

ORIGINAL

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE
DENTAL PLAQUE SUBCOMMITTEE

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WEDNESDAY
DECEMBER 2, 1998

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The meeting took place in the Conference Room,
FDA Building, 5630 Fishers Lane, Rockville, Maryland
at 8:30 a.m., Robert J. Genco, D.D.S., Ph.D., Chair,
presiding.

PRESENT:

- ROBERT J. GENCO, D.D.S., Ph.D., Chair
- KATHLEEN REEDY, Executive Secretary
- WILLIAM H. BOWEN, Ph.D., D.Sc., Member
- LEWIS P. CANCRO, Ph.D., Member
- RALPH D'AGOSTINO, Ph.D., Member
- MAX A. LISTGARTEN, D.D.S., Member
- EUGENE D. SAVITT, D.M.D., Member
- STANLEY R. SAXE, D.M.D., M.S.D., Member
- CHRISTINE D. WU, Ph.D., Member
- FRED HYMAN, D.D.S., M.P.H., FDA Representative
- LINDA KATZ, M.D., M.P.H., FDA Representative
- ROBERT SHERMAN, FDA Representative
- BILL SOLLER, Ph.D., Public Comment
- CLIFFORD W. WHALL, JR., Ph.D., Public Comment
- PATRICE WRIGHT, Ph.D., Public Comment

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ALSO PRESENT:

DONALD WHITE, Ph.D.
MARK S. LEUSCH, Ph.D.
MICHAEL L. BARNETT, D.D.S.
NANCY L. BUC
MARLENE B. FEDER
ELIZABETH ANDERSON
MATTHEW J. DOYLE, Ph.D.
W. GREG COLLIER, Ph.D.
JEROME A. MERSKY, Ph.D., D.A.B.T.
PETER B. HUTT

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P R O C E E D I N G S

8:43 a.m.

1
2
3 DR. GENCO: Good morning, ladies and
4 gentlemen. I'd like to welcome you all to this final
5 meeting of the Dental Plaque Subcommittee. We have a
6 lot to do and I'd like to thank everyone here and the
7 Panel in advance for all the efforts through the last
8 few weeks to prepare for this final meeting.

9 I'd like to ask Sandra Titus to give us
10 her meeting statement.

11 DR. TITUS: The following announcement
12 addresses conflict of interest issues associated with
13 this meeting and it is made a part of the record to
14 preclude even the appearance of a conflict. The
15 purpose of the Subcommittee is to review information
16 on ingredients contained in products bearing
17 anti-plaque and anti-plaque-related claims to
18 determine whether these products are safe and
19 effective and not misbranded for their labeled use.

20 Since the issues to be discussed by
21 the Subcommittee will not have a unique impact on any
22 particular firm or product, but rather may have
23 widespread implications with respect to an entire
24 class of products, in accordance with 18 U.S.C. 208(b)
25 waivers have been granted to each member and

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1 consultant participating in the Subcommittee meeting.

2 A copy of these waiver statements may be
3 obtained by submitting a written request to the
4 Agency's Freedom of Information, located in Room 12A30
5 of the Parklawn Building.

6 In the event the discussions involve any
7 other products or firms not already on the agenda for
8 with an FDA participant has a financial interest, the
9 participants are aware of the need to exclude
10 themselves from such involvement and their exclusion
11 will be noted for the record.

12 With respect to all of the participants we
13 ask in the interest of fairness that they address any
14 current or previous financial involvement with any
15 firm whose product they may wish to comment upon.

16 DR. GENCO: Thank you, Dr. Titus. I now
17 call on Bob Sherman for some announcements.

18 MR. SHERMAN: Can we have introductions?
19 We skipped that.

20 DR. GENCO: Sorry.

21 MR. SHERMAN: That's all right.

22 DR. GENCO: Let's start on the right with
23 introductions.

24 MR. CANCRO: Lew Cancro, Industrial ILR.

25 DR. SAVITT: Gene Savitt, periodontist,

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1 Wellesley, Mass.

2 DR. WU: Christine Wu, Periodontics,
3 University of Illinois at Chicago.

4 DR. D'AGOSTINO: Ralph D'Agostino,
5 Biostatistician, Boston University.

6 DR. SAXE: Stanley Saxe, Geriatric
7 Dentistry and Periodontics, University of Kentucky.

8 DR. GENCO: Bob Genco, Periodontics, State
9 University of New York at Buffalo.

10 DR. TITUS: Sandy Titus, Executive
11 Secretary for NDAC.

12 DR. BOWEN: Bill Bowen, Center for Oral
13 Biology, University of Rochester.

14 DR. LISTGARTEN: Max Listgarten,
15 University of Pennsylvania, Periodontal.

16 DR. HYMAN: Fred Hyman, Dental Officer,
17 Division of Dermatologic and Dental Drug Products,
18 FDA.

19 MR. SHERMAN: Bob Sherman, CDER liason,
20 Division of OTC Drug Products, FDA.

21 DR. KATZ: Linda Katz, Deputy Director of
22 OTC Drugs.

23 DR. GENCO: Thank you. Bob?

24 DR. SAXE: I had a couple of
25 announcements. One, there's a change in the agenda

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1 that was originally announced in the Federal Register
2 notice of the meeting. The ingredients triclosan and
3 the combination of triclosan and zinc citrate will not
4 be reviewed at this meeting. Those submissions
5 concern foreign marketed ingredients that are not
6 included in the Subcommittee report and those will be
7 done separately.

8 There's a late addition to the agenda.
9 Dr. Clifford Whall of the American Dental Association
10 has asked to speak to this Subcommittee and has
11 submitted some brief comments.

12 This will be the final formal meeting of
13 the Subcommittee and in the next two days as much as
14 possible we're going to try to address all of the
15 comments that we've received. The comments include
16 some strictly format issues that won't change the
17 content of the report, so we're not going to deal with
18 those here in the interest of time. There are others
19 where there are suggested revisions that we can
20 discuss at the Chairman's discretion. In cases where
21 the comments are large or there's a missing or
22 incomplete information, Dr. Genco may make assignments
23 where we would work with the subcommittee, where the
24 Agency would work with the Subcommittee over the next
25 few months to finalize the document and there will be

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1 an additional -- as usual, there will an additional
2 comment period after publication of the Subcommittee
3 report.

4 And that's all for now.

5 DR. GENCO: Thank you. We'll begin with
6 a summary and review of the combination of zinc
7 chloride, sodium citrate, hydrogen peroxide, sodium
8 lauryl sulphate by Max Listgarten.

9 DR. LISTGARTEN: This report was presented
10 once before so I don't think I'm going to review the
11 entire report. However, at the time it was initially
12 reported there was some missing data which was
13 obtained since that time. The missing data concerned
14 safety considerations in experimental animals and one
15 additional clinical study.

16 What I'd like to do is just go over the
17 new material and review the conclusions which, by the
18 way, have not been changed as a result of the
19 submissions.

20 One of the animal studies consisted in the
21 topical application of the product to hamster cheek
22 pouches. Seventy-six hamsters were divided into three
23 groups with equal numbers of males and female animals
24 in each group. The test group received daily topical
25 applications of the mouth rinse to the cheek pouches

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1 for a 30-day period. The negative controls received
2 comparable applications of water. The positive
3 control group received 5 percent sodium lauryl
4 sulphate. An additional group of 10 animals received
5 Listerine and water. At the end of the 30-day period,
6 the cheek pouches were examined clinically and
7 histologically. The results of the study indicated no
8 evidence of mucosal irritation in the form of
9 epithelial damage, inflammation, hyperplasia, atrophy
10 or hyperkeratosis as compared to the water controls.

11 In another hamster study of 30 days
12 duration the author or the investigators compared
13 topical applications of prevention mouth rinse to
14 abraded and nonabraded hamster cheek pouches with
15 applications of 0.2 percent chlorhexadine gluconate,
16 1, 2 and 3 percent hydrogen peroxide, 5 percent sodium
17 lauryl sulphate and tap water. The animals on the
18 prevention mouth rinse gained weight normally and did
19 not demonstrate any evidence of mucosal irritation in
20 the form of inflammation, epithelial ulceration,
21 hyperplasia, atrophy or hyperkeratosis as compared to
22 the water controls.

23 The mouth rinse did not interfere with the
24 healing of abraded pouches.

25 In the additional clinical study that was

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1 submitted, 119 adults participated in a double blind
2 clinical trial. All subjects were fitted with a tooth
3 shield for either the right or left mandibular
4 quadrant that was designed to prevent tooth brushing
5 from disturbing plaque accumulation. All subjects
6 received an initial prophylaxis and were assigned to
7 one of three experimental groups, each of which
8 brushed their teeth except for the shielded quadrant
9 once a day and used a different mouth rinse
10 formulation twice a day for one minute. The final
11 examination took place after three weeks. One hundred
12 and two subjects successfully completed the trial.
13 Two rinses were variations of the two-phase system
14 formula used in the so-called perio and ortho
15 formulations. The third formulation was a control
16 rinse dispensed as a two-phase system.

17 The resultsshow no statistically
18 significant differences in gingival index scores or
19 bleeding sites among the three experimental regimens
20 either on the shielded or nonshielded teeth. Plaque
21 scores as measured by the Modified Turesky Plaque
22 Index were higher on shielded versus nonshielded
23 teeth. The plaque scores after three weeks were lower
24 for the two test rinses compared to the control rinse
25 for both the shielded and nonshielded teeth. However,

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1 the differences in plaque scores, while statistically
2 significant, were not clinically significant.

3 The results of this study indicate that
4 the test rinses had a marginal effect at best on
5 plaque reduction since plaque scores actually
6 increased for all groups on shielded teeth although
7 less so for the experimental rinses.

8 None of the tested rinses had any effect
9 on preventing the development of gingivitis.

10 The revised conclusions changed the
11 wording a little bit from the original one and I will
12 read the summary statement. The available data
13 indicate that the product is safe for use as a mouth
14 rinse and therefore it would be a Category I for
15 safety. The animal and clinical data fail to support
16 the claims made for this product and some of these are
17 listed in the indication section. Specifically, in
18 the indications for the use of this rinse, there are
19 statements to the effect that it's good for gingival
20 hemorrhage, puberty gingivitis, as a pre-treatment
21 rinse two weeks prior to periodontal treatment. I
22 don't think these indications are supported by the
23 clinical data.

24 Therefore, while the product may be
25 considered safe, it is not considered to be effective

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1 for the periodontal indications listed and for those
2 periodontal indications, the product would have to be
3 categorized as a Category III product.

4 DR. GENCO: Thank you, Dr. Listgarten.
5 Comments, questions about the report? Are we ready to
6 take a vote? Does anyone want to make a motion. On
7 safety first.

8 DR. LISTGARTEN: Can I make a motion?

9 DR. GENCO: Okay, safety.

10 DR. LISTGARTEN: For safety, the product
11 should be categorized as a Category I product.

12 DR. WU: Second.

13 DR. GENCO: Seconded. Comments?
14 Discussion? Okay, the voting members this morning.
15 Are myself, Dr. Bowen, Dr. Listgarten, Dr. Savitt, Dr.
16 Saxe, Dr. Wu and Dr. D'Agostino. So let's start at
17 that end of the table with Gene.

18 DR. SAVITT: Yes.

19 DR. WU: Yes.

20 DR. D'AGOSTINO: Yes.

21 DR. SAXE: Yes.

22 DR. GENCO: Yes.

23 DR. BOWEN: Yes.

24 DR. LISTGARTEN: Yes.

25 DR. GENCO: Okay, thank you.

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1 Effectiveness? Do I hear a motion?

2 DR. LISTGARTEN: For effectiveness, the
3 product should be categorized as a Category III
4 product.

5 DR. GENCO: Second?

6 DR. BOWEN: Second.

7 DR. GENCO: Bill Bowen seconds. Comments,
8 discussion? Yes.

9 DR. D'AGOSTINO: Can you just go over
10 again the notion of the statistical significance and
11 the clinical significance so that it's clear on why we
12 don't think the effect is large enough?

13 DR. LISTGARTEN: Can I help? If you look
14 at the report on page 5 --

15 DR. D'AGOSTINO: We don't have the report.

16 DR. LISTGARTEN: Oh, you don't have the
17 report. Okay, well let me give you some examples --
18 I'll read them out to you. I'm sorry you didn't get
19 the report.

20 I won't go over the gingivitis which was
21 not statistically significant, but let me give you
22 some examples of statistically significant differences
23 for plaque. On shielded teeth, using the test
24 material or using the control, for example, the
25 control went from a score of 2.15 to a score of 3.03

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1 with the standard error of 0.09 for both. One of the
2 test products went from 2.21 to 2.73 with a standard
3 error of 0.08 for both. The other test product went
4 from 2.14 to 2.61 with a standard error of 0.09 for
5 both.

6 And the data is similar for the
7 nonshielded teeth where the control went from 1.91 to
8 2.24 with a standard of error of 0.07 for baseline and
9 0.06 for the three week reporting. One of the test
10 products went from 1.95 to 1.76 with a standard error
11 of 0.07 for both. The other one went from 1.88 to
12 1.63 with a standard error of 0.08 for the first and
13 0.09 for the second reading.

14 While these may be statistically
15 significant, they're just -- it just doesn't make any
16 difference clinically.

17 DR. D'AGOSTINO: Thank you.

18 DR. GENCO: Okay, fine. Would anyone like
19 to see the report? We could make copies.

20 MR. CANCRO: Yes.

21 DR. GENCO: Would you? Yes, Bill?

22 DR. BOWEN: Max, could I ask you where was
23 that clinical study conducted?

24 DR. LISTGARTEN: I don't recall offhand.
25 It was submitted with the report, but I didn't make a

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1 note of that.

2 All I can tell you it was done in an
3 organization that specializes in doing trials of this
4 type.

5 MR. CANCRO: Max, the distribution of the
6 scores and you're obviously reading an average of 10
7 or 12 percent difference between two treatment groups,
8 as I can judge from what you've said, but the
9 distribution between scores that may well show -- I
10 don't know that they do or they don't, that you have
11 a number of zeroes which obviously don't change in
12 either direction and that you have a bigger reduction
13 on certain teeth. So is there any description of
14 basically that kind of a distribution? I mean the
15 average is one thing, but what might be of
16 significance quote, could be that when you look at the
17 plaque bearing teeth, they exhibit maybe a bigger
18 reduction than 10 percent and when you throw in the
19 zeros you --

20 DR. LISTGARTEN: The standard errors are
21 pretty small, so you're not dealing with crazy data.
22 I'll let Ralph answer that.

23 DR. D'AGOSTINO: I think that's true, but
24 the distribution may be important in terms of where
25 the -- sort of where the action is. The differences

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1 between the control and treatment aren't very
2 exciting, there's no doubt about that and the changes
3 don't sound, as you said, clinically meaningful, but
4 it would be nice to know what the data looks like. Do
5 we have the data?

6 DR. LISTGARTEN: I believe there is raw
7 data available in the reports.

8 DR. GENCO: Bill?

9 DR. LISTGARTEN: I also want to point out
10 that to be faithful to our original discussions, there
11 were absolutely no changes whatsoever in gingivitis
12 scores.

13 DR. BOWEN: Thanks, Bob. That was the
14 point I wanted to make.

15 DR. GENCO: Okay, we can wait for the data
16 for the vote, if you'd like, if you want to take
17 another look at it, anybody.

18 Were there longer studies? I think our
19 standard of evidence has been six months study.

20 DR. LISTGARTEN: The longest study was the
21 six weeks study.

22 DR. GENCO: Six weeks.

23 DR. LISTGARTEN: So there's basically two
24 studies, the six week study and the three week study.

25 DR. GENCO: And the three week study,

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1 okay, thank you.

