COHEN: Ralph?

14 DR. D'AGOSTINO: Yes?

15 MS. COHEN: I know that this is going beyond
16 this, but it all depends how they promote it. You can't
17 separate out the promotion from the box because if they
18 promote it very heavily and make certain claims, then I
19 don't think there's going to be that consideration that
20 someone is go and stand in front of the two boxes and make
21 up their mind, well, they say this is going to be better,

1 it's going to grow more hair, it might grow faster versus
2 the other. I think you might very well take the 5 percent.
3 So, the promotion has to go along with it. I don't think
4 you can separate it.

5 DR. D'AGOSTINO: Yes. I think that comment is
6 correct. From what we've heard, there really isn't start
7 at the lower level and then move up. You start at whatever
8 level you start at, and if you happen to start at the 5 and
9 you get irritation, they suggest you drop to the 2. I
10 think that's all we have before us, isn't it?

11 Now I'm going to ask again the FDA, what do
12 they mean by "appropriately choose" here?

13 (Laughter.)

14 DR. BOWEN: However you decide to break that
15 one out.

16 (Laughter.)

17 DR. D'AGOSTINO: There is nothing before us in
18 terms of the -- maybe the safety aspect or something in
19 terms of more irritation and so forth, but that again is if
20 you start off with the 5 and you drop down to the 2. I'd
21 just like to get some help in terms of making sure, when we

1 vote on this, we feel comfortable with the statement that
2 we're making.

3 DR. BRASS: Well, if you want to create an
4 issue, the issue is -- and I agree completely with Beth,
5 and I think that's a logical response by the consumer. The
6 question is whether they recognize that they'll be at
7 increased risk if they make that decision to start with 5
8 percent versus 2 percent.

9 The label comprehension study depends
10 completely on what your threshold for accepting a label
11 comprehension study is and how it was done. Clearly we've
12 seen that one can structure those studies to get a 95
13 percent response rate.

14 I still have not seen any real world data that
15 says what percentage of consumers read the label at all,
16 period, to put any of this in any kind of context.

17 DR. D'AGOSTINO: Well, didn't the label
18 comprehension studies seem to indicate that there was only
19 about a 50 percent response in terms of realizing what the
20 side effects could be? So, the comprehension studies are
21 saying that people aren't responding to what it's saying on

1 the --

2 DR. BRASS: In the complete read-- again, I
3 don't remember the exact numbers, but this is what I come
4 back to, what the threshold is and designing the tests,
5 that in the complete read it was something high, 60 or 70.
6 I don't remember what it was.

7 VOICE: 70.

8 DR. BRASS: Thank you. 70, which again one
9 might say, well, if you read the box and had the question,
10 you should have done better. We've see people who do it
11 that way. They give them the box and give them the
12 question and keep having them look at the box until they
13 find the answer. And those studies always come out 90
14 percent and we're really impressed.

15 So, I just don't know how to evaluate this kind
16 of data in this way. Yes, I wish the number was higher
17 than 53 initially and higher than 70 afterwards, but I
18 think that's the context of that decisionmaking to offset
19 the benefit.

20 DR. D'AGOSTINO: So, in order to answer this, I
21 think we have to narrow it down. Basically wherever you

1 start, you start. And is there enough information on the
2 label and is there enough in the label comprehension study
3 for us to feel that if a condition exists, such as dryness
4 and itching, that in fact the subjects, the males, will in
5 fact move down to the Regular Strength. And we can't
6 respond beyond that.

7 DR. BRASS: Well, again I think there are some
8 labeling issues we might suggest as to how improve that,
9 but I think they're number 4, and not number 2.

10 DR. D'AGOSTINO: Yes. That's a different
11 question I think.

12 Is that all right? That's the only way I think
13 we can interpret this. And we're not getting any help from
14 the FDA. They made that clear.

15 (Laughter.)

16 DR. D'AGOSTINO: Let's just see the way it's
17 going to go here now. So, we're saying if you vote yes on
18 this, it means that you think that the label and the label
19 comprehension studies indicate that those who start off
20 with 5, develop the itching, dryness, will move down to the
21 2 or stop, but move down to the 2 is what the box will say.

1 If we vote yes, that's what we're saying, that there's
2 enough information for us to think that will happen.

3 All those in favor of that, please raise your
4 hand.

5 (A show of hands.)

6 DR. D'AGOSTINO: All those opposed?

7 (A show of hands.)

8 DR. D'AGOSTINO: Any abstentions?

9 (No response.)

10 DR. D'AGOSTINO: 15 yes, 3 noes.

11 The next question now says, based on the data
12 presented, would you recommend that the safety and
13 effectiveness of this product make it appropriate for OTC
14 use in the intended target population?