2 Ralph?

3 DR. D'AGOSTINO: Just one more comment in
4 terms of the zeros. I think it would be interesting
5 to look at the data and the raw data may be available,
6 but nonetheless the analysis was on the means and
7 that's pretty much where we have to judge where the
8 statistical significance is coming from. It's pretty
9 hard to dissect out the individual distributions after
10 you have the means as the major efficacy variable.

11 DR. GENCO: Okay, take a few minutes and
12 look at the report, if you'd like, before we take a
13 vote.

14 DR. LISTGARTEN: The data I was describing
15 is on pages 5 and 6.

16 DR. GENCO: And on page 4, Max, is the
17 gingivitis --

18 DR. LISTGARTEN: Page 4 is the six week
19 study.

20 DR. GENCO: Six week gingivitis and
21 plaque.

22 DR. LISTGARTEN: Yes.

23 DR. GENCO: And there was no statistical
24 significance in the gingivitis.

25 DR. LISTGARTEN: That's correct.

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1 DR. GENCO: Lew?

2 MR. CANCRO: Is the -- on page 5, the
3 MPTI, is that a plaque index?

4 DR. LISTGARTEN: Yes. It's the modified
5 Turesky plaque index.

6 (Pause.)

7 Ralph?

8 DR. D'AGOSTINO: We've been fairly
9 consistent about the six months and types of studies
10 as opposed to these --

11 DR. GENCO: I think we have. Does anybody
12 know of anything that we have evaluated as effective
13 for gingivitis with no six month study or less than a
14 six month study? I don't think so.

15 Stan?

16 DR. SAXE: Well, I think this clearly
17 suggests with the limitation of the studies in terms,
18 as presented here, that a motion for a Category III is
19 in order.

20 DR. GENCO: Okay, further comments,
21 discussion? Has everybody had a chance to look at the
22 data?

23 Okay, let's start with Max for the vote.

24 DR. LISTGARTEN: What are we voting for?

25 DR. GENCO: Okay, we're voting for

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1 effectiveness Category III. You made the motion and
2 Bill seconded it. And we had the discussions.

3 DR. LISTGARTEN: Yes.

4 DR. BOWEN: Yes.

5 DR. GENCO: Yes.

6 DR. SAXE: Yes.

7 DR. D'AGOSTINO: Yes.

8 DR. WU: Yes.

9 DR. SAVITT: Yes.

10 DR. GENCO: Thank you. Okay, let's
11 proceed now to the open public hearing. This portion
12 of the meeting was open to all and two individuals
13 asked for time, Dr. Clifford Whall from the ADA and
14 Bill Soller from the NDMA. I ask Dr. Whall to make
15 his comments.

16 DR. WHALL: Thank you, Dr. Genco. Is this
17 mike on? Yes, it's on. Thank you.

18 I'd like to preface my comments by saying
19 that my comments are going to be on -- are not going
20 to be on the part of the monograph or the proposed
21 report that deals with the actual review of the active
22 ingredients. It's everything up to that part of the
23 report.

24 I'm here today to offer the ADA's
25 perspective on the Plaque Subcommittee's draft report

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1 to the FDA titled "Report on Over-the-counter Drug
2 Products for the Reduction or Prevention of Dental
3 Plaque and Gingivitis."

4 The ADA is making these comments because
5 it has the same goal as both the Subcommittee and the
6 FDA and that is to insure that products offered to the
7 public for the control of plaque and gingivitis are
8 safe and effective.

9 I addressed the Subcommittee at your first
10 meeting five years ago and at many meetings since then
11 to give you the benefit of the ADA's experience and
12 expertise for the evaluation of the safety and
13 efficacy of this class of drug products. The ADA has
14 this expertise and experience because of its own
15 rigorous evaluation of the these chemotherapeutic
16 plaque and gingivitis products since 1986 in the ADA
17 acceptance program.

18 Crucial to the ADA's ability to evaluate
19 both OTC and prescription plaque and gingivitis
20 products has been and continues to be the support and
21 assistance of many of you on the Subcommittee as well
22 as many of your peers in the dental, academic and
23 research communities.

24 In general, the ADA is very pleased with
25 the Subcommittee's draft report because in large part

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1 it espouses many of the same principles and
2 conclusions regarding evaluation of this category of
3 dental product that the ADA had arrived at previously.
4 These principles and conclusions are embodied in the
5 ADA's guidelines for the acceptance of
6 chemotherapeutic products for the control of
7 supragingival plaque and gingivitis first published in
8 1986 and then revised in September of 1997.

9 I provided these documents to Bob Sherman
10 or actually to you at several of your meetings earlier
11 and also I've given copies to Bob Sherman if you need
12 them today.

13 Let me briefly review some of the
14 important areas of agreement between the
15 Subcommittee's draft report and the ADA position. We
16 agree on the following basic principles. One,
17 products must demonstrate a significant benefit in
18 reducing or preventing gingivitis as a therapeutic
19 endpoint.

20 Two, because plaque is the etiologic agent
21 for gingivitis, plaque claims cannot be considered
22 cosmetic claims. Plaque claims for these types of
23 chemotherapeutic products are drug claims and products
24 that wish to make claims about reduction in plaque or
25 in plaque virulence or pathogenicity must also

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1 demonstrate that they cause significant reductions in
2 gingivitis.

3 Three, any reference to tartar will be
4 interpreted as a cosmetic claim because OTC products
5 that reduce tartar build up have not shown any effect
6 on gingivitis.

7 Four, clinical evaluations must use final
8 product formulations rather than just active agents
9 since inactive ingredients may alter active ingredient
10 activity.

11 Five, products with combination active
12 ingredients are acceptable as long as each component
13 contributes to the overall effect. Combinations of
14 anti-gingivitis agents with anticaries and tooth
15 desensitizing agents are rational.

16 Six, mechanical plaque removal by daily
17 brushing and interdental cleaning is the primary
18 method for maintaining good oral hygiene.
19 Chemotherapeutic products should be used primarily as
20 adjuncts if mechanical plaque removal is insufficient
21 to control gingivitis.

22 The Subcommittee and ADA also agree on the
23 specifics of what types of clinical studies should be
24 performed to adequately demonstrate safety and
25 efficacy of chemotherapeutic products that control

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1 plaque and gingivitis so that they can be classified
2 as Category I ingredients. These specifics include
3 the following. Product efficacy must be demonstrated
4 over a six month period in at least two independent
5 well-controlled clinical studies and effectiveness
6 shall be based on a comparison of the test product
7 versus the placebo control.

8 Two, it is necessary to demonstrate that
9 no opportunistic or pathogenic organisms proliferate
10 with long-term use and that would be six months or
11 longer, by conducting microbial studies of
12 representative oral microbes.

13 Three, in demonstrating product safety,
14 companies must adequately investigate adverse
15 reactions and untoward side effects including
16 irritation of soft oral tissues in humans.

17 Four, in demonstrating product safety,
18 companies must conduct a variety of acute and chronic
19 toxicological studies, including studying the
20 mutagenic and carcinogenic potential of their
21 products.

22 After the reviewing the draft Subcommittee
23 report, it is apparent that the main principles,
24 requirements and conclusions, especially those
25 detailed in Section H, general guidelines on safety

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1 and efficacy are the same as in the ADA guidelines.
2 This agreement supports the credibility of the ADA
3 acceptance program in its science-based evaluation of
4 the safety and efficacy of dental products.

5 Although the ADA is in agreement with most
6 of the Subcommittee's draft report, there are some
7 important areas that the ADA believes should be
8 modified for greater clarity and scientific accuracy.
9 Before highlighting some of these areas, however, I
10 would like to raise one area of nonscientific concern
11 about the report that the Subcommittee may wish to
12 address.

13 Nowhere in this report is any reference
14 made to the assistance provided by the ADA through the
15 testimony provided and the materials given to you at
16 many of the Subcommittee meetings, nor is any mention
17 made of the ADA guidelines being used as a basis for
18 many of the Subcommittee's recommendations, especially
19 in the area of requirements for safety and efficacy.

20 I hope the Subcommittee agrees that the
21 ADA testimony and guidelines were helpful and that
22 appropriate recognition of the ADA's lead in this area
23 should be made in the Subcommittee's final report to
24 the FDA.

25 I will now briefly highlight some of the

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1 ADA's suggestions for modifying the Subcommittee's
2 draft report. The full text of these comments is
3 presented in Appendix 1, in the back of this report.

4 On page 12 of the report in the definition
5 of gingivitis, it would be helpful to add that
6 "gingivitis is an early form of gum disease that is
7 often reversible with proper oral hygiene (that is,
8 daily brushing and interdental cleaning to remove
9 plaque) whereas periodontitis is a more advanced form
10 that must be treated by the dentist." This important
11 distinction between gingivitis and periodontitis
12 should be made early on to let the public know it can
13 generally control gingivitis.

14 On page 13 in the definition of
15 periodontitis, it would be helpful to add
16 "periodontitis is an advanced form of gum disease that
17 requires professional dental treatment."

18 And since true periodontal pocket depth
19 measured from the gingival margin is normally such an
20 important factor in recognizing periodontitis,
21 increased pocket depth should be included as one of
22 the characteristics of periodontitis.

23 Four, on page 14, the statement "plaque is
24 not easily removed" in the paragraph 3 on page 14 is
25 contrary to the health message that the ADA gives to

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1 the public and would tend to discourage the public
2 from even trying to remove plaque. A statement should
3 be added to the effect that plaque is a soft, sticky
4 substance that can be effectively removed by proper
5 daily brushing and interdental cleaning.

6 On page 18, it starts at the bottom of
7 page 18 and then goes to 19. In several places in the
8 section on drug cosmetic status of anti-plaque
9 products, the report limits discussion to mouth
10 washes. The Subcommittee has recognized two mouth
11 rinses and one toothpaste as being effective in
12 reducing gingivitis and it is conceivable that there
13 may be additional delivery systems, for example,
14 impregnated dental floss for Category I active
15 anti-plaque, anti-gingivitis products in the future.
16 Therefore, where reference is now made only to mouth
17 rinse, it is suggested that this be broadened to
18 something like mouth rinses, tooth pastes or other
19 active agent delivery systems.

20 Nine, on page 22 I have a general comment
21 about the use of mouth rinse versus mouth wash, the
22 word "mouth rinse" versus "mouth wash." In Section D
23 under indications in your report, the phrase
24 "anti-plaque oral rinse drug product" is used. In
25 Section B, under directions for use the phrase "OTC

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1 oral rinse drug products" is used. Both of these are
2 consistent with the ADA's classification of these
3 types of therapeutic anti-gingivitis products as mouth
4 rinses instead of mouth washes. The ADA believes that
5 the term "mouth wash" should be used to represent
6 cosmetic products. It is suggest that the term "mouth
7 rinse" be used throughout the document.

8 The one sentence on drug cosmetic status
9 of tartar control products, this is No. 10 on the
10 list, I've rewritten it a bit, now reads, "the
11 Subcommittee proposes that any reference to tartar
12 will be interpreted as a cosmetic claim." The ADA
13 suggests adding at the end "since none of the OTC
14 products marketed for reduction and tartar build up
15 have demonstrated a therapeutic effect on gingival
16 health."

17 Number 11, the directions for use, Section
18 B. This is an issue that's come up time and time
19 again. It says "dentist or doctor" and the ADA would
20 request that it be changed to dentist or physician
21 since dentists are also doctors.

22 Number 12, concerning your general
23 combination policy, it's not clear why the
24 Subcommittee is concerned about whether or not there
25 is a "significant target population that can benefit

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1 from the use of the combination." As long as the
2 combination is safe and effective and meets all the
3 other criteria, why should this matter? This is
4 really a market place issue rather than a scientific
5 issue and as such, the ADA recommends deleting this
6 statement for the same reason the ADA also recommends
7 deleting the statement, "if there is a significant
8 target population that suffers from the concurrent
9 systems" in paragraph 3 on page 24.

10 And number 13, testing of OTC
11 anti-gingivitis, anti-drug products. It's not clear
12 what a novel formulation refers to in the statement,
13 "the Subcommittee recommends that novel formulations
14 be required to demonstrate anti-gingivitis and
15 anti-plaque effectiveness by a single six month
16 clinical trial." This section discusses ingredients
17 that the Subcommittee has already classified as
18 Category I which would mean that most Category I
19 products would only need to satisfy the tests listed
20 that you have listed for each ingredient. It would be
21 helpful if the Subcommittee could expand on what makes
22 a product which incorporates one of these Category I
23 active ingredients a novel formulation requiring one
24 six month clinical study.

25 In closing, I'd like to say that the ADA

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1 congratulates the members of the Subcommittee on their
2 dedication and hard work and on the fine document that
3 they have produced for the FDA. Based on our past
4 interactions with these noted dental experts through
5 their assistance to the ADA acceptance program, we are
6 not surprised of the high quality of their work.

7 On behalf of the ADA, thank you for
8 allowing me to comment.

9 DR. GENCO: Thank you, Dr. Whall. Are
10 there any comments or questions of Dr. Whall?

11 Now we will get a chance to go through
12 those comments one by one shortly, but before you
13 leave I'd like to thank you for -- and the ADA for
14 thoughtful and very constructive help throughout these
15 deliberations and they've been very helpful to us.
16 Thank you.

17 DR. WHALL: Thank you.

18 DR. GENCO: I'd like now to ask Dr. Bill
19 Soller of the NDMA to give an overview of their draft
20 Committee report.

21 Dr. Soller?

22 DR. SOLLER: Thank you, Dr. Genco, members
23 of the Panel, I'm Bill Soller, Senior Vice President,
24 Director of Science and Technology for the
25 Nonprescription Drug Manufacturers Association, a

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1 117-year-old trade organization representing the
2 manufacturers and distributors of nonprescription
3 medicines and dietary supplements. And I'm here on
4 behalf of the NDMA CTFA Joint Oral Care Task Group
5 whose members belong to NDMA and/or CTFA. With me in
6 presenting the Task Group's comments is Dr. Patrice
7 Wright who is Director of Pharmacology and Toxicology
8 at NDMA in Science and Technology, and Betsy Anderson
9 is the other staff person at CTFA, a lawyer with CTFA.
10 She's helping us with the overheads, but from an
11 association standpoint this has been sort of the three
12 people that have been following you lo these five
13 years that you've been deliberating.

14 We've sent you detailed comments
15 concerning your draft report and these are in the blue
16 bound copies and I believe you all have copies of
17 that. What I'd like to first do is to turn your
18 attention to a letter that is addressed to you,
19 individually, in front of you on NDMA letterhead. It
20 concerns our appreciation for your Public Health
21 Service on behalf of the American consumer and I guess
22 with more foresight we would have gotten you a placque
23 for the Plaque Subcommittee rather than papyrus, but
24 the sentiment is the same. And it's addressed to each
25 of you as members of the Plaque Subcommittee. It's

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1 signed by NDMA President Jim Cope and it reads "your
2 service to the public health has significantly
3 contributed to even better oral health through
4 self-care with over-the-counter drug products and we,
5 the industry, most affected by your deliberations,
6 congratulate you on your efforts. While there were
7 issues about which we had different views, there were
8 many where we were of one mind. In either case,
9 however, science was at the cornerstone of our mutual
10 effort with data as the pivotal point in your
11 discussions and open dialogue as a facilitator of
12 information transfer between you and our regulatory
13 scientists. You have achieved much and should take
14 satisfaction in your effort." Signed, James D. Cope,
15 President of NDMA.

16 I know these sentiments are shared by the
17 Cosmetic, Toiletry and Fragrance Association and I
18 extend my personal thanks as well.

19 The second main point, this represents
20 your last meeting. It is a very significant one.
21 Just a little bit of history, one of you on the Panel
22 was at the last Panel meeting of the original 17
23 Panels, some 17 years ago and we were remarking about
24 that because I was presenting at that Panel meeting as
25 well as Ralph D'Agostino and Ralph, some things don't

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1 change. The first Panel meeting the audience is
2 packed and at the last one it gets a whole lot more
3 spare as the diehards remain after five years. But
4 don't take that as a signal. This is a very, very
5 significant meeting to us. Your decision on how you
6 finalize your Panel report is essentially one that
7 determines your legacy to the American public, to FDA
8 and to industry.

9 Now what do I mean by this, your legacy?
10 On one level, your final recommendations about the
11 ingredients that are generally recognized as safe and
12 effective for anti-plaque, anti-gingivitis purposes
13 and about which you are preparing the labeling and the
14 dosages and so on will be the basis for oral care
15 choices by the American public. On another level,
16 your detailed report on anti-plaque, anti-gingivitis
17 drug products will be the basis for future R & D in
18 the industry, for future product introductions and for
19 future FDA industry interactions. As a result the
20 scope, the character, the depth of your report is
21 vital.

22 So our plan this morning is to convey to
23 you why it's important for us to continue to work
24 together in this final stretch, so that your Panel
25 report is the best possible, the most complete record

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1 that it can be.

2 And I would say at the outset and I would
3 say this several times through that we're not asking
4 and we're not debating at this meeting final
5 recommendations. What we're talking about is the
6 scope, the character and the depth of your report and
7 how that is done.

8 I'll explain how, first, how the Panel
9 reports have been used and are important to industry.
10 Dr. Wright will provide selected highlights of our
11 detailed comments that we sent to you ahead of time
12 and then Mr. Cancro, as the industry liaison
13 representative is available as you go through page by
14 page to provide additional comment.

15 I will mention that the people on our Task
16 Group reflected a number of times in our prep meetings
17 that we got three weeks to comment. We are very
18 pleased and thank FDA that we got that time to comment
19 before you came to this meeting. But it is a
20 situation where some companies have had two overheads
21 and kind of go through, what they put up and what's in
22 the draft report, to make sure that even the numbers
23 are the same. And so it's a very serious process that
24 we take to make sure that it's accurate, that it is
25 complete, that what is said and was conveyed by

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1 industry, all that information appears in the
2 scientific didactic that you create to come to your
3 recommendations.

4 So the importance of the Panel report.
5 It's a vital, scientific regulatory document for FDA
6 and industry. It's literally the definition of the
7 regulatory disposition of products covered under the
8 OTC review as recognized as -- generally recognized as
9 safe and effective and that's important, obviously,
10 from a compliance standpoint, but those are really the
11 bottom line considerations. Is it Category I? What
12 are the actives? What is the labeling? What are the
13 dosages -- all the things that end up in the Code of
14 Federal Regulations. That is not what we're about
15 today. What we are about today as an industry is
16 everything that goes before that, that is the written
17 documentation of your thinking and that is in your
18 Panel report.

19 The Panel report serves as a written
20 synopsis of the many days of background work that you
21 as individual reviewers have put in and the days of
22 deliberations that you have had as a publicly held
23 Committee meeting. Each Panel report details the
24 Committee's scientific evaluation of the specific data
25 and when I say each Panel report I'm thinking of the

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1 other 17 Panels that went before you. Details the
2 Subcommittee's scientific evaluation of the specific
3 data submitted in support of various ingredients
4 reviewed by the Subcommittee so that all interested
5 parties may have insight as to the Subcommittee's
6 views about the strengths and the limitations and
7 weaknesses of the submitted data, thereby, being the
8 basis for the next four stages, really the next five
9 stages of the OTC review process, the next stage being
10 after the Panel report is published the post-proposed
11 monograph or post-Panel report public comment period,
12 the tentative final monograph, the post-tentative
13 final monograph public comment period, the final
14 monograph and yes, a fifth, amendments to the final
15 monograph that may occur as R & D goes on.

16 The Panel report provides the
17 Subcommittee's final recommendations on the regulatory
18 status of specific ingredients that has obviously
19 marketing consequences, but without a logical and
20 complete scientific critique of all of the underlying
21 data, a Panel's or Subcommittee's recommendations may
22 not be as likely to be adopted by the Agency and at a
23 minimum, if incomplete, is open to greater challenge.
24 We would like to see that avoided, obviously, to be
25 sure that all of your thinking is adequately

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1 documented in written form.

2 And years after the final meeting of the
3 Subcommittee, the Panel report serves as a detailed
4 basis on which advancements in science associated with
5 a product category can be judged. As a result, it's
6 very important that you, the Plaque Subcommittee,
7 carefully review your report, take the time that is
8 needed to insure that it is complete, it is accurate,
9 it flows logically, and with the purpose that I've
10 just articulated. Do not be rushed by anybody to come
11 to a report that you may not be fully satisfied with.

12 An example is worth considering here. In
13 July, July 8, 1977, a proposed monograph on internal
14 analgesics, antipyrets was published in the Federal
15 Register. Now the Panel reviewed about 15 principal
16 ingredients and they issued a report that was 148
17 Federal Register pages long which is substantially
18 longer than even the additions we put in with our
19 comments. Of note, is the detailed discussion on the
20 age breaks, the dosage schedule, the age breaks for
21 pediatric dosages. This was the subject of multiple
22 Panel meetings. It covers in the proposed monograph
23 three Federal Register pages documenting all the
24 important and relevant studies and data needed to
25 support the recommended schedule.

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1 Why was this important? About 11 years
2 later, June 20, 1988, FDA issued a request for
3 information stating its intention to consider issuing
4 a proposed rule on pediatric dosing. The purpose was
5 to rectify certain pediatric dosing recommendations of
6 the Cough/Cold Panels with those of the internal
7 analgesic Panels. They were different. And in
8 retrospect, the detailed, data driven, carefully
9 documented approach taken by the Internal Analgesic
10 Panel as shown in the recommendations to FDA in the
11 report is widely considered as being vital to the
12 resolution of this issue.

13 The point is the report must be complete.
14 It must contain detailed, scientific discussions of
15 the submitted data, literally, for posterity's sake.
16 We can't feign to know exactly how or why we will need
17 it, but what we can tell you is the industry that is
18 most affected by this process that our experience
19 tells us that we will need it.

20 With this in mind what I would like to do
21 turn the microphone over to Dr. Patrice Wright who
22 will highlight specific aspects of our report.

23 DR. WRIGHT: Thanks, Bill. Can everybody
24 hear me okay? Okay, is there a pointer up here?
25 Okay, good.

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1 As the individual responsible for
2 supplying you with an additional tome to carry around
3 to this meeting, I get the job of being the messenger
4 and I thought at first this morning when I was labeled
5 with this nice fuscia tag that that was the reason,
6 but I see some other people have that on too. So I
7 don't feel so bad.

8 What I'd like to do is briefly talk about
9 our concerns with the draft report and talk a little
10 bit about the process used to develop your conclusions
11 and how that really relates to our concerns with the
12 report and then go through some examples because this
13 report is really important to us. In my job, I really
14 do to this day go back even when we have final
15 monographs to some of the older Panel reports for the
16 other ingredients, the other categories, to learn why
17 some of the decisions were made as we get questions a
18 lot. So I think it really is an important document
19 and it must be as complete as possible which -- to
20 support your conclusions.

21 I think you saw from our comments that
22 it's no surprise that we do have some concerns
23 regarding the Panel report. What I'm going to do is
24 I'm actually going to take the slides in reverse order
25 and talk about our concerns and the time frame. You

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1 didn't have a very long period of time to go through
2 the document and neither did we. But given the short
3 period of time for review, our comments reflect
4 changes to correct and accurate information to
5 highlight missing information in the report and some
6 comments to improve the general format to make it more
7 user friendly.

8 Even though we have managed to come up
9 with over 100 spots in the document where we've made
10 comments, don't rely that that is the totality of what
11 our comments could be or interpret our comments as an
12 agreement with the substance and conclusions of what
13 is in the report.

14 What we used as the premise for making our
15 comments was just to make sure that the report was
16 complete and it included all the necessary
17 information, so our concerns with the draft report
18 are, in fact, that it is not a complete document. It
19 does not adequately support the Panel's conclusions
20 and that's not to say that information was not
21 available to support those conclusions or that those
22 conclusions were arbitrary. In fact, there was a long
23 process that happened to support those conclusions,
24 but the report does not reflect the totality of the
25 deliberations.

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1 Briefly, I'd just like to go through the
2 process by which this Subcommittee was able to draw
3 the conclusions that it did over the past five years.
4 Each step in this process resulted in some type of
5 information that was important to the ultimate
6 generation of the conclusions. And back in 1990, FDA
7 published in the Federal Register a call for data for
8 plaque and plaque ingredients making plaque and
9 plaque-related claims. And in response to that all
10 interested parties submitted information to FDA on the
11 ingredients to support the safety and effectiveness of
12 those ingredients. So after these submissions were
13 made, FDA constituted the Plaque Subcommittee and, as
14 you know, it started in 1993 and through the course of
15 those deliberations each Subcommittee member was
16 assigned an ingredient to review and review the
17 submitted information. You all received what I
18 understand are orange crates of information to look
19 at, to carefully review and to prepare a report of
20 what was submitted initially for the Subcommittee to
21 discuss.

22 At the meeting when these reports were
23 discussed there was usually an industry presentation
24 on the ingredient as well which talked about the
25 information that had been submitted, but also if there

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1 was new information available that was included at
2 that time. Then at that meeting there was an open
3 Panel discussion where concerns were discussed, issues
4 were raised and usually requests for additional
5 information was made by the Subcommittee. Then we
6 went back and did our homework. Industry did
7 research, conducted additional clinical studies,
8 provided additional reports and submitted that
9 information to the Panel. The Panel then went back,
10 at a subsequent meeting and deliberated on this
11 information and sometimes the result of Step No. 7 was
12 we went back to Step No. 6. But sometimes at the
13 result of Step No. 7, we went and were able, the Panel
14 was able to draw conclusions and a final vote.

15 Now I want to add that the conclusions
16 drawn in Step 8 were not always the same as the
17 initial review and that is as a result of this
18 additional interaction, deliberations and information
19 that happened between industry, all interested parties
20 and you, the Subcommittee. And it's these steps which
21 we believe are not captured in the report and it
22 should reflect these in a balanced manner so that your
23 conclusions can be supported.

24 I'm going to briefly hit two examples of
25 ingredients or issues that were reviewed by the

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1 Subcommittee. These are only two examples and I could
2 probably stay up here all day and provide additional
3 examples, but I don't know if we're going to do that
4 in the course of your deliberations.

5 The Subcommittee discussed the safety of
6 alcohol and mouth wash and if you look at page 52 of
7 the report that FDA gave you and if you're working
8 from our report on page 319, there are some
9 recommendations that are stated in the context of the
10 report and it's not really clear to us, in fact, that
11 these were ever really voted on by the Subcommittee
12 and are in fact actual recommendations of the
13 Subcommittee. They were presented by the initial
14 reviewers as recommendations which were subsequently
15 put into the process and information was generated and
16 discussions occurred and there was a subsequent
17 recommendation made. So that's something that needs
18 to be looked at.

19 In addition for alcohol, we had a workshop
20 in June of 1996 that was sponsored by FDA to talk
21 about purely the issue of alcohol, mouth wash and oral
22 cancer. A lot of people were invited to the meeting.
23 There were invited guests from academia, from NIH to
24 sit on the Panels and industry presented re-reviews of
25 analysis of epidemiologic studies and there's no

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1 mention of any of the reviews or any of the commentary
2 from the Panelists in the context of the report. And
3 by emitting this information, the scientific support
4 and knowledge for the conclusions is missing and the
5 Panel's report is weak and open to challenge.

6 The other example that I'd like to give is
7 where the safety of hydrogen peroxide was discussed.
8 On page 99 of the report that FDA had initially
9 provided to you the Subcommittee concludes and it's
10 stated that hydrogen peroxide is Category I for safety
11 and Category III for effectiveness which was the
12 appropriate conclusion.

13 In the context of the report that we have
14 now, there's 10 pages. A Committee member's review,
15 initial review was discussed and in the context of
16 that initial review, some safety concerns were raised.
17 We then again went back into the process and we
18 through the loop a couple of time son this one and to
19 address the safety concerns and there's no reference
20 to any of the input that was provided in the context
21 of the draft report. So what we have done is on page
22 168 of our comments, we've summarized the missing
23 information, briefly, as far as the studies that were
24 missing in the presentations that were made.

25 Another thing that we need to watch out

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1 for in the context of the Panel report are
2 inconsistencies. Page 99 and 109 of FDA's original
3 report, page 99 as cited above says hydrogen peroxide
4 is Category I for safety. Page 109 says that there's
5 a lack of information to classify it regarding safety.
6 So there are some inconsistencies that we need to also
7 have corrected.

8 Another example of how the process isn't
9 reflected in the context of the report is that when we
10 discuss hydrogen peroxide, after the initial review,
11 a Committee member raised some concerns about the
12 safety in special populations which we then again went
13 back into the process and went through the loops a
14 couple of times to address those safety concerns and
15 there's no reference to the industry presentations or
16 the Committee members' discussions in the context of
17 the report.

18 Here, I've got a summary chart of all of
19 the ingredients that you have reviewed. The hydrogen
20 peroxide and the alcohol mouth wash examples are only
21 examples. We could talk about stannous, we could talk
22 about essential oils. We could probably talk about
23 any one of these ingredients, but I think this listing
24 shows that there's a little bit, quite an amount of
25 work to be done to look at each of these ingredients

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1 and make sure that the whole process has been fully
2 reflected.

3 So to summarize, the Panel report should
4 reflect the entirety of the Panel's deliberations. If
5 the Panel's interpretation of the information is not
6 captured, it could be lost or misinterpreted. And
7 without substantiation of the Panel's conclusions,
8 they are likely to be challenged as unfounded during
9 the public comment period and I think you've all
10 worked way too hard to have that happen.

11 I'll turn the mike over to Bill.

12 DR. SOLLER: Thank you, Dr. Wright. Could
13 I have the first overhead, Betsy? Just to summarize
14 the reflection on the three weeks that we've had to
15 evaluate the draft report, and to recognize that our
16 comments represent examples of needed additions and
17 amendments to your draft report. The second point, as
18 you look to put some additional work into your draft
19 and it is needed, remember that we're not asking for
20 changes at this stage for the Panel's recommendation.
21 We are looking to make this as complete as possible.
22 It is your legacy and it's vital to the industry. We
23 request that Dr. Genco, as you look at it, that you
24 not send this on to the Agency until you're satisfied
25 as a Panel that it captures everything that you want

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1 it to capture.

2 The third point, FDA needs to define a
3 process on how this additional work will be done.
4 We're willing to participate further to provide that
5 additional input. We'd like to suggest recognizing
6 that it was an informal three week comment period and
7 we're very appreciative of that, that there would be
8 an additional limited time period that might be kept
9 open after this meeting. And in that process I think
10 it would be fair if FDA were to stipulate that you're
11 not looking for new data that might change
12 recommendations that are made, but rather, you're
13 looking for the kind of information that would insure
14 that the numbers that are quoted and so on are
15 accurate and that the deliberations that may have
16 taken place that are important to the history of what
17 you've done are accurately reflected in those
18 documents.