15 Who raised the question over here? Was it
16 Bill? You raised the question about the inappropriateness
17 of OTC. Do you want to begin this discussion? Now we're
18 asking, given the data that was presented to us where we
19 see the effectiveness and we also see the safety data and
20 we also have the input that an approvable letter has been
21 set out on the 5 percent for Rx, do we think that it

1 actually is appropriate for the OTC use?

2 DR. ROSENBERG: In my mind, I think it's a
3 perfect drug for OTC for a number of reasons. This is a
4 condition that some men and many women are concerned about.
5 We know that. It's a condition that many health
6 professionals consider trivial and are not concerned about
7 and are not in a perfect position to have the enthusiasm or
8 the information or the desire to try and spend the time
9 with the patient on this that the consumer would be willing
10 to spend looking.

11 There's a world of information that consumers
12 get beyond the label: the medical press, the daily press,
13 the self-help magazines, the look better/feel better
14 magazines. This is a major source of information and they
15 are going to get much more information in this direction
16 than they would in a professional office.

17 In terms of the criteria for self-treatment,
18 can they self-diagnosis it? Yes, it's diagnosed. Can
19 directions be written for use? Yes. Is it safe and
20 effective? We've been told it's so.

21 So, I think it's a perfect drug for OTC use in

1 my opinion. If it's going to be around at all, it ought to
2 be OTC.

3 DR. D'AGOSTINO: Other comments, Eric?

4 DR. BRASS: I have two concerns in the safety
5 and efficacy which blur between 3 and 4 and I request your
6 indulgence because I'm going to need to leave at 2:30. I
7 want to make sure I raise these two issues.

8 The first is in terms of the efficacy as
9 presented to us, I remain uncomfortable with the "faster"
10 claim. If that's included in the effectiveness that's
11 being claimed --

12 DR. D'AGOSTINO: I was going to mention that I
13 think that all we have on the effectiveness is in fact the
14 more hair. We do not have --

15 DR. BRASS: Okay, I just wanted to make sure
16 that was clear, the differentiation.

17 I have one safety concern as presented for the
18 5 percent particularly. Again, this is in terms of OTC
19 appropriateness. If a patient came to me who was using a
20 topical product that had caused local irritation, I would
21 tell them to stop using the product until the skin had

1 healed rather than telling them to use a lower dose unless
2 there was a compelling reason to continue using the
3 product.

4 Thus, I think from a safety perspective, given
5 the high percentage of people who are going to develop a
6 skin irritation on 5 percent, I would prefer to see the
7 instruction be to stop using the product and then restart
8 after healing with 2 percent if desired by the consumer.
9 I'm not sure that's a real safety issue, but I'd feel more
10 comfortable.

11 DR. D'AGOSTINO: I don't think we have any data
12 -- I think someone raised it, probably you -- saying that
13 the 5 percent to 2 percent is sort of better than the 5 to
14 stop. I think it's a real question what should you do if
15 you have the irritation, and I think we can raise that as
16 we go into the labeling in directions and suggestions to
17 the FDA.

18 Yes?

19 DR. MINDEL: I'm still concerned about the
20 safety of the drug. The FDA has approved the drug, the 5
21 percent, in an in-house approval process. I assume it

1 didn't go outside for a committee like this. Is that
2 correct?

3 DR. WEINTRAUB: No.

4 DR. MINDEL: So that it didn't have the
5 opportunity for people outside the FDA to review it.

6 DR. D'AGOSTINO: Michael, does anyone know?

7 DR. WILKIN: It was not approved. It was
8 approvable.

9 DR. MINDEL: So, it hasn't been approved.

10 DR. WILKIN: Yes.

11 DR. MINDEL: There are probably many
12 interpretations of the data that has been presented, but
13 the data is compatible with -- I use the word "compatible"
14 not proof, but compatible that the 5 percent has a toxic
15 effect. You get an initial benefit that's accelerated,
16 followed by a drop-off in the benefit.

17 I would like to see data that shows that
18 there's a leveling off. What you have is you go up, and
19 then you see it going down, and you haven't reached a
20 steady state or level point. You've gone out 48 weeks. I
21 think you have to have the data on the counts to show that

1 there is some stabilization for the safety and efficacy.

2 The last point I want to say is, which is more
3 important: the amount of drug or the concentration or
4 both? In something that dries on the hair, concentration
5 may not be the major advantage. It's the amount of drug.