19 We are not looking to extend this process
20 out. We'd like it to be completed as expeditiously as
21 possible and what we are asking for is a limited time
22 frame and Dr. Genco, I'm sure that tomorrow as Mr.
23 Cancro reflects on the deliberations over today and
24 tomorrow that this question will be asked of you and
25 the Committee as well as to whether we might be able

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1 to have some additional time over the next several
2 weeks at the very least.

3 Now one other point here. And that is
4 that perhaps one of the best ways to think about this
5 as you go through page by page is the same framework
6 that we use for evaluating the completeness of the
7 report. First, are all the relevant data justifying
8 an ingredient status included and accurately
9 represented in the Subcommittee's report? Does the
10 report adequately document the scientific deductive
11 reasoning leading to the Panel's conclusions? This is
12 extremely important to insure that your report is not
13 open to unreasonable challenges.

14 Is the report formatted in a user-friendly
15 fashion? And just to comment here, what happens in
16 the process is if we identify typographicals or errors
17 in the numbers that are in the report, that will be
18 published in the Federal Register as a correction to
19 the Panel report. That could occur to a tentative
20 final monograph as well. If that happens more than
21 once, and it has in the past, that is a difficult
22 thing five years from now to go back and try and put
23 together multiple documents to be sure that what you
24 have as a report is, in fact, the accurate
25 representation of that. So it's worth the time to

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1 make sure that it is formatted in as a user-friendly
2 fashion as possible. Is it clearly written and then
3 based on 1, 2, 3 and 4 and 5, 4 is -- question 5, is
4 the report complete? Thank you. Slide off.

5 So in conclusion, we again thank you for
6 your efforts. We've pointed out how important a
7 detailed scientific elaboration of all your
8 recommendations is to the future interactions between
9 industry and FDA. We've given you specific areas.
10 Mr. Cancro is available for your page by page review
11 and remember, your Panel report on anti-plaque,
12 anti-gingivitis drug products is your public health
13 legacy and whatever time and effort that is needed to
14 insure that it is complete and to your satisfaction
15 should be taken to assure that it's useful,
16 user-friendly, complete for future scientists and
17 regulators. Thank you.

18 DR. GENCO: Thank you, Dr. Soller. Any
19 comments? Questions of Dr. Soller of a general
20 nature? Of course, we're going to go through the
21 specific comments in detail later. Thank you.

22 I'd like to take this opportunity to thank
23 you and Betsy and Patricia and all those at NDMA and
24 CTFA for their splendid efforts in interaction with
25 the Committee. I think you've been very thorough.

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1 You do have the perspective of industry and you have
2 as practitioners of the reality of the market place an
3 important context for us to function in, our products,
4 what we're dealing with, the products that are
5 targeted to the consumers. We appreciate your
6 information and your perspectives.

7 I'd like to thank you personally. Bill,
8 you've been a great help to us and always with a smile
9 on your face.

10 I'd like to read a letter from former
11 member of the Committee, Gerry McEwen, who is also
12 Vice President, Science for CTFA and he wrote and
13 said, "Dear Bob, I'm unable to attend the final
14 meeting of the Plaque Subcommittee due to competing
15 responsibilities. I'd appreciate it if you would pass
16 along my appreciation and best wishes for the future
17 to all of the members of the Committee and to the FDA
18 staff." He goes on to say, "I truly value the time I
19 spent with the Subcommittee. It was an interesting
20 and rewarding experience. I have a great deal of
21 respect for all of you and applaud the effort you
22 expended on this important project. Best regards,
23 Gerry."

24 With that I'd like now I think it would be
25 appropriate if we took about a 10 minute break. Let's

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1 back at 11 o'clock and we'll start going through the
2 comments in some detail. Thank you. Ten o'clock.

3 (Off the record.)

4 DR. GENCO: I ask you to please take your
5 seats and let's proceed.

6 Okay, the process that we suggest is the
7 following. This we all understand is a draft. And
8 like all drafts, it's not final. Our task at this
9 meeting and subsequent to this meeting will be to
10 finalize the draft and to make a final monograph.

11 As a report from this Committee and I
12 speak for everyone here, on the Committee, we want it
13 to be complete and accurate, clearly. And we want it
14 to reflect key essential data and discussion. So what
15 I'd like to do is to take the reports as they come,
16 have come to us in this order, the ADA report, Warner-
17 Lambert, Procter & Gamble and then NDMA report and go
18 over point by point. Certain issues will be readily
19 resolved, typographical errors, for example,
20 affiliations. Others may take more discussion.
21 Others may not get resolved in the next two days and
22 at that point we will assign a Committee member or two
23 to work with the FDA in resolving the draft on those
24 items.

25 There may be a situation where we'll need

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1 assistance from industry, NDMA, CTFA. We will
2 certainly consider those additional items that maybe
3 we request or maybe that are submitted to us. But I
4 think that our responsibility is to provide a report
5 to the FDA that we can be proud of in a timely
6 fashion, the time being five years plus maybe three
7 months, the three months being from now. The process,
8 I think, has gone on and in an appropriate fashion
9 with a lot of deliberation, but must come to this
10 point which is not an end. Obviously, there is much,
11 much more opportunity for everyone to comment.

12 So with that, I'd like to take the ADA
13 report that Dr. Whall gave us this morning and start
14 on page -- actually, he makes on -- it's not
15 paginated, but if you go one count, two, three, four,
16 five, it's actually the page before Appendix 1, Dr.
17 Whall was asking us to report -- that the report
18 should make reference to the ADA's contribution
19 assistance, give credit to the ADA and also give
20 credit to the ADA guidelines and I'd like to ask the
21 Panel what their feelings are on and including a
22 statement of appreciation, acknowledgment, both for
23 the assistance given during these five years and also
24 for the ADA guidelines for plaque and gingivitis
25 agents.

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1 Can the FDA give us any guidance along
2 those lines? Is there any --

3 MR. SHERMAN: You just might consider a
4 brief statement to acknowledge their assistance, a
5 thank you statement. That's up to you to come up
6 with.

7 DR. GENCO: Okay. Does anybody feel
8 uncomfortable with that? Gene?

9 DR. SAVITT: I for one found the ADA's
10 help in writing my report on hydrogen peroxide quite
11 useful, specifically in terms of consulting with their
12 toxicologist.

13 DR. GENCO: So the Panel then feels, would
14 like to acknowledge the help and assistance of the ADA
15 through these deliberations and also through reference
16 to their guidelines in the preparation of this report.
17 A statement like that. Reasonable? Okay.

18 Now the Appendix 1, item 1, page 5 and 6
19 is affiliations. Dr. Siew and Dr. Whall. Any
20 problems with it?

21 MR. SHERMAN: Bob, that's kind of a
22 standard format where just presenters are listed and
23 that's something that we'll consider, but we won't be
24 -- let's move on to --

25 DR. GENCO: Okay, No. 2, definition of

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1 gingivitis. Early form of gum disease that is often
2 reversible with proper oral hygiene. Perhaps it might
3 be important for the Panel to go to page 12 of the
4 original document to see what the original definition
5 is.

6 DR. SAVITT: I believe it's further on in
7 the report, 16 or 17.

8 DR. LISTGARTEN: It's on page 18.

9 DR. WHALL: So Cliff, these pages aren't
10 --

11 MR. SHERMAN: These are pages are as I
12 pulled them off the internet. I don't know if that
13 differed from the way it's paginated here, but it
14 looks to be 18 of the copy that we have. Does
15 everyone on the Subcommittee have a copy of the, of
16 our draft that was in dockets? Okay.

17 DR. GENCO: Okay, so let's compare the two
18 definitions.

19 (Pause.)

20 They've introduced the concept of
21 periodontitis in the definition of gingivitis. And
22 the rationale is to make that distinction early on.

23 I point out that on page 19 we have
24 redefined periodontitis, too. So the issue here is
25 really do we include the distinction between

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1 gingivitis and periodontitis in the definition of
2 gingivitis. What's your feeling? Gene?

3 DR. SAVITT: Well, I would suggest to
4 leave it out. I think it's cleaner the way it is.

5 DR. GENCO: Lew?

6 MR. CANCRO: Bob, I think the definition
7 as you originally captured it is very relevant to
8 gingivitis and drawing a distinction from
9 periodontitis you have already done when you talk
10 about periodontitis on page 19.

11 DR. GENCO: Okay.

12 MR. CANCRO: So I think the distinction
13 does exist.

14 DR. GENCO: Okay, does anybody disagree?
15 The consideration is to leave it as it is in the
16 original report, the definition of gingivitis.

17 Okay, let's proceed to the third comment
18 which will be on some page, not 13, but it's in the
19 definition of periodontitis which is on page 19. Add
20 "periodontitis is an advanced form of gum disease that
21 requires professional dental treatment."

22 Okay, so the definition as it stands on
23 page 19 of our report is straight forward. It should
24 be "a disease, condition of the periodontal
25 characterized by inflammation of the gingiva, the

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1 structure of the periodontal ligament and the adjacent
2 supporting bone."

3 What the ADA is suggesting is that we add
4 a statement that "periodontitis is an advanced form of
5 gum disease that requires professional dental
6 treatment."

7 Any comments? Bill?

8 DR. BOWEN: I don't think it's necessary
9 to define a disease by how it should be treated or by
10 whom. I think the existing definition is adequate.

11 DR. GENCO: Stan?

12 DR. SAXE: Yes. One, I agree with Bill in
13 the second statement. The other thing I wanted to say
14 was that it's a form of gum disease. I think our
15 definition is much more professional than the lay term
16 "gum disease."

17 DR. GENCO: Okay, the feeling is to leave
18 our definition as is with respect to that first
19 statement (a).

20 Okay, with respect to the second statement
21 the ADA would like us to add to that our definition
22 "true pocket depth" as another condition,
23 characterized by inflammation of the gingiva,
24 periodontal pocket depth, for example, add and
25 destruction of the bone, etcetera.

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1 What is your feeling on that to add true
2 -- or add periodontal pocket depth as the term is now
3 probing depth.

4 Max, you look ready to make a comment,
5 having coined the term "probing depth."

6 DR. LISTGARTEN: Well, I don't have any
7 objections in adding it.

8 DR. GENCO: Okay. So the consensus is to
9 add probing depth after inflammation of the gingiva.

10 DR. LISTGARTEN: You could add it by
11 saying inflammation of the gingiva, increasing probing
12 depth.

13 DR. GENCO: Okay.

14 DR. LISTGARTEN: And destruction.

15 DR. GENCO: Okay, thank you. Now the
16 fourth one is the statement "plaque is not easily
17 removed." So if their page 14 might translate to
18 maybe what, add about 5 or 6. 20, Stan says, begins
19 on page 20.

20 The statement "plaque is not easily
21 removed." I don't see it, do you? Oh, I see it.
22 It's on page 21, the third paragraph down. Is that
23 it? Thank you.

24 Okay, plaque is not easily removed, which
25 is in the third paragraph down, one, two, three,

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1 fourth line of the third paragraph. They're objecting
2 to that. They suggest that we leave that out. Or
3 substitute that plaque is a soft, sticky substance
4 that can be effectively removed by proper dental
5 brushing and interdental cleansing. So I would
6 envision that -- okay, that's the beginning of the
7 second line of that paragraph, third paragraph.
8 Because the matrix provides plaque organisms with
9 strong adhesive and cohesive properties, plaque is not
10 easily removed. We'd have to substitute that sentence
11 for the sentence they're suggesting. Plaque is a
12 soft, sticky substance that can be effectively removed
13 by proper daily brushing and interdental cleansing.
14 That's the substitution we're asked to consider.

15 Stan?

16 DR. SAXE: I believe when it says strong,
17 adhesive and cohesive properties could be a period.

18 DR. GENCO: Okay. Any -- Bill?

19 DR. BOWEN: The existing definition is
20 adequate. We do draw a distinction to this not
21 removed by flushing the mouth with water. And that's
22 an important part in defining or identifying plaque
23 from so-called debris. I think the definition is
24 again adequate. If we start defining it on how it can
25 be removed or not removed by brushing or interdental

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1 cleaning it's bringing a red herring into a
2 definition. That issue comes up much later when we're
3 examining the effective ingredients and guidelines and
4 so on. So I think the definition is adequate.

5 DR. SAVITT: I might suggest adding an
6 addition to after "it's not easily removed" to say
7 something like compared to removing debris or some
8 sort of reference to debris which is -- it's really a
9 comparison to debris that's being discussed here.

10 DR. GENCO: Is debris defined some place?
11 You mean materia alba?

12 DR. SAVITT: Yes, that's -- where is it?

13 DR. GENCO: Would you considering striking
14 "plaque is not easily removed" from the fourth
15 sentence and the issue that Bill brought up, it's not
16 removed by flushing the mouth with water would deal
17 with it, it would seem.

18 DR. SAVITT: I would tend to agree.
19 Actually, I am reading it. It's just discussed in the
20 next line and I would tend to agree with Bill --

21 DR. GENCO: Leave it?

22 DR. SAVITT: The difference is relevant.

23 DR. GENCO: Max?

24 DR. LISTGARTEN: Why don't we just leave
25 the two sentences we have as is and add an additional

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1 sentence saying dental plaque can be removed by proper
2 daily brushing and interdental cleansing.

3 DR. GENCO: Okay, is there agreement to
4 that?

5 Okay, so the paragraph, third paragraph
6 down stands, but has as an addition a rephrase of the
7 ADA plaque can be effectively removed by proper daily
8 brushing and interdental cleaning.

9 Okay? Bob, are you clear on that? Thank
10 you.

11 Let's proceed to their fifth comment which
12 would probably be -- let's see, it would be under
13 calculus, page -- is this page 22, Cliff? That's page
14 22, item 3. It says (3) calculus -- okay. "Calculus
15 is a hard concretion." All right.

16 The second sentence. Suggestion to modify
17 human calculus is essentially a mineralized dental
18 plaque. Oh, you want to add the term "non-vital"?
19 Sure. Right. "Mineralized, non-vital dental plaque."
20 Does everybody see that?

21 Okay, it's on page 22. There's an item 3.
22 Calculus. It's the last paragraph on page 22. It's
23 the second sentence, beginning "human calculus is
24 essentially mineralized dental plaque." They would
25 like to suggest, they suggest that we consider adding

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1 non-vital dental plaque. Mineralized and non-vital
2 dental plaque.

3 DR. LISTGARTEN: Is it really necessary?

4 DR. BOWEN: Take calculus, you can
5 consider the range of micro-organisms from it. To say
6 it's non-vital implies that it doesn't contain vital
7 micro-organisms. It clearly does.

8 DR. GENCO: The feeling is it wouldn't be
9 borne by the experiment, by the evidence. That it's
10 totally non-vital. Okay. Any other comments then?
11 So we don't include that.

12 By the way --

13 DR. LISTGARTEN: By saying, by qualifying
14 the statement saying that it's covered by vital dental
15 plaque it sort of suggests that it's not terribly
16 vital.

17 DR. GENCO: Everybody happy about that?
18 By the way, if there are duplicate or overlapping
19 comments from any of the other companies, would you
20 please let us know so we don't go over this again. I
21 mean we will know that, but if someone else has made
22 that comment, Procter & Gamble, NDMA, etcetera, please
23 let us know now so they won't duplicate it.

24 MR. CANCRO: Well, I'm sorry, Bob. There
25 were a few up front that we did have a comment.

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1 DR. GENCO: Were duplicate?