6 The previous Rogaine brochure says that the
7 Upjohn company carefully determined the correct amount of
8 Rogaine and more frequent or larger doses do not have a
9 benefit. While the efficacy and benefit discussions have
10 been cut short because of these other questions, I still
11 have some question in my mind why, if you used 2 percent
12 more frequently or in larger volumes, you wouldn't get the
13 same effect.

14 And you could cut through a lot of that if you
15 could show that the blood levels of two different
16 concentrations or preparations of the drug -- if the blood
17 levels were the same, even though the blood level doesn't
18 represent the effective drug, you would cut through a lot
19 of the availability to the hair follicle by that kind of
20 analysis which I don't know whether that has been done.

21 DR. D'AGOSTINO: I feel it's appropriate to ask

1 the sponsor if they have a response to the concerns that
2 are being raised, and if they do, why don't they give it to
3 us. Do you have a response to this? Please identify
4 yourself.

5 DR. WHITING: I'm Dr. David Whiting. I'm a
6 clinical professor of dermatology and pediatrics at
7 Southwestern Medical Center in Dallas, Texas, and I'm the
8 Medical Director of something called the Baylor Hair
9 Research and Treatment Center. I've been in dermatological
10 practice and in hair practice for very many years.

11 I'm not only a dermatologist, but I'm a
12 dermatopathologist, so I do vast numbers of scalp biopsies
13 which I examine in two different ways in order to count
14 hair counts in them. I have seen at least, I'm sure, 600
15 biopsies which I've sectioned vertically and horizontally
16 in androgenetic alopecia on patients that have been treated
17 and patients that have not been treated with minoxidil and
18 various other things. So, I've got a little experience in
19 that.

20 But it does strike me that I really must thank
21 the chairman to give me an opportunity just to clarify

1 briefly the pitfalls and the problems that we have in
2 conducting hair studies and testing new remedies for hair
3 growth. I think that this may be a little bit basic, but
4 it probably makes it all a lot more understandable if you
5 understand something about the hair cycle.

6 We have about 100,000 hairs on our scalp and
7 once we have grown up, these hair follicles all operate
8 independently and they all cycle through periods of growth,
9 or anagen, and rest, or telogen, independently of one
10 another. Generally, in the normal scalp, about 90 percent
11 of our hairs are growing and about 10 percent of our hairs
12 are resting.

13 Now, of course, this is quite different to what
14 happens when we are being developed in our mother's womb
15 because as a fetus, we are rather like animals, and we have
16 a wave pattern of hair growth where you start with a wave
17 of growth in the front and it goes on to the back and you
18 lose hair behind it as the hair falls out when it goes into
19 a resting phase.

20 Now, this sort of is worthwhile remembering
21 because let's see what happens in androgenetic alopecia

1 where you have a process of hair miniaturization going on,
2 and the reason that happens is that the hair cycle of
3 growth, which normally extends somewhere from 2 to 7 years
4 in the normal person so the hair can grow long, gets
5 shorter and shorter and shorter, down to a couple of
6 months, so the hair gets smaller and smaller.

7 So, that means the time your hair is growing,
8 your anagen or growing phase becomes very short, but
9 funnily enough, the resting time, which is normally 3
10 months, remains the same. So, thus, when you have
11 androgenetic alopecia, or common baldness, which is what
12 we're talking about here, you have lots and lots of little
13 hairs coming along and many of them are resting for long
14 periods.

15 Now, when you use something like minoxidil
16 which is a drug which pushes hair back into anagen and
17 therefore puts it back into a growth phase, you are
18 automatically stimulating a whole lot of hairs to go back
19 into a growth phase en masse, almost like a wave growth
20 that you had when you were a fetus. So, you get this
21 fairly prompt response. Once these hairs that have been

1 programmed to being such small hairs for so long, gradually
2 wake up and respond to this minoxidil, they grow and they
3 respond more quickly to a higher concentration in all
4 probability. So, you get this sudden rise in hair growth.

5 Then you can only change that cycle so much to
6 begin with. Imagine succeeding waves of cycles getting
7 longer and longer and longer with the minoxidil. So,
8 therefore, this is what happens.

9 And we see it in patients all the time and I
10 warn them about it, that if you're going to have minoxidil
11 helping you, you're going to find after about 4 months --
12 this is the 2 percent -- that you're going to maybe start
13 growing hair and you'll grow hair for a while and then that
14 hair will get to the end of that particular length and
15 cycle and it will fall out and it will stay out. So, you
16 actually get a decrease in hair again, accounting for a lot
17 of those little ups and downs that you see on that graph.
18 Then more hairs get recruited and they grow up again. So,
19 you have this gradually diminishing business of these ups
20 and downs that you have to warn them about.

21 So, that in a way explains some of the stuff

1 that you were commenting on regarding, say, as a toxic
2 thing.

3 Now, as far as the toxic aspect of that is
4 concerned, I've looked at an enormous quantity of biopsies
5 in great detail by the normal way that you'd maybe measure
6 some sort of toxic reaction on the hair shafts from the
7 point of view of cells dying or getting plugs in the
8 follicles or getting inflammatory changes. I certainly
9 don't see any more of that after prolonged minoxidil usage
10 than I do in the normal.

11 So, I just think that a general understanding
12 of the hair cycle like that gives you a better feel for the
13 way that these trials are conducted and the way these
14 things go. You really have to watch this over a fairly
15 long period to see the sort of trends that happen. I think
16 the one trial that you were shown earlier where you saw
17 that hair weight study of Vera Price's, which has been
18 extended for two years, there wasn't a downgrade back to
19 baseline. That certainly hasn't been the experience with
20 minoxidil in the past.

21 Thank you very much.

1 DR. D'AGOSTINO: Thank you.

2 Yes?

3 MS. COHEN: Thank you. I was just reading -- I
4 hope I can find it -- some warnings about you should not
5 use Rogaine. It talks about the use of some prescription
6 and nonprescription medications, certain severe nutritional
7 problems. It all said, if I can find it, that if your
8 scalp is red or irritated, you should stop the use of
9 Rogaine. I would assume if your head becomes dry and it
10 becomes itchy what you're going to do is scratch it and
11 from scratching, you're going to have an irritated head.
12 From their warning here on one of their labels, it says you
13 don't use Rogaine. So, I think in their own information
14 they tell you that.

15 Now, I'll find the page in a minute. You know,
16 you never can find what you want.

17 DR. D'AGOSTINO: It is also on the label what
18 you're saying.

19 MS. COHEN: Yes.

20 DR. D'AGOSTINO: Yes, Joel?

21 DR. MINDEL: What I'd like to do is just for

1 the data to show that the steady state is reached or that
2 there is a blip upward. I accept that your explanation is
3 perfectly reasonable but it also is reasonable that you're
4 seeing a toxic effect. So, I'd like to know how long do
5 you have to go out before you see the evidence that it
6 isn't a toxic effect and why don't we just wait the
7 additional time?

8 DR. TRANCIK: This is Ron Trancik again.

9 We have long-term data on 2 percent. These are
10 data that were published by Dr. Alyse Olson in the Journal
11 of the American Academy of Dermatology where she has
12 followed patients -- I think one cohort was 45 or 50
13 patients and another was 60 or 65 patients -- out to over 5
14 years on 2 percent.

15 She has shown basically, if you're talking
16 about a toxic effect, what happens is just exactly what Dr.
17 Whiting said and what I said earlier, that you get early
18 growth and then you get a sustaining of the growth or a
19 stabilization effect. These people, as she described,
20 really basically held their hair. They didn't lose their
21 hair and there was no toxic phenomenon that was reported.

1 DR. MINDEL: I'm not saying for 2 percent there
2 is. I'm asking the question how long should you go out
3 before you see stabilization of the downward trend which
4 all the data that we have shows a downward trend. That's
5 all I want to know. Is it a year?

6 DR. D'AGOSTINO: Dr. Wilkin may have some
7 information in the discussion here.

8 DR. WILKIN: Well, I was intrigued with Dr.
9 Whiting's interpretation of what might be happening with
10 the telogen/anagen/catagen cycle that is occurring.

11 Peccarero and colleagues have monitored what
12 they called the trichogram, which is the proportion of
13 anagen and telogen hairs after pregnancy in the condition
14 known as postpartum telogen effluvium. What they've found
15 is this oscillatory kinetics that Dr. Whiting is
16 describing. The numbers would go like so. But the period
17 is one of six months. It's not a year. So, it's much
18 shorter than the time frame that we're seeing in the data
19 in the present study.

20 The other thing is we would expect over time a
21 damped oscillatory type of kinetics. What we're really

1 seeing here is a rise to an observation point. We don't
2 really have intermediate points. Then it goes on after
3 that.

4 So, we're continuing our discussions with the
5 sponsor when they wish to go on and evaluate data in women
6 to do those studies. We clearly would like them to be
7 pursued long enough and perhaps with the right kind of
8 seasonal balance, so there's not a seasonal effect so that
9 we can do the right type of interpretation.

10 One possibility is that what is happening with
11 the drug -- and again, it's only speculative -- is that
12 it's resetting the level of the net population and that it
13 is maybe giving an extra three years or something like that
14 or maybe six months. I don't know what it would be. But
15 over time it really does continue the same biologic rate of
16 loss after the reset. But even with that, that could still
17 respond to Dr. Mindel's concern. There may be some value
18 in that. The sponsor may be able to document that that
19 still contributes something positive.