2 MR. CANCRO: May I suggest henceforth and
3 we'll go back to the few --

4 DR. GENCO: I'm sorry I didn't mention
5 that. Let's go back and --

6 MR. CANCRO: You want to catch them?

7 DR. GENCO: Sure.

8 MR. CANCRO: The one that comes to mind
9 and I'm sorry, it's going to be difficult for me to
10 find it in this manuscript is the visible symptoms of
11 gingivitis. And I don't quite know what page --

12 DR. GENCO: Page 18 is the definition of
13 gingivitis.

14 MR. CANCRO: Yes.

15 DR. GENCO: Take a minute and find it.

16 (Pause.)

17 MR. CANCRO: The issue here is
18 temperature. At the end of the sentence, "gingivitis
19 is characterized by tissue swelling and redness, loss
20 of stippling, glossy surface and increased tissue
21 temperature."

22 DR. GENCO: Right.

23 MR. CANCRO: I thought there was the word
24 "visual" but I sure don't see it at this point.

25 DR. GENCO: It's in another area? Okay.

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1 MR. CANCRO: It's in another area.

2 DR. GENCO: Let's proceed then. Is there
3 anything else we've gone over that you think is
4 overlap with comments that you're aware of?

5 MR. CANCRO: We --

6 DR. LISTGARTEN: Do you want typos at this
7 time?

8 DR. GENCO: I think typos will be taken
9 care of automatically. Suffice to say they're noted
10 and FDA will correct them. I don't think we have to
11 discuss them unless you have a correction of the typo
12 that's different than is suggested or changes the
13 meaning.

14 DR. LISTGARTEN: I mean there are
15 typographical errors in the draft.

16 DR. GENCO: Fine, so those will be taken
17 care of.

18 Lew?

19 MR. CANCRO: My view is that we have some
20 additional comments earlier that are best taken up
21 when we get to the other manuscript.

22 DR. GENCO: Fine, let's do that.

23 MR. CANCRO: Okay, we're up to the ADA
24 comment 6 which is page, probably would be 15, maybe
25 -- let's see, studies. We're talking about calculus

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1 and anti-tartar agents here.

2 DR. WHALL: It's the third paragraph under
3 calculus, suggesting adding a sentence at the end of
4 that third paragraph under calculus.

5 DR. GENCO: So that would be page 22 is
6 the first paragraph. Page 23 has the second
7 paragraph. It's the bottom of page 23, "calculus
8 facilitates the retention." Is that the paragraph?

9 DR. WHALL: "Calculus may form
10 subgingivally." It's the one before that.

11 DR. GENCO: Okay. That's the second
12 paragraph.

13 DR. WHALL: I'm sorry.

14 DR. GENCO: That's okay. This is very
15 helpful, Cliff. If you could kind of get a little
16 ahead of us and find out where this is in our draft.
17 Oh, you don't have our draft.

18 DR. WHALL: Oh, I can tell you where --
19 I'll give you some guidance in the land mine.

20 (Laughter.)

21 DR. GENCO: So we're on page 23 and it's
22 the second paragraph beginning "calculus may form
23 subgingivally" and ADA wants us to consider adding to
24 the end of that paragraph "however, studies that have
25 examined the effect of OTC anti-tartar products have

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1 not shown any therapeutic effect on gingival health."
2 Okay, I know we've dealt with that, but is it
3 important to put that here?

4 Lew?

5 MR. CANCRO: I think the statement is
6 entirely too broad. It assumes that we've really
7 looked at this in its entirety. I mean in this sense
8 it's just a hypothesis and while some of the studies
9 don't support that -- that statement is too broad. I
10 don't think it should be included.

11 Anybody else on the Panel want to discuss
12 that?

13 Lew? Gene?

14 DR. SAVITT: I think the placement is
15 wrong at the very least. If a sentence like that
16 would be included, it should go somewhere other than
17 in these definitions.

18 MR. CANCRO: I agree with Gene.

19 DR. GENCO: Cliff, do you want to keep
20 that in your mind or make a note of that when that
21 issue comes up again about the effectiveness of
22 anti-tartar agents relevant to gingivitis and let's
23 see if you're happy with the way it is or maybe we can
24 make a revision.

25 DR. WHALL: All right, we can do that.

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1 DR. GENCO: Thank you. Excuse me?

2 MS. FEDER: Dr. Genco, Marlene Feder from
3 Procter & Gamble. We have a process question. When
4 you asked people from the audience if there are
5 similar comments, do you want comments on similar
6 content or do you want to -- let's say you're dealing
7 now with the calculus definition section. If we have
8 additional comments that are somewhat different from
9 ADA's but are also on that section, do you want us to
10 bring those up at this time or do you want us to wait
11 until you're going through our body of comments?

12 DR. GENCO: No, I think it would be
13 helpful to bring them up at this time.

14 MS. FEDER: Okay, so you want to go
15 through a given section --

16 DR. GENCO: Right.

17 MS. FEDER: And deal with all the comments
18 on that section at the same time.

19 DR. GENCO: Right, and then when we come
20 to your report, if you'll remind us that we dealt with
21 that.

22 MS. FEDER: Okay. That's helpful. Thank
23 you.

24 DR. GENCO: Thank you. Do you have such
25 comments now about calculus?

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1 (Laughter.)

2 Okay, while they're getting their ideas
3 together, Bill?

4 DR. BOWEN: While I realize that the
5 purpose is to expedite the process, from a physical
6 point of view it's very difficult to put all the paper
7 out in front of us.

8 MR. SHERMAN: It may be better just run
9 through each one point by point. If it has been
10 covered, we can just say so. If there's an addition,
11 we can address it again.

12 DR. GENCO: I agree, I think what's
13 happened is the pages have gotten mixed up and we're
14 getting -- we could get confused. I don't think we
15 will, but it's possible. At least I had to take my
16 jacket off. It's getting hot up here.

17 Okay, last -- item 7. Last paragraph.

18 DR. WHALL: Okay, that's under gingivitis.
19 And it's actually the second paragraph under
20 gingivitis.

21 DR. GENCO: So that's page 24, "gingivitis
22 is a response to injury". Is that the paragraph?

23 DR. WHALL: That's correct.

24 DR. GENCO: Thank you. Okay, is everybody
25 on page 24, "gingivitis is a response to injury."

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1 What ADA is suggesting that the last sentence --

2 DR. WHALL: It's the third sentence.

3 "While all cases of periodontitis" --

4 DR. GENCO: Do you see it? It's the last

5 on page 24. "While all" -- flip to 25 --

6 "periodontitis", you would like us to

7 consider that while most cases --

8 DR. LISTGARTEN: Instead of all cases.

9 DR. GENCO: Well, all cases, yes. Any
10 objection to that?

11 Okay, so Bob, do you see that? It's the
12 last word on page 24, change "all" to "most."

13 MR. SHERMAN: Yes.

14 DR. GENCO: Next item, 8. Page 18.

15 DR. WHALL: Okay, that occurs under item
16 C, drug and cosmetic status and anti-plaque products.
17 And it's really -- whatever page that is. 31.

18 DR. GENCO: 31 did somebody say? Thank
19 you. Okay, drug cosmetics, cosmetic status.

20 DR. WHALL: The comment is basically you
21 refer only to mouthwashes and there are mouthwashes
22 and toothpastes and some other things.

23 DR. GENCO: Oh yes. Several have made
24 that comment. Well, let's deal with that now. I know
25 that NDMA made that comment and so did P & G. So

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1 could the representatives from P & G and NDMA and
2 anybody else make sure we get this right.

3 The issue here is to make this a general .
4 statement for anti-plaque, anti-gingivitis products,
5 rather than to talk about mouthwashes, mouth rinses.
6 Okay, so the first time it occurs is on page 31 under
7 anti-plaque products. The very first paragraph it
8 says "classification of mouthwash products." So this
9 should be anti-gingivitis, anti-plaque -- or
10 anti-plaque/anti-gingivitis.

11 Any objection to that? I know NDMA went
12 through this very carefully and so did Warner. And
13 that's the term you'd like? You've suggested
14 anti-plaque/anti-gingivitis. Okay, thank you.

15 Now is it the case that every time
16 mouthwash appears in this section on page 31, 32 we
17 would substitute anti-plaque/anti-gingivitis?

18 Bill?

19 DR. SOLLER: The meeting where you decided
20 anti-gingivitis/anti-plaque --

21 DR. GENCO: Yes, that's why I asked that.
22 It was anti-gingivitis/anti-plaque. And you agree to
23 that. Yes, that was Dr. Soller. Please use the
24 microphone, Bill.

25 DR. SOLLER: I was only reflecting that

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1 you had a discussion as to whether the
2 anti-plaque/anti-gingivitis, I think you came out
3 anti-gingivitis/anti-plaque.

4 DR. GENCO: Right. Everybody agree with
5 that? In other words, in this section wherever
6 mouthwash appears we substitute
7 anti-gingivitis/anti-plaque. Does that handle the ADA
8 comment here? Okay.

9 MS. BUCK: Mr. Chairman?

10 DR. GENCO: Yes.

11 MS. BUCK: I'm Nancy Buc, I represent
12 Pfizer, Inc. I think using the term
13 anti-plaque/anti-gingivitis products as an adjective
14 or as an adjective for products seriously confounds
15 the very issue that you're trying to decide in this
16 section and I would suggest substituting -- because
17 the whole question or one of the whole questions is
18 whether anti-plaque products are in fact anti-
19 gingivitis products. Without reopening the Panel's
20 determination, I think that using that combination to
21 modify the word "products" in this context where
22 you're asking that very question is going to have very
23 unfortunate consequences for the clarity of the
24 section. If I might suggest either using the term
25 "dentifrice" which is a term that FDA has repeatedly

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1 used for mouthwashes, pastes and powders, or simply
2 using some other term, some other collective noun that
3 doesn't inject into it the very issue you're trying to
4 decide, I think that the logic would be improved.

5 DR. GENCO: Let's look at that suggestion.
6 Dentifrice.

7 MS. BUC: Oral care products, dentifrices.

8 DR. GENCO: Dentifrice, doesn't that mean
9 toothpaste? Yes, in common vernacular --

10 MS. BUC: Not in FDA's regulations FDA's
11 cosmetic regulations in fact define it as powders,
12 pastes and rinses, I believe, something like that.
13 But oral care products --

14 DR. GENCO: It's confusing at least.

15 MS. BUC: Okay, oral care products would
16 be fine.

17 DR. GENCO: Oral care products could be
18 something to relieve apthos ulcer though. Do we want
19 to get that broad?

20 MS. BUC: I might suggest that in the
21 first paragraph and in most of the other ones that
22 I've been able to find quickly, simply using the word
23 "these products" since you're in this monograph would
24 work fine.

25 DR. GENCO: Okay.

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1 MS. BUC: And I think it would work in
2 many, if not all, of the further locations.

3 DR. GENCO: Okay, I think we have
4 direction here and we can come to some reasonable
5 final draft with these directions.

6 Do you agree? Okay. So we will find a
7 term that words, that's clear, accurate and
8 grammatical even. And we'll spell it correctly.

9 Okay, next comment is the ninth comment
10 from the ADA.

11 DR. WHALL: I listed page 22, but it's
12 really throughout the monograph and it's just using
13 the term mouth rinse instead of mouthwash.

14 DR. GENCO: Yes, I think we're advised.
15 Throughout the monograph to use this generic term,
16 whatever it is, oral care products or these products,
17 whatever works and is clear and accurate.

18 Okay, the next comment, 9, again, that's
19 the same comment, isn't it, pretty much?

20 You don't want -- you're suggesting not to
21 use mouthwash. When specifically one talks about the
22 rinses, to use the mouth rinse rather than wash.

23 DR. WHALL: I'm sorry, that's question 9?

24 DR. GENCO: That's 9.

25 DR. WHALL: Right, exactly.

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1 DR. GENCO: It's not the same comment, I'm
2 sorry. Okay, any objection to that? Does anybody
3 have problems with that? In other words, use the term
4 mouth rinse when the rinses are being discussed rather
5 than mouth wash. Does this make sense? The point is
6 that wash, mouthwash is cosmetic, mouthrinse is
7 therapeutic.

8 DR. LISTGARTEN: What if the mouth rinse
9 is not therapeutic?

10 DR. WHALL: Then you call it a mouthwash.

11 DR. GENCO: Is that a distinction that's
12 going to help make this clearer? Does anybody want to
13 make a comment from industry on that?

14 There's not a great level of support for
15 that.

16 Yes?

17 DR. SAXE: I think that mouthwash does
18 have inference of a cosmetic, a washing, while mouth
19 rinse is perhaps a little more neutral and could be
20 either therapeutic or not, could be either a drug or
21 a cosmetic. It's got a more neutral term.

22 DR. GENCO: So you would like to
23 substitute throughout the monograph, mouth rinse for
24 mouthwash?

25 DR. SAXE: Correct.

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1 DR. GENCO: Max's point is what if an
2 agent isn't really therapeutic and we're discussing it
3 in the monograph, shall we call it a wash?

4 DR. LISTGARTEN: No. The reason I raised
5 the issue, I don't think if you look up a definition
6 in Webster's dictionary for mouth rinse or mouthwash
7 that you're going to find that there's a difference.
8 They probably are synonymous. It's just in the mind
9 of some people it may make a difference, but I'm not
10 sure that you're going to actually find a definition
11 that will separate the two, as you suggest.

12 DR. GENCO: Lew and then Bill.

13 MR. CANCRO: I'd reinforce Max's thought
14 here. I mean this is very arbitrary to me, to declare
15 mouthwash as a cosmetic term for delivering something
16 and mouth rinse is a therapeutic term. It's just an
17 arbitrary thing.

18 DR. GENCO: Okay, for linguistic
19 consistency, would you like to stick with one
20 throughout the report?

21 DR. LISTGARTEN: Yes.

22 DR. GENCO: Which one?

23 DR. LISTGARTEN: Mouth rinse.

24 DR. GENCO: Rinse.

25 DR. LISTGARTEN: It's a little bit more

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1 professional.

2 DR. GENCO: Okay. Higher level. Our
3 legacy.

4 (Laughter.)

5 Okay, thank you. Number 10. Tartar
6 products.

7 DR. WHALL: That's item 2. It's just
8 called tartar products. It occurs right before your
9 section D, labeling of OTC drug products.

10 MR. CANCRO: Page 34.

11 DR. WHALL: Page 34. And it's just a
12 short sentence and the purpose was just to try to give
13 a reason for why you interpret it as a cosmetic claim.

14 DR. GENCO: Okay, the sentence reads "the
15 Subcommittee proposes that any reference to tartar
16 calculus will be interpreted as a cosmetic claim,
17 since none of the OTC products marketed for reduction
18 in tartar build up have demonstrated a therapeutic
19 benefit on gingival health."

20 DR. LISTGARTEN: No.

21 DR. GENCO: Add the phrase.

22 DR. LISTGARTEN: Absolutely not. That is
23 not the rationale for saying that.

24 DR. GENCO: Okay. Anybody have any
25 further comments?

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1 Let's go to 11. Oh yes.

2 MR. LEUSCH: Dr. Genco, Mark Leusch,
3 Procter & Gamble Company. In that section, you might
4 want to add some clarity including the word
5 "supragingival" for "tartar."

6 DR. GENCO: I think we're going to be
7 discussing that later. One of the issues I have with
8 that is that if you reduce gingivitis, subgingival
9 becomes supragingival and the distinction is really
10 not absolutely clear.

11 DR. LISTGARTEN: I think I would like to
12 go along with the suggestion because subgingival
13 calculus may, in fact, not be a cosmetic problem.
14 It's a health problem.