20 DR. D'AGOSTINO: The situation right now,
21 though, I guess is that we don't have data out that far to

1 answer that question.

2 DR. MINDEL: Well, it seems that the approval
3 for prescription use is up to some question, much less
4 over-the-counter use. If I'm understanding what you're
5 saying, you're continuing to monitor this. The 6-month
6 period is past and the data still shows continued hair
7 loss, and you're going to monitor this further. Is that
8 correct?

9 DR. WILKIN: In the last meeting we had with
10 the sponsor on this, I think that they had some very good
11 ideas on how to pursue this in upcoming studies where we
12 can learn a lot about the biology and we can extrapolate
13 what we learn to other concentrations. We don't have data
14 now.

15 DR. D'AGOSTINO: Yes, Bill?

16 DR. ROSENBERG: I think we've spent an awful
17 lot of time talking about women. This is a product for men
18 and I want to talk about men for a minute because it is a
19 product for men. Assuming that the data indicate that the
20 5 percent is better than the 2 percent, I'll accept that.

21 I would just reiterate that if we require the

1 man who wants it to go and get a prescription, we're living
2 in an era of managed care. He's going to be seeing a
3 primary care physician who's got a lot on his mind, is less
4 interested in the nuances of this than he is in analgesics
5 or gastrointestinal products or cough/cold products or
6 other aspects of the OTC scene, is unlikely refer him to a
7 dermatologist and get on the black list of his carrier, and
8 I think the guy is just not going to be able to get a hold
9 of something if he'd like to do so. I think this is his
10 only opportunity is OTC for the man who wants it.

11 DR. D'AGOSTINO: Yes?

12 MS. COHEN: I made a mistake. It wasn't on the
13 label. It was on the insert, and it says, "Do not apply
14 Rogaine on the scalp if the skin is red or inflamed,
15 infected, irritated, painful to touch."

16 DR. D'AGOSTINO: It is on the label also.

17 MS. COHEN: Is that also on the label?

18 DR. D'AGOSTINO: Yes, it is.

19 Are there other comments?

20 (No response.)

21 DR. D'AGOSTINO: I think we've had our

1 discussion. Hopefully it has been complete enough for the
2 members of the committees to vote on it.

3 I do think it appropriate to remove the
4 "faster" when we make this vote. We're talking about what
5 the primary efficacy variable was, so it's the more hair
6 and the safety and effectiveness, effectiveness relating to
7 the more hair, and it's only for men.

8 All those in favor?

9 DR. DRAKE: Mr. Chairman, is this in favor of
10 doing it?

11 DR. D'AGOSTINO: This is question 3. We're
12 answering question 3. The question 3 is, based on the data
13 presented, would you recommend that the safety and
14 effectiveness of this product make it appropriate for OTC
15 use in the intended target population? So, a yes vote
16 means that you're voting for an OTC approval of the OTC.
17 Is that clear?

18 DR. DRAKE: Yes, sir. Thank you very much.

19 DR. TONG: You gave us some conditions.

20 DR. D'AGOSTINO: "Faster" is being removed.

21 Any other comments, clarifications we need?

1 (No response.)

2 DR. D'AGOSTINO: All those in favor, please
3 raise your hand.

4 (A show of hands.)

5 DR. D'AGOSTINO: All those opposed?

6 (A show of hands.)

7 DR. D'AGOSTINO: Any abstentions?

8 (No response.)

9 DR. D'AGOSTINO: 13 and 4. 13 yes, 4 no, and
10 no abstentions.

11 Maybe it would be helpful actually if the ones
12 who voted no would state why. I think it might be helpful
13 to the FDA to know that. Phil, you voted no.

14 DR. LAVIN: Yes. My feeling is, as I said this
15 morning, I'd be interested in seeing what happens to people
16 who go from the 2 percent to the 5 percent because I think
17 that's what the real world is going to be doing. They're
18 all going to switch over to it. I think that that
19 experience, whether or not they get a boost and whether or
20 not the comments that were made by their investigator
21 indicated whether or not there will be this boost, is I

1 think important to see and know.

2 I think the safety issues have to be weighed
3 against that empiric difference of 7 and 9 hair counts per
4 patient, which was the mean increment between the 2 percent
5 and the 5 percent. So, you're weighing that very small
6 increment against what the safety issues are.

7 DR. D'AGOSTINO: Joel?

8 DR. MINDEL: I think I've said everything I
9 want to say. For those of us that voted no, though, I've
10 been told in the past that the discussion is more of merit
11 than the vote, and I'm happy I said what I said.

12 DR. D'AGOSTINO: Exactly and that's exactly why
13 I want to make sure that if there are other things, they
14 should be raised because I think the discussion is very
15 important.

16 Eduardo? Who was the other one who voted no?

17 MS. COHEN: I think it has been said and I am
18 concerned that women are going to use it. And women who
19 might be pregnant -- I think there are still a lot of
20 things that haven't been answered. And also to go to the 2
21 to 5 percent. I think there should be a hiatus if people

1 have dry, itchy scalp.

2 DR. D'AGOSTINO: Thank you.

3 The next question talks about --

4 DR. JOHNSON: Do you want to why I voted no?

5 DR. D'AGOSTINO: I'm sorry. Go on, Cage, let's
6 hear it.

7 DR. JOHNSON: I stated it before, but I want to
8 be sure. The only residual problem I have with this
9 application is I'm uncertain about the toxicity with
10 respect to the tachycardia/hypotension question, and I
11 think that's just a big unknown. In the over-the-counter
12 market, I'm uncomfortable allowing this formulation in the
13 over-the-counter market without having a clearer idea of
14 the risk to the patient population.

15 DR. D'AGOSTINO: Thank you. So as not to leave
16 anyone else out, did we get all the no votes?

17 Question number 4 now says, please provide
18 additional comments on the draft labeling contained in your
19 briefing package.

20 One of the comments that I'll start off with is
21 that I don't think that we really have appropriate data for

1 the "grows more hair faster," and that I think should be
2 removed.

3 Are there other comments in terms of the
4 labeling? Yes, Eva?

5 DR. SIMMONS-O'BRIEN: I'd like to agree with
6 Mrs. Cohen and with what Dr. Brass has said. As a
7 practicing dermatologist, when we encounter a patient who
8 has scalp irritation based on something that we believe
9 they may in fact be using, we tell them to stop, and then
10 not only stop, we might in fact try to treat it.

11 Oftentimes we create scalp irritation by using
12 a topical solution that very well may contain propylene
13 glycol, as many of the topical steroids do if we're using
14 them for whatever reason, and the majority of us would not
15 then switch to another preparation with propylene glycol in
16 it to help resolve the process because we don't know
17 whether that person is having an irritant reaction, a
18 contact irritant reaction versus a contact allergic
19 reaction versus a reaction to the actual product itself.

20 So, I would propose if scalp irritation
21 persists, that the individual discontinue use of the

1 product. I think to suggest to consider switching to
2 Rogaine Regular Strength and then down in the warnings say
3 "stop if scalp is red, inflamed, infected, irritated, or
4 painful," I believe what's said in the top portion of the
5 box is misleading. It does not gibe with what's in the
6 warning because scalp irritation in my mind implies
7 inflammation plus/minus erythema depending on that
8 patient's skin type. They might not see redness if they
9 are dark skinned. They might only feel or have the
10 sensation of itching or burning.

11 So, I'm very unhappy with where it's placed I
12 guess. I think I would prefer if scalp irritation
13 persists, then immediately say, see warning. Deflect that
14 person's attention down to the lower portion of the box so
15 that they can see the warning, not that they can
16 immediately go to the other substance which might in fact
17 be causing the problem to begin with because lowering the
18 percentage of the irritant not necessarily right away is
19 going to resolve the process of the irritation.

20 DR. D'AGOSTINO: Thank you.

21 Are there other comments on the labeling? Mary

1 Anne?

2 DR. KODA-KIMBLE: First, I want to congratulate
3 the manufacturer for making an effort to discourage women
4 from using it. I've never seen something as a boxed yellow
5 warning and signs and that sort of thing. I can't
6 understand why so many women said they would use it. But I
7 think it's just this equality thing.

8 (Laughter.)

9 DR. KODA-KIMBLE: But I do wonder, since we
10 have acknowledged that women will use it and the FDA I
11 think recommended that they take the warning label off for
12 breast-feeding and pregnancy, if we think women are going
13 to use it, whether we ought to put it back. I know it's a
14 mixed message. I'm just asking the question. That's
15 question number 1.

16 Then I would just repeat what I had said
17 earlier about suggesting an actual percent content on the
18 propylene glycol for all products.

19 DR. D'AGOSTINO: Thank you.

20 I think the women issue and the pregnancy and
21 so forth is very important if we say we know they're going

1 to use it, and how do you handle that? So, I think all the
2 points up to this point have really been very important.

3 Do you have a comment also?

4 DR. MCKINLEY-GRANT: That was exactly what my
5 question was going to be, that I thought that the agency
6 should address that.