15 DR. GENCO: Okay, so --

16 DR. LISTGARTEN: I think that helps to
17 clarify.

18 DR. GENCO: To clarify. I'd agree with
19 that.

20 DR. LISTGARTEN: I think it clarifies and
21 I'd agree with that.

22 DR. GENCO: Any other comments? In other
23 words, to this sentence, the Subcommittee proposes
24 that any reference to tartar, then in the brackets
25 would be supragingival calculus.

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1 DR. LISTGARTEN: No, no, put supragingival
2 in front of tartar. Calculus is simply another way of
3 saying -- calculus is the more professional way of
4 saying tartar. Supragingival modifies both of them.
5 So it should read "reference to supragingival tartar
6 [calculus] or supragingival calculus [tartar]."

7 DR. GENCO: Okay, I think -- supragingival
8 calculus [tartar] -- is that a reasonable statement?
9 Okay.

10 Now let's go to comment 11 from the ADA.
11 It's under directions for use.

12 Have you found that, Cliff?

13 DR. WHALL: It's item 4, directions for
14 use, under the labeling section.

15 DR. GENCO: Okay, so -- that's going to be
16 on page 38.

17 DR. WHALL: It's in item B, Section B of
18 that section.

19 DR. GENCO: Okay, which is the last
20 paragraph on page 38.

21 DR. WHALL: And it's just the comment
22 instead of saying dentist and doctor, saying dentist
23 and physician because dentists are also doctors.

24 DR. GENCO: Yes, that would be on page 39,
25 fourth line and any other time that occurs.

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1 Any comments about that?

2 DR. SAVITT: I would suggest we make that
3 change.

4 DR. GENCO: Thank you. Okay, next is --

5 MR. SHERMAN: I'm sorry, could you repeat
6 that

7 DR. GENCO: Surely.

8 MR. SHERMAN: What was the decision on
9 that?

10 DR. GENCO: Okay, on page 39, whenever
11 dentist and physician are described, to use the term
12 physician rather than doctor. Dentist or doctor is --
13 raises the hackles of your average dentist. Dentist
14 or physician.

15 DR. LISTGARTEN: While we're on page 39,
16 could I just make a comment regarding paragraph A
17 where it says if you accidentally swallow more than
18 used for brushing, contact the Poison Control Center.
19 I think maybe "swallow more" is a bit too excessive.
20 I mean "several times more". I mean it's easy to
21 swallow a little bit more than you normally need for
22 brushing. That's not a cause for contacting a Poison
23 Control Center.

24 DR. GENCO: Any comments on that?

25 DR. WHALL: I think that's the phrase that

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1 the FDA is mandating on all sorts of products not and
2 to which we have officially objected, but that's what
3 they're now putting on all labels of fluoride
4 toothpaste and mouth rinses and everything.

5 DR. LISTGARTEN: Because it's easy to
6 swallow more. All you've got to do is just get
7 surprised and take an extra swallow.

8 MR. SHERMAN: This was the phrase that was
9 modified specifically for anticaries monograph. I
10 think that the general reg is in case of accidental
11 ingestion contact a Poison Control Center. It was
12 specifically modified in the anti-caries monograph to
13 this statement and you -- the Subcommittee at a
14 previous meeting accepted that. If you feel that you
15 want to change it, you can do that.

16 DR. GENCO: Anybody have strong feelings
17 about changing it besides Max?

18 DR. LISTGARTEN: I don't have strong
19 feelings. If this is something that's been discussed
20 before, I'll bow to it.

21 DR. GENCO: Okay. So we'll leave it as
22 is, then.

23 The next comment is page -- excuse me,
24 comment 12, general combination policy.

25 DR. WHALL: And that's under combination

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1 drug products E and the first item general
2 accommodation policy and in that first paragraph
3 subitem E there is significant target population that
4 can benefit from the use of the combination. You
5 stipulated a whole bunch of conditions that a product
6 must comply with and our concern was this was really
7 a marketplace issue, if there are a million people
8 that need it or 10,000 or 100,000. It's really up to
9 the manufacturer whether they want to make such a
10 product. It's not really a scientific issue.

11 DR. GENCO: Okay, this is now on page 41,
12 would be line 5E. "There is significant target
13 population can benefit from use of the combination."
14 Do you see that, page 41, item E, fourth line down,
15 fifth line down? ADA wants to strike that. I think
16 that we were -- yes, we were instructed by the
17 regulations to look at clinical significance as having
18 target population in mind. I think that's, as I
19 recall. We had some expert advice on that.

20 Okay. Item 13. Testing of OTC
21 anti-gingivitis/anti-plaque drug products.

22 DR. WHALL: That's the first paragraph.

23 DR. GENCO: Yes. Okay, that would be page
24 43, first paragraph. This is -- the term "novel
25 formulation." I think others have brought this up

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1 too. What is the term that one was suggesting here,
2 instead of novel? New? Different?

3 MR. CANCRO: No, I think, Bob, that this
4 really relates to a change in dosage form where you
5 identified, if that occurred, if you had a change in
6 dosage form, you'd need the six month trial. In terms
7 of the concept of novel or changed formulations, you
8 had the standards. That's the other part that you
9 indicated. So formulation change really in this
10 context is not what you mean. You're looking at a
11 dosage form change here. I think that's the way you
12 -- this thing evolved.

13 DR. GENCO: That term, "novel formulation"
14 is in the last sentence of that first paragraph on
15 page 43. "The Subcommittee recommendations that novel
16 formulations be required to demonstrate anti-
17 gingivitis/anti-plaque effectiveness by a single six
18 month trial."

19 So what is the term here that you're
20 suggesting? Not novel formulations, but new dosage?
21 I know you've dealt with this and it seemed logical.
22 What is it, Lew? Dosage forms?

23 MR. CANCRO: The Subcommittee, here's the
24 suggestion we're making. The Subcommittee recommends
25 that dosage form changes of ingredients at

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1 concentrations to achieve comparable dosage levels,
2 dose levels, you're required to demonstrate
3 anti-plaque/anti-gingivitis effectiveness by a single
4 six month trial. Now that relates it to a dosage form
5 change.

6 DR. GENCO: Okay, what if somebody --
7 dosage form means going from mouth rinse to
8 dentifrice.

9 MR. CANCRO: Right.

10 DR. GENCO: What is somebody changes the
11 mouth rinse formulation?

12 MR. CANCRO: That's a difference section,
13 Bob.

14 DR. GENCO: Okay, that's not dealt with
15 here.

16 MR. CANCRO: No, you're only here with
17 traditional dosage forms.

18 DR. GENCO: Is that clear and would you
19 agree with his suggestion?

20 DR. LISTGARTEN: I'm not clear on what it
21 means.

22 DR. GENCO: Okay. Go ahead.

23 MR. CANCRO: We're recommending that this
24 have the subpoint 1 and under that, the title would be
25 traditional dosage forms different from the standard

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1 product formulation so that this discussion then
2 relates specifically to a dosage form change. Where
3 you're changing the formula, where you're putting in
4 a flavor or you're changing some ingredient in the
5 formula, that goes under your testing principles for
6 the Category I ingredient.

7 DR. GENCO: Okay, so --

8 DR. LISTGARTEN: If you're going from a
9 mouth rinse to a dentifrice, aren't you changing
10 significantly the delivery method of your ingredients?

11 MR. CANCRO: Yes, you are.

12 DR. LISTGARTEN: And then isn't that a
13 significant change that should be tested clinically?

14 MR. CANCRO: That's what you're
15 recommending. That's exactly what you're
16 recommending.

17 DR. GENCO: I think I understand it.

18 DR. LISTGARTEN: I'm with you then.

19 DR. GENCO: Okay, good. On page 43 there
20 will be an F and under F there would be a dosage
21 formulation and then the last sentence, "The
22 Subcommittee recommends that" --

23 MR. CANCRO: "Dosage form changes of
24 ingredients at concentrations to achieve comparable
25 dose levels be required to demonstrate

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1 anti-gingivitis/anti-plaque effectiveness by a single
2 six month clinical test."

3 DR. GENCO: Now there will be another
4 section, you're saying, 2 or B, whatever it is.

5 MR. CANCRO: Yes.

6 DR. GENCO: Change in formulation of same
7 dosage form, mouth rinse with new flavor.

8 MR. CANCRO: And these are what you might
9 call formulation changes, whether you call them novel
10 or new or whatever, but they are formulation changes
11 in which the active does not change, but the formula
12 changes.

13 DR. GENCO: In which case, what is the
14 testing?

15 MR. CANCRO: It's different for the
16 different actives, but it's performance standards.

17 DR. GENCO: Right. Not a clinical trial.

18 MR. CANCRO: Right.

19 DR. GENCO: In other words, if somebody
20 comes up with another Cepacol mouth rinse, the
21 recommendation is that there not be -- as long as it's
22 bioequivalent --

23 MR. CANCRO: Correct.

24 DR. GENCO: And we've outlined that.
25 There not be the need for another clinical trial.

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1 That's really the issue here. I'm not so sure that we
2 agree to that.

3 MR. CANCRO: You use the word Cepacol,
4 it's the ingredients you're talking about, CPC.

5 DR. GENCO: Excuse me, cetylpyridinium
6 chloride.

7 DR. SAXE: I think here in this last
8 sentence, the last wording, "single six month clinical
9 trial" is written, I think the meaning was and we talk
10 about six months, that this is actually a randomized
11 control trial and I think that was the meaning of the
12 Subcommittee and I would certainly offer that. That
13 was our -- that was the intent and I would like to see
14 the wording, a single, six month randomized control
15 trial.

16 DR. GENCO: Okay.

17 DR. SAXE: So that's one issue. Now the
18 other issue is in this section we have another
19 subsection called change in formulation of the -- you
20 have that written out, I read it, of the same dosage
21 form, that is, cetylpyridinium chloride in another
22 formulation in a mouth rinse, then only
23 bioequivalence, based upon the various ex vivo, in
24 vivo tests is needed and not another six month trial.
25 It's a big, big --

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1 MR. CANCRO: Yes, and you actually spell
2 that out as you go through your ingredient review.
3 And what you propose is Category I and then the
4 testing you propose, so it's just to clarify why that
5 single six month trial, randomized, well-controlled
6 six month trial was being done. It's a dosage change.
7 That's what you intend.

8 DR. GENCO: So to clarify, Agent X in the
9 monograph is Category I. Category I for safety and
10 efficacy is in today a mouth rinse. Somebody wants to
11 put it into a dentifrice, a toothpaste, then the six
12 month trial applies. If they make another formulation
13 of Agent X in a mouth rinse, then a six month trial is
14 not needed, but bioequivalence, based upon in vivo, ex
15 vivo experiments are needed.

16 MR. CANCRO: That's the --

17 DR. GENCO: That's the intent. We'll make
18 the wording. Does that fit with other FDA regulations
19 for similar changes, Fred?

20 If somebody wanted to put Agent X that's
21 now through the drug -- through the PMA route for
22 over-the-counter, to change the dentifrice, let's say
23 with triclosan, would you require a six month trial in
24 a new dentifrice? I'm curious. Or would you require
25 only that it's bioequivalent.

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1 DR. HYMAN: Repeat the whole thing,
2 exactly, one more time.

3 DR. GENCO: Surely. There's another route
4 to get things on the over-the-counter market, another
5 agent, anti-gingivitis has taken that route in a
6 dentifrice.

7 DR. HYMAN: Right.

8 DR. GENCO: One formulation. What if
9 somebody wanted to make -- if they could, legally,
10 etcetera, another dentifrice formulation with that
11 agent, already approved by the FDA for over-the-
12 counter, would they need a six month trial or would
13 bioequivalence be adequate?

14 Maybe it's not relevant, but I'm curious.

15 MR. CANCRO: Bob, the difficulty I'm
16 having is obviously I'm managing three manuscripts
17 here and trying to add to this subject, but we created
18 under page 61 of the book we're going to go through,
19 the issue of testing of formulation changes and that's
20 spelled out here in this thing.

21 DR. GENCO: Right. I want to get that
22 principle, if everybody on the Committee, if we have
23 consensus that for change in formulation a six month
24 trial is needed, excuse me, for change in dosage form
25 a six month trial is needed. For change in

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1 formulation, only bioequivalence is needed. I want to
2 get that established. Then we can work on the wording
3 and where it goes in the document.

4 MR. CANCRO: Yeah, and I think you have to
5 spell out both of them. One is the testing of --

6 DR. GENCO: Right, we will do that. But
7 I want to make sure that everybody agrees to that.

8 DR. HYMAN: After conferring with my
9 colleagues, the answer is it's on a case by case
10 basis. There's really -- I can't give a general
11 answer to that.

12 DR. GENCO: That's interesting.

13 MR. CANCRO: You did deal with it on a
14 case by case basis.

15 DR. GENCO: I know.

16 MR. CANCRO: There are three Category I
17 agents. You've set the conditions under which they
18 can change dosage forms. You've also set the
19 conditions under which formulation changes can occur
20 for each of the three Category I materials. So you
21 have to do it on a case by case basis.

22 DR. GENCO: But you're asking us to do it
23 general, in a general way here. See, that's the
24 problem. Here's the general testing of OTC
25 anti-gingivitis, anti-drug products with the change in

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1 dosage form six month trial, then you're asking us to
2 add if it's only a change in formulation, no six month
3 trial. It's not case by case then.

4 MR. CANCRO: In the sense that the review
5 has at this juncture declared three Category I
6 ingredients of 19, but in the intervening years you
7 may well find several more of these things meeting the
8 standards you've set to become Category I in which
9 case why wouldn't the general principles apply for
10 formulation changes. I don't see why they wouldn't.
11 There would be performance tests or whatever the
12 manufacturer is recommending and that would be a
13 reasonable way to change color or change flavoring
14 agent, whatever the change would be.

15 DR. WRIGHT: And you do go through it,
16 ingredient by ingredient.

17 MR. CANCRO: Right.

18 DR. WRIGHT: In the following sections
19 under that. I mean for CPC this is what you have to
20 do. For stannous, this is what you have to do. So
21 it's not really leaving it open in general.

22 DR. GENCO: Well then why not put -- if
23 the general statement would be case by case for change
24 in formulation? Ex vivo, in vivo and possibly
25 clinical trial, case by case.

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1 MR. CANCRO: Well, it would mean somebody
2 would have to revisit the concept. In other words, if
3 you said we will look at this as each and every
4 ingredient comes in and then make the judgment whether
5 performance testing or no testing or six month test is
6 needed for formulation change, you are revisiting the
7 subject, not necessarily this Panel, but somebody has
8 then got to go back and say what's now Category I,
9 here's a formulation change and we don't have a
10 guideline.

11 DR. GENCO: No, the guideline is case by
12 case which is the guideline.

13 MR. CANCRO: Then who would basically make
14 that decision?

15 DR. GENCO: FDA. You would petition the
16 FDA. I'm painting a scenario. Mike?

17 DR. BARNETT: Dr. Mike Barnett,
18 Warner-Lambert. Bob, I think we ought to go back and
19 just maybe recall some of the discussions we had
20 several meetings ago when all of these things came up.
21 This whole question of how do you know that a change
22 in formulation is as effective as the originally
23 reviewed clinically tested product was really based on
24 precedent from previous monographs which had this
25 whole concept of final formulation testing and you

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1 recall that it was this Panel's intent that the test
2 that the suggested for each of the ingredients be
3 ingredient specific, not that the principle be done on
4 a case by case basis, but rather that the test be done
5 on a case by case basis.