7 DR. D'AGOSTINO: Ted, did you have a comment
8 also? Are there other comments for the labeling? Yes?

9 DR. HASHIMOTO: I just wonder if the labeling
10 say the heart disease patients shouldn't use or the
11 symptoms listed there is adequate because a lot of
12 population is retired and taking multiple vasodilating
13 agents, and some of the data shows that maximum blood level
14 high percent reaching to 2.5 oral dosage.

15 So, another thing is, for example, nifedipine,
16 we use for scleroderma. The patient never knows that this
17 is a cardiovascular vasodilator.

18 So, somewhere maybe in a very rare instance,
19 but some accident may happen. If this is a prescription
20 drug, the physician knows or the pharmacy has computer
21 data. Just to have the customer go to the pharmacy and

1 picks it up and buys it without knowing that this is a
2 cardiovascular type of agent, there may be some accident.
3 That's my little bit worry about it.

4 DR. D'AGOSTINO: Yes, Beth.

5 MS. SLINGLUFF: The other members of this
6 committee know that we certainly spent all day Monday
7 talking about labeling, and so I would simply reiterate
8 some of the points we hit there which discussed things like
9 reverse type. Actually I can read the white on black
10 better. I personally think it's a little tough to read the
11 black on blue.

12 I realize that this box is actually not the
13 label that was tested in the April 1997 test that was done
14 with women. One of the really simple things that was
15 apparent was that non-high school graduates seemed to
16 answer more often that they would use the product. For
17 whatever other reasons may have motivated women to use the
18 product, maybe they just couldn't read some of the
19 information on here. If they can't read basic warnings,
20 then they're going to have a lot of trouble with things
21 like "topical prescription products" as a phrase. So, I

1 think that this needs to be checked for language use to
2 take it down as far as possible for the average consumer to
3 be able to read and understand.

4 I think there are some format issues here that
5 revert to Monday's discussion which I have no intention of
6 repeating here.

7 DR. D'AGOSTINO: I think it's important to
8 mention them, though. Thank you very much.

9 Other comments on the labeling? Yes?

10 DR. DRAKE: I just kind of want to support what
11 Beth alluded to in part. The age group of people who
12 probably want to use this product are the age group like me
13 going out to the dime store and buying glasses because I'm
14 having trouble reading it. I actually had trouble seeing
15 some of the slides. I've decided I'm really getting blind.
16 I don't know what's going on.

17 But the bold print on here, the really dark
18 print, is much easier to read than the lighter print. I
19 don't know what the space requirements would be, but if you
20 can increase the font size, it will certainly help those of
21 us who are having a little difficulty in our aging years

1 reading anything.

2 DR. D'AGOSTINO: As Beth said, we did have a
3 whole meeting on Monday in which these points were
4 mentioned.

5 Yes, Eva.

6 DR. SIMMONS-O'BRIEN: I have another comment.
7 Switching hats as an internist, I would prefer to see "stop
8 use and seek immediate medical attention if you have chest
9 pain, rapid heart beat, faintness, or dizziness." Some
10 people might literally call up to get an appointment with
11 their doctor, which could take 10 years. I think that if
12 someone is having chest pain and maybe it has nothing to do
13 with this product, but yet they remembered from this
14 product, if they had chest pain, rapid heart beat,
15 faintness, they need to seek immediate attention which is
16 oftentimes very different from seeing your doctor, but
17 maybe the fastest and the most efficacious.

18 DR. D'AGOSTINO: Thank you.

19 Any other comments? Did you want to make a
20 comment? Yes, please.

21 DR. TRANCIK: This is Ron Trancik again from

1 Pharmacia & Upjohn.

2 I know we were chartered at the end of the
3 morning session to go away and come back with some
4 additional comments for the advisory committee as it
5 relates to time to response, and I would like to request
6 that we have that opportunity. I know that you have
7 recommended to delete the faster response from the
8 labeling, but could I have the first slide please? I just
9 wanted to address it one more time.

10 DR. D'AGOSTINO: Please do so.

11 DR. TRANCIK: As was stated this morning, this
12 claim or this observation was in fact post study. It was
13 not a priori put into the protocols prior to their
14 initiation, but I think the thing I would like to emphasize
15 again -- and we can show these data graphically now instead
16 of as numbers in a chart -- that in both our definitive
17 trials in males, namely the protocol 285 and 286 studies,
18 in both cases the profiles for the treatment groups, namely
19 the 5 percent and the 2 percent, the two active treatment
20 groups, were on top of each other.