6 With respect to the dosage delivery,
7 change in dosage form, if you recall I think the
8 rationale for asking for a six month trial under those
9 circumstances was based on the fact that because it's
10 a new dosage form, no previously clinically tested
11 standard in that dosage form exists, would exist
12 heretofore and therefore the first time that the
13 dosage form was changed, one ought to have at least
14 one six month study, one six month study and that once
15 it was established that you had an effective change in
16 dosage form, then one could ask the question what
17 shorter term final formulation test might be then
18 suggested with that dosage form?

19 So I think we're talking about two
20 different -- and the rational for the six month, was
21 that very specific circumstance when no pre-existing
22 standard formulation in that dosage form with those
23 ingredients existed.

24 DR. GENCO: So you've introduced a new
25 concept here, another concept, and that is the first

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1 time a dosage form is changed the six month trial, so
2 we ought to include that in here if we agree to that.

3 It's getting complicated now. We have two
4 issues on the table. One is the -- one issue is to
5 make it general that any time a formulation is
6 changed, that there's no need for clinical trial, ever
7 will be.

8 DR. BARNETT: Can I just talk about that?

9 DR. GENCO: Surely.

10 DR. BARNETT: I think we ought to define
11 six month clinical trial because some of the suggested
12 final formulation tests, if you recall, did involve a
13 clinical trial.

14 DR. GENCO: Okay.

15 DR. BARNETT: Much shorter term, though.

16 DR. GENCO: Yes, I know that, but if we --
17 we have to word this carefully. Let's work on the
18 wording. In other words, for formulation changes,
19 obviously, clinical changes are already in the
20 monograph, I thought so. So we don't want to word it
21 that way. We want to word it formulation changes be
22 in vitro and as needed, clinical.

23 Okay, I see a lot of agreement to that.

24 Bill?

25 So we can craft that language or use some

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1 suggestions.

2 DR. BOWEN: If we have an ingredient in
3 Category I, there are three there we've accepted in
4 principle profiles for modifications in formulation.
5 And are we not being inconsistent by asking for a six
6 month study when we say change from a mouthwash
7 formulation or a mouth rinse to be politically correct
8 to a toothpaste formulation or even a gel. Why would
9 not the profiles that we've accepted for Category I,
10 the three that we've accepted, why would that not
11 suffice? We came to this conclusion very early on in
12 our deliberation, before we got into specific
13 ingredients, as you will recall. I have a feeling,
14 initially, that we're being inconsistent.

15 DR. GENCO: What would you suggest then,
16 Bill? Do you have any problem with changing the
17 dosage formulation, that the six month randomized
18 control trial be necessary? Excuse me, the dosage,
19 yes, the dosage form. But what about the formulation
20 of not dosage form, changing one mouth rinse to
21 another mouth rinse?

22 DR. BOWEN: Then I presume we have to have
23 final formulation testing.

24 DR. GENCO: Right, but not to exclude
25 clinical testing in the case by case situation.

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1 DR. BOWEN: In the case by case situation.

2 DR. GENCO: So we'll craft -- is that
3 agreeable to everybody? All right, so we'll craft up
4 that language. Is that clear, Bob?

5 MR. SHERMAN: Okay, I think so.

6 DR. GENCO: This is -- on page 43, it's
7 sort of an overview of testing and so the overview
8 would cover all instances. Change in formulation --
9 excuse me, dosage form would require the six month
10 clinical trial. Michael Barnett brought up the point
11 this is the first time it's done, mouth rinse goes to
12 a dentifrice.

13 MR. SHERMAN: Okay, I think if there's a
14 different formulation of an accepted ingredient --

15 DR. GENCO: Right --

16 MR. SHERMAN: An accepted dosage form,
17 performance testing should cover that. If you're
18 talking about a new or novel dosage form that hasn't
19 been seen before, then you need the clinical trials.

20 DR. GENCO: Right, but we also said there
21 might be circumstances where you'd want clinical
22 testing on a change in formulation.

23 DR. WHITE: Pardon me, Mr. Chairman, in an
24 accepted dosage form, that isn't what we had -- what
25 you had agreed to. I thought that you agreed that you

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1 approved three -- pardon me, Donald White, Procter &
2 Gamble.

3 I think what we agreed to previously or
4 what we heard the Panel agree to is that three
5 Category I ingredients were approved in dosage forms
6 and it happened to be a toothpaste for stannous
7 fluoride and two mouth rinses for the others.

8 For changes in those formulations, the
9 testing which you folks approved was adequate. If you
10 change the dosage form of those three ingredients to
11 be anything what you approved, then you would need a
12 single six month double blind controlled trial and may
13 I make this suggestion, maybe one word takes care of
14 all of our problems here. Maybe in the sentence where
15 you say you're giving an introduction here as to what
16 the testing should be, maybe instead of calling it
17 traditional dosage forms, maybe what you mean to say
18 is the accepted dosage forms because that's what
19 you're essentially saying. You're saying formulation
20 testing can be used to qualify these ingredients in
21 the accepted dosage forms and then the next sentence
22 would read "the Subcommittee also recommends that new
23 dosage forms are permissible, however, they require a
24 six month double blind study." Maybe that would
25 completely clarify the section because you know that

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1 in the dosage form you've approved, you would use the
2 test and you know that if you go to a different dosage
3 form, you know exactly what the clinical requirement
4 would be. What does the Panel think of that as a
5 suggestion?

6 DR. GENCO: Okay, you've got two ideas
7 here. Maybe identify yourself for the record, please.

8 DR. WHITE: I did. Donald White, Procter
9 & Gamble.

10 DR. GENCO: Okay, thank you, Don. The
11 issue of the dosage form I don't think is what we're
12 really hung up on. I think it's making a generic
13 statement for the three products already approved and
14 any others that never in changing formulation would
15 you need a clinical trial. That's the problem. And
16 you brought that point up is the future.

17 DR. WHITE: But that is the monograph.
18 Anybody can make a sodium fluoride toothpaste, let's
19 say --

20 DR. GENCO: Right.

21 DR. WHITE: And all they have to do is
22 pass the monograph test, even if it's -- as long as
23 they have the accepted ingredients that can be -- and
24 they have the right concentration of active
25 ingredient, but anyone can make a toothpaste and it's

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1 sold under the monograph as an effective anticaries
2 products.

3 The same thing will be true for these
4 gingivitis products. Anybody can make a CPC rinse and
5 as long as they follow -- get the appropriate test
6 results for that rinse, that you folks have
7 established, and they can market that and make that
8 claim. If someone changes it to let's say a dental
9 floss, however, they would require a six month
10 clinical.

11 DR. GENCO: Does everybody agree with
12 that?

13 MR. CANCRO: I think just to add to that.
14 I mean the reality is that any time you have moved
15 into the Category I status, there is general
16 recognition that that ingredient is effective and
17 safe, so that if the form in which it's been
18 traditionally delivered changes, you have a rule for
19 that. It goes to a new form. You've got a clinical.
20 On the other hand, if the formula only changes by a
21 dint of some excipient ingredient, then the question
22 is what will you need to establish bioequivalency? In
23 the three ingredients you've reviewed, you've set that
24 course.

25 DR. GENCO: Okay. Gene and then bill.

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1 DR. SAVITT: I'd just make the comment
2 that when we discussed in the meeting before, maybe it
3 was two before, we came up with various final
4 formulation testing and one of the things that we did
5 at one of these last few meetings was to standardize
6 the final formulations because actually when we went
7 through them we recognized that there was variation
8 depending upon which particular ingredient we looked
9 at as to what was specified in final formulations and
10 after some discussion it was felt that it was
11 inappropriate to demand particular testing for a
12 certain product when we didn't require it for another
13 product. And in fact, it was utilizing the
14 discussions of individual products that led us to a
15 more universal overview of what we should do with
16 final formulations and I think my own view is that it
17 is appropriate to make it as a general statement for
18 Category I products.

19 DR. GENCO: Okay. Bill?

20 DR. SOLLER: Yes, Bill Soller, NDMA. On
21 this point, Dr. Genco, what I have observed in the
22 past Panels is that when there is a lightning rod that
23 is obviously identified in a report or a discussion,
24 sometimes that is referred to a subgroup. And I would
25 recommend on this issue because it is so important to

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1 our future R & D that you actually walk away from
2 these two days with the words exactly in your mind for
3 this particular section. And maybe it's Max and Bob
4 and Lew that could come back to this group at some
5 other point, either today or tomorrow and have
6 suggested wording.

7 This is too important a point as to say
8 we'll do it at some point in the future.

9 DR. GENCO: Thank you. Okay, let's
10 proceed with one decision anyway, and that is to take
11 that term "novel formulation" and to use a phrase
12 "dosage form."

13 Lew, do you want to read that again? At
14 least we can -- I think we can agree on that. The
15 issue isn't now --

16 MR. CANCRO: It's highlighted by the
17 heading which we think would clarify. Under F it
18 become point 1 and the heading would be "Traditional
19 dosage forms different from the standard product
20 formulation." That's the header.

21 DR. GENCO: Okay.

22 MR. CANCRO: And then the sentence "The
23 Subcommittee recommends that dosage form changes of
24 ingredients at concentrations to achieve comparable
25 dose levels be required to demonstrate

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1 anti-gingivitis/anti-plaque effectiveness by a single
2 six month clinical trial" and if Stan wants to put in
3 "well controlled randomized" that's fine.

4 DR. GENCO: Okay, is the Panel agreed on
5 that aspect?

6 Now is the Panel agreed also on the aspect
7 of the formulation change not require anything more
8 than bioequivalence? What's the Panel's feeling? For
9 the three agents we've discussed for which we have
10 unique bioequivalence assessment, no clinical trials
11 for those formulation changes, only bioequivalence as
12 we have defined them." Is that agreed?

13 Okay, furthermore, if that's agreed, need
14 that be part of this section?

15 DR. D'AGOSTINO: I thought the next
16 paragraph was doing that.

17 DR. GENCO: Yes, that's what I was going
18 to come up to. Need we change this any more because
19 it's there and furthermore it's in detail as each
20 product is discussed?

21 MR. CANCRO: It seems to me, Bob, that you
22 have a natural division here. You're labeling F as
23 testing of OTC anti-gingivitis/anti-plaque drug
24 products and then further you're subdividing that into
25 dosage forms and into formulation changes.

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1 DR. GENCO: So before the last paragraph
2 you'd like to insert B, formulation changes. Would
3 you agree with that, okay, for clarity?

4 DR. D'AGOSTINO: Yeah, I think the
5 confusion I had before, now it is that this is for the
6 formulation changes.

7 DR. GENCO: Right, okay. And the
8 subheading, in other words F would have an A and a B.
9 The A would be immediately after F, dosage forms, and
10 the B would be immediately after the six month
11 clinical trial prior to the last paragraph,
12 formulation changes.

13 Do you agree in principle? We can work
14 out the words, or have Bob work that out with Lew and
15 Max. I think that's a good suggestion.

16 MR. SHERMAN: You can look at NDMA's page
17 61. It's laid out for you.

18 DR. GENCO: Okay, good.

19 MR. SHERMAN: In their blue binder. 61.
20 Page 61.

21 DR. WRIGHT: Page 61, it lists the F and
22 then it goes down and it sets out -- F.1 the
23 traditional form dosage changes and inserts the
24 sentence Lew mentioned and then goes and inserts the
25 section 2.

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1 MR. CANCRO: If you look at page 61 --

2 DR. WRIGHT: So it's divisional.

3 MR. CANCRO: It gives you that division.

4 It starts on line 17 as the first division and then on
5 line 4 of page 62 is the second aspect of testing.

6 DR. GENCO: Okay, is everybody on the
7 Panel got 61 and 62 and do you -- what are your
8 feelings about those recommendations? It's a change
9 in the structure and some of the words are changed.

10 DR. D'AGOSTINO: Well, I think the
11 formulation identification is important. I'm not so
12 sure that the substantial equivalence, changing the 80
13 percent to substantial equivalence is a problem.

14 DR. GENCO: You would recommend not
15 changing that. That's line 11 on page 62 of the NDMA,
16 11 and 12. You would not want to strike that.

17 DR. D'AGOSTINO: I mean it's the usual
18 statement.

19 DR. GENCO: It's the usual. Any other
20 comments with respect to page 62 up to line 17?

21 MR. CANCRO: May I make a comment? Ralph,
22 I think the thought here was that when you're doing
23 microbiological tests that this particular 80 percent
24 with 95 percent confidence limits may not be
25 appropriate in the sense that you're dealing with a

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1 lot of changes and the statistics you use could be
2 different.

3 DR. D'AGOSTINO: Yeah, I took it, maybe I
4 was wrong, I took it as a for example, this is what
5 people usually do with something like that. But it's
6 the equivalence notion that's important that you want
7 to show equivalence.

8 DR. GENCO: Would it work to add for
9 example 80 percent with a 95 percent confidence?

10 DR. D'AGOSTINO: That's again where I was
11 coming from.

12 MR. CANCRO: Well --

13 DR. D'AGOSTINO: The important point is
14 that it's the -- the important thing is it's the
15 formulation you're talking about and you're not doing
16 other clinical trials. You're getting at the
17 bioequivalence aspect. And I certainly don't want to
18 get hung up on the 80 percent hypothetical comment.

19 DR. GENCO: So striking it would not be a
20 problem. Okay.

21 Yes, Bob?

22 MR. SHERMAN: Excuse me, could we possibly
23 revisit that as we go through NDMA's comments in
24 detail and just for this discussion see if you accept
25 their proposal of the separate sections?

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1 DR. GENCO: Okay, good.

2 MR. SHERMAN: And we can deal with the
3 wording later. Is that --

4 DR. GENCO: All right, good. Separate
5 sections and --

6 MR. SHERMAN: You know, as in their
7 section 1 and 2 under F. Are those reasonable. And
8 the change in the wording in the first sentence, at
9 the bottom of NDMA's page 61.

10 DR. GENCO: Any comments from the Panel on
11 that? You're pretty much agreed and we'll revisit the
12 80 percent and 95 percent.

13 Fred?

14 DR. HYMAN: I actually just wanted to jump
15 in here and make a comment. The question you had asked
16 earlier it was hard to answer because at first the NDA
17 process is obviously very different than this.

18 DR. GENCO: I know.

19 DR. HYMAN: And at first I thought what
20 you were getting at is what kind of minor formulation
21 changes would require, whatever. I want to answer it
22 in a better way now that I've heard more of the
23 discussion.

24 For the NDA process and I think the
25 example you were alluding to was Colgate's triclosan

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1 toothpaste, so it's a similar type product. Because
2 the NDA's are reviewed on an individual basis, if
3 another product which is not being covered in this
4 monograph whose active ingredient is not being covered
5 were to come in, if it were a different dosage form,
6 i.e., a rinse versus a paste versus a chewing gum,
7 whatever, it would have to come in as an entirely new
8 NDA. We'd have to review the usual clinical trials.

9 If it were a minor formulation change of
10 an existing product, that would be done on a case by
11 case basis, depending on how minor that change is and
12 obviously as has been discussed, the past monographs
13 have given ways of looking at bioequivalence which
14 handles those kind of things. So I hope that helps.

15 DR. GENCO: Thank you. I think it does.
16 I think that perspective is good for us.

17 Okay, then pretty much the Panel is in
18 consensus to agree to the two subcategories under F,
19 1 and 2, and we'll revisit the 80 percent, 95 percent.

20 Okay, thank you.

21 I think that finishes the -- wait a
22 minute. Yes, that completes the ADA comments. Cliff,
23 do you want to make any further --

24 DR. WHALL: No, just thank you for
25 considering our comments.

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1 DR. GENCO: Thank you for presenting them.

2 Okay, we have approximately 35 minutes
3 before noon. Let's start the Warner-Lambert which is
4 a two-page list of comments.