21 In other words, 5 percent was not only greater

1 than the 2 percent in terms of magnitude of response, but
2 again, if you look at the hair count data, you can see that
3 you achieve a 30 mean change in hair count at week 16 for
4 the 2 percent product and that same level of response is
5 achieved at week 8 for the 5 percent product. The 2
6 percent product at week 8 is about 25 or 24 hair counts.

7 The same sort of pattern was seen in the
8 earlier definitive trial in males, namely the 001 study.
9 If I could have the next slide. Again, you can see that
10 the 5 percent not only had a greater magnitude of response,
11 but I look at this as achieving a response faster, a more
12 rapid onset of response.

13 Granted, this observation may not meet rigorous
14 statistical considerations. Also again I will mention that
15 these were not endpoints that were put into the protocol a
16 priori, but again from a clinical perspective, from my
17 perspective and I think from a clinical perspective, you're
18 getting to a point sooner with the higher concentration
19 than you are with the 2 percent concentration.

20 Could I have the next slide? I'd also like to
21 point out that based on our Rx experience with 2 percent as

1 a product in which -- again as an Rx experience, we had the
2 benefit here of having physicians coach the patient, that
3 is, try to encourage patients to continue to use the
4 product because, as you know, on the 2 percent OTC product
5 and on the Rx product, we specifically have a time frame in
6 which the product should be used in order to see a response
7 and it's namely 4 months. One must use the product for 4
8 months to begin seeing a response, and optimally this
9 should be 8 to 12 months in males and females.

10 You can see, based on these data, that after 4
11 months almost 60 percent of the patients had discontinued
12 use of the product. So, I think there's really a need for
13 a product out there that would -- a user be it -- in this
14 case, it would be in an OTC environment. A male user in an
15 OTC environment would need to have a product where he sees
16 a response so that he would continue to use the product.
17 He no longer even has the coach of a physician to encourage
18 him to continue to use the product.

19 Next slide. So, in summary, again I thank you
20 for letting me have the opportunity to again try to make
21 our case as it relates to a sooner onset of activity, but

1 we believe that we do have clinical information to support
2 this claim. I think we need to establish in our labeling
3 reasonable expectations with consumers. As I mentioned the
4 2 percent label does have a time frame which is specified
5 on the labeling. I think that as you saw with the Rx
6 experience, discontinuations do occur and about 60 percent
7 of the patients discontinued using the product by month 4.

8 Also, I would like to just mention in closing
9 that I would like to leave it open for additional
10 discussions with the FDA regarding this issue. I know that
11 we certainly would be able to discuss other versions of the
12 labeling in which we might be able to address some specific
13 time frame in which one would observe a response, not only
14 a magnitude of effect, but a time to response. And I'm
15 confident that we could come up with some labeling which
16 would be more palatable to all of us.

17 Thank you.

18 DR. D'AGOSTINO: Thank you.

19 I think that the comment that we made or the
20 reason we took it out is that "faster" wasn't a primary
21 endpoint and it was clear in the discussions that in fact

1 it was post hoc and the appropriate analysis that one would
2 need for statistical validation of it wasn't presented.
3 So, I think we'd feel much more comfortable as a committee
4 going with the primary endpoint that was in fact in the
5 clinical trials.

6 Obviously, you'll have a discussion with the
7 FDA and I would presume that all of the claims that are
8 made will in fact have to be supported by data, and that
9 the committee I think is very comfortable with. It's just
10 as this committee, we do not feel that "faster" belongs in
11 the material. It just is not supported by the protocols.

12 Are there any comments?

13 DR. WEINTRAUB: Yes, I'd like to make a couple
14 of comments.

15 First of all, I want to thank the committee.
16 You're right. We do pay much more attention to the
17 discussion than to the votes, but the votes are important
18 as well.

19 I do want to say one thing about the sponsor.
20 We've had a lot of negotiations with Pharmacia & Upjohn,
21 and I hope that they have been in good faith on both sides.

1 I believe we have and I really think they have as well.
2 So, I'm not too worried about the label because I think
3 we'll work it out. We've worked well with them in the
4 past, not perfect, but well and we'll work on this and get
5 the order right and we'll get the wording changed and we'll
6 get more room and we may even sneak in some bigger type,
7 something like that because this morning, as several of us
8 were talking, we said it always comes down to the size of
9 the type.

10 But anyway, we're very grateful for all of your
11 participation, and thank you very much.

12 DR. D'AGOSTINO: In behalf of the committee, we
13 also want to thank the sponsor for their presentations and
14 their thoroughness and also for the FDA presentations which
15 were extremely excellent.

16 The meeting is now adjourned.

17 (Whereupon, at 2:55 p.m., the meeting was
18 adjourned.)

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