5 Is there more, do I have everything, do we
6 have everything from Warner-Lambert? Two pages? Is
7 that -- okay, fine, thank you.

8 MR. SHERMAN: Right, as I understand it,
9 the rest of their comments would be covered under the
10 --

11 DR. GENCO: Okay, so this is a letter from
12 Jack Vincent.

13 DR. BARNETT: We can go through those. I
14 just have two additional comments to make in addition
15 to those, but we might want to consider those because
16 one of them, the first one actually relates very
17 directly to the discussion you've just been having
18 about the criteria formulation test --

19 DR. GENCO: That's one of your additional
20 comments?

21 DR. BARNETT: No, no. That's the one you
22 have there, Bob.

23 DR. GENCO: Okay.

24 DR. BARNETT: Two of the ones we submitted
25 in that letter pertain directly to the discussion

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1 you've just begun.

2 DR. GENCO: Oh, I see. Let's see. On the
3 first page there's general criteria for formulation
4 comparability. That's one of them.

5 Now how are we doing with respect to your
6 question here?

7 (Laughter.)

8 DR. BARNETT: Actually, not bad.

9 DR. GENCO: Good.

10 (Laughter.)

11 DR. BARNETT: The first point we made had
12 to do with this whole discussion about the 80 percent
13 and it really stemmed from a discussion that we all
14 had toward the end of the last meeting when Bob
15 Sherman had presented some overheads for these
16 criteria. And I think the point I made at that time
17 was that because the various, the individual tests
18 that have been proposed and accepted for each of the
19 ingredients individually are so diverse, then one
20 criterion such as this might not fit all and therefore
21 the criteria for comparability or equivalence and I
22 guess comparability may be a better term here, ought
23 to be specific for each of the tests, so as I think
24 Lew pointed out, a microbiological test might require
25 different criteria from this. So one of the

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1 suggestions we made, we made two suggestions with
2 regard to that statement in brackets. One is that it
3 be deleted entirely or the other which had been
4 suggested, I think, by somebody here earlier, was that
5 the words "for example" be placed prior to those.

6 DR. GENCO: Okay, maybe we can discuss
7 that now.

8 Bob, you wanted to defer it, but this
9 might be a good time to resolve that.

10 MR. SHERMAN: We can resolve that.

11 DR. GENCO: Okay. Ralph, do you have --

12 DR. D'AGOSTINO: I don't have strong
13 feelings one way or the other, but I think the far
14 example, then sort of brings you to something
15 specific, but you don't want to limit it to that.

16 DR. GENCO: So it's clear 80 percent, 95
17 percent where appropriate and the "for example" helps
18 that.

19 What does the rest of the Panel feel about
20 that?

21 In other words, we put --

22 DR. LISTGARTEN: Well, it seems to me that
23 there may be some other statistical analyses that may
24 be quite different for different types of variables.
25 I mean you may not necessarily want this type of an

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1 analysis.

2 DR. D'AGOSTINO: Well, that's why I was
3 saying the "for example". The point is you want to
4 show equivalency with the new formulation. You want
5 to beat out the negative control and so you're saying
6 --

7 DR. LISTGARTEN: Somebody mentioned micro
8 organisms. That's a good example. You're going to
9 get such tremendous variation in recovery of micro
10 organisms. You're going to have a lot of zeros and
11 some way out very high levels. There's got to be some
12 other way to look at this.

13 DR. GENCO: Well, I would think that the
14 "for example" would cover that, but many of the
15 bioequivalencies are chemical, extract into HPLC and
16 there you can apply the 80 percent, 95 percent.

17 DR. LISTGARTEN: I don't have a problem
18 with "for example."

19 DR. GENCO: Okay.

20 DR. LISTGARTEN: Which page is that on
21 again?

22 DR. GENCO: Okay, on our copy it's page
23 43.

24 MR. SHERMAN: It's on the last line on
25 page 43.

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1 DR. GENCO: Do you see it at the bottom of
2 the page? It says "for a product to be considered
3 effective, it must demonstrate that it is
4 statistically substantially equivalent." Ralph's
5 point is that's the operative term. But, for example,
6 80 percent, add the "for example", 80 percent with a
7 95 percent confidence interval to give some clarity
8 and direction to what substantially equivalent means
9 when you can apply that test.

10 DR. SOLLER: Dr. Genco, Bill Soller. I've
11 seen "for examples" in regulatory documents
12 interpreted as verbatim and our preference is to have
13 it out. But if you do have it in, then I would
14 suggest that it's "for example" but not necessarily
15 limited to.

16 DR. GENCO: I think that's the intent.

17 DR. SOLLER: And then put "etcetera".

18 DR. GENCO: Yes, thank you.

19 DR. SOLLER: And that would clearly show
20 that that's not necessarily the standard.

21 DR. GENCO: Any problem with that? The
22 alternative is to strike it.

23 DR. LISTGARTEN: I don't think it helps,
24 particularly, to have the example.

25 DR. GENCO: You would argue to strike it.

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1 DR. LISTGARTEN: I mean if the example is
2 not a requirement, then it doesn't help to have it.

3 DR. GENCO: Okay. And is this kind of
4 well-known in the field?

5 DR. D'AGOSTINO: Yes, the term
6 "equivalent" is the important term.

7 DR. GENCO: Yes. So you would not object
8 to striking it?

9 DR. D'AGOSTINO: No.

10 DR. GENCO: Okay, so does anybody on the
11 Panel have strong feelings about striking it? Would
12 not like to strike it, think it should be there,
13 qualified. So there is sentiment to strike it.

14 Yes, Mike? You're getting tired of
15 sitting?

16 (Laughter.)

17 Okay, second point. Criteria for
18 comparability of mouth rinse formulations with the
19 fixed combination of essential oils. Section F.3.

20 Does anybody have that page? 45? Okay,
21 it's page 45. Oh yes, okay. It's about in the middle
22 of the page, 3, fixed combination, etcetera. All
23 right. The suggestion here is to insert or -- okay,
24 at the conclusion of 3a which is the paragraph, fourth
25 paragraph on the page, the paragraph ends with "an

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1 initial inoculum of 1 percent transmission should be
2 used" and the suggestion is to insert a sentence that
3 says, "a new mouth rinse formulation will be
4 considered comparable to the clinically tested
5 standard formulation if there is no greater than .25
6 log difference in CFU per milliliter for each of the
7 test organisms when compared to the clinically
8 positive control," etcetera. You can read that.

9 What is the Panel's feelings? That really
10 spells it out in some detail.

11 Gene? No harm in spelling it out, are you
12 comfortable with that?

13 Max?

14 DR. LISTGARTEN: How did you come up these
15 details?

16 DR. BARNETT: These actually had been
17 presented in our initial submission when we included
18 these testings. And unfortunately, our
19 microbiologist, Pauline Pan, isn't here, but there was
20 a rationale for the .25. And it was based on some
21 precedent for antiseptic testing. I can get that
22 information for you. I just don't recall the
23 publication offhand.

24 DR. LISTGARTEN: This basically
25 corresponds to your testing criteria?

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1 DR. BARNETT: Right, right. In both these
2 suggestions the criteria -- the intent was if we're
3 taking out the 80 percent, whatever percent which may
4 not be applicable to the various tests, then we
5 provide at least criteria for each of the individual
6 tests and so what I've proposed here are fundamentally
7 the same criteria that were included in our submission
8 the first time around regarding the final formulation
9 testing.

10 DR. GENCO: Now we're proscribing actual
11 differences that may vary with the laboratory though
12 and Ralph's point is substantially -- statistically
13 substantially equivalent. It might be in another
14 laboratory, .25 logs is not the value. It might be
15 .30. So should we get this detail?

16 DR. D'AGOSTINO: If we follow the notion
17 that maybe we don't want to be that specific, we can
18 get very, very specific here. I realize we're on a
19 particular sort of combination of product, or
20 ingredients, but it's very, very specific.

21 DR. GENCO: Now the variability in another
22 laboratory may be greater than your laboratory and .3
23 might be the difference that's not statistically
24 different.

25 One could argue to leave this at

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1 statistically substantially equivalent which then
2 would be up to the laboratory to document.

3 DR. BARNETT: Yeah, I guess Max could
4 answer this better than I. He's a microbiologist and
5 a couple of others. But I guess the question is if
6 you're looking at comparable activity of formulations
7 would this carry over from laboratory to laboratory
8 and account for the variability?

9 DR. LISTGARTEN: Well, I agree with Bob
10 that different labs may have different results and
11 that keeping it general and just saying that it has to
12 be statistically equivalent is what I would prefer
13 because there may be differences among laboratories.
14 This is very specific to your lab.

15 DR. GENCO: And it might be a particular
16 strain and the fifth passage versus the tenth passage.
17 It might not have anything to do with the laboratory,
18 but with the strain, so these things are hard to --

19 DR. BARNETT: Again, I'll just reiterate
20 and unfortunately I don't have the reference here, but
21 the .25 was not an arbitrary number. It was selected
22 from a handbook for microbiologic testing and so there
23 was some rationale for selecting that and I'm not sure
24 then that it was specific to our lab. I think we took
25 that because there was a rationale for taking a .25

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1 log difference that was said in precedent that was not
2 ours.

3 DR. LISTGARTEN: But if I wanted to
4 develop a new product and I decided I was going to use
5 Listerine as my control and I couldn't find anything
6 provided there was enough power to the experiment, for
7 example, 80 percent --

8 (Laughter.)

9 -- and found no substantial difference, I
10 think I would feel much more comfortable simply
11 including Listerine as the appropriate control than
12 trying to duplicate what another laboratory is
13 getting. I think that's probably a much more practical
14 way of going about it.

15 DR. GENCO: Any objection to that? In
16 other words, the feeling I get is that there's no
17 interest to include that kind of specificity and that
18 it's covered by substantially statistically
19 significant.

20 Yes, Bill?

21 DR. BOWEN: From a statistical point of
22 view, what is meant by statistically substantially
23 equivalent?

24 DR. LISTGARTEN: Eighty percent power.

25 DR. BOWEN: I'm getting a little --

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1 DR. D'AGOSTINO: Well, in the
2 bioequivalency, you know the rate of how much is in
3 the blood how much is removed. It depends on looking
4 at generic drugs versus standard drugs. I mean both
5 things are considered one at a time and things like
6 the bioequivalency with the confidence intervals, as
7 long as what's present in the blood or whatever the
8 peak flow is and what have you, the area under the
9 curve is within 20 percent of each other, that's
10 considered equivalent. There's a whole literature on
11 bioequivalency and that's what we're basically
12 appealing to with some of these equivalent notions.

13 DR. BOWEN: Well, would it be appropriate
14 to put a reference to that literature in this so that
15 some sort of firm guidance on what is expected?

16 DR. BOWEN: I think so.

17 DR. GENCO: Suggestion being that where we
18 dealt with this before, where it's -- and that is on
19 page 43 at the bottom, the second to the last
20 sentence, for a product to be considered effective it
21 must demonstrate that it is statistically
22 substantially equivalent reference -- add a reference
23 -- and that would, in principle, cover the micro too.
24 Okay.

25 DR. BOWEN: Yeah.

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1 DR. D'AGOSTINO: I presume that whoever
2 who put in that 80 percent was trying to get that,
3 that this is sort of the way you think of it.
4 Reference would be much more usual than a
5 parenthetical comment.

6 DR. GENCO: Okay, now there's another
7 comment on that second issue brought up by Warner-
8 Lambert and that is on their second page, the second
9 paragraph. We also suggest the following be inserted
10 at the conclusion of Section 3b which is on page 45.
11 It's the bottom paragraph. All right. Which
12 describes the clinical trial. Now this is the
13 clinical trial for formulation change for the
14 combination fixed combination. And it's a two week
15 clinical trial and clinical comparability here.
16 You're suggesting the Kingman article be used as the
17 basis for clinical equivalence. Is that the issue
18 here?

19 DR. BARNETT: Well, actually there's a
20 little bit more flexibility here than in our original
21 proposal. In the original submission, we had proposed
22 using the statistical criteria that had been proposed
23 by Kingman to show a formulation at least as good
24 as -- and I remember there was some discussion about
25 whether or not that might be too proscriptive at the

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1 time. So we added the phrase here "or another
2 generally accepted statistical test of clinical
3 comparability" to account for the previous
4 discussions.

5 DR. GENCO: That sounds like it would be
6 -- it sounds like it's useful to provide guidance.
7 And it's not specifically saying you have to use the
8 Kingman. It might be Bruce Pihlstrom's article and
9 others that might be relevant.

10 DR. BARNETT: Exactly.

11 DR. GENCO: What does the Committee feel
12 about that, considering that in the revision, that we
13 insert a new sentence and the bottom of page 45 which
14 reads "formulation comparability in this test is
15 established as the new formulation satisfies the at
16 least as good as criteria of Kingman for both plaque
17 and gingivitis or another generally accepted
18 statistical test for comparability." With the
19 reference of Kingman, yes. But I think "or another
20 generally accepted statistical test" -- we just leave
21 that open. I mean we could add Pihlstrom or you could
22 add -- just leave it open and it would seem to me to
23 be reasonable.

24 Any concerns with considering that in the
25 revision? How about the last sentence, "The criterion

1 for study validation is statistically significant
2 differences of both plaque and gingivitis between the
3 clinically tested standard of the negative control."

4 The standing meaning what?

5 DR. BARNETT: The formulation that had
6 been --

7 DR. GENCO: New formulation.

8 DR. BARNETT: No, that had been clinically
9 tested and that formed the basis for the data
10 submitted to this Committee.

11 DR. GENCO: That's the positive control.

12 DR. BARNETT: Yes, yes.

13 DR. GENCO: So you have a three arm study
14 minimum?

15 DR. BARNETT: Right, exactly.

16 DR. GENCO: Positive control, negative and
17 new formulation.

18 DR. BARNETT: Yes.

19 DR. GENCO: Is that reasonable?

20 DR. D'AGOSTINO: Again, you know, it's to
21 beat out the negative and to make sure your study is
22 valid, so you want the old formulation to do the same
23 and then the equivalence between the new formulation
24 and the standard, so I think we cover all the pieces.

25 DR. GENCO: Good.

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1 MR. SHERMAN: Could you go over again
2 what's being added there.

3 DR. GENCO: Pretty much I think my view or
4 take on this is that the Panel agrees with the entire
5 addition suggested in that second paragraph on their
6 second page. We also suggest that the following be
7 inserted, the conclusion of Section F(3)(b) and then
8 it begins, formulation goes right to the end of the
9 paragraph. Pretty much adding that and that's -- Bob,
10 on page 45, it would be added right to the last
11 sentence there, to the bottom of 45.

12 MR. SHERMAN: Thank you.

13 DR. GENCO: Okay, now the third item here
14 -- I'm sorry, Christine?

15 DR. WU: Can I get back to page 1? I have
16 a question. We discussed the criteria. We proposed
17 to strike that part that talks about the part that
18 says no greater than .25 log difference in colony
19 forming units. The last third line of the first page,
20 right?

21 But then they also talk about the criteria
22 for test validation is more than three log reduction
23 in CFU per ml. Are you going to strike that also?

24 DR. GENCO: The feeling was that none of
25 that specificity be added. It's not in there now.

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1 The suggestion for us to consider is to add that, both
2 items, the .25 log difference and the 3 log reduction.
3 And the feeling as I heard it was that we didn't that
4 kind of specificity was necessary as long as the
5 experiment was done according to good statistical
6 methodology for that particular microbiologic test.

7 DR. WU: Because I do think that the 3 log
8 reduction should be included to show that it is doing
9 some killing. That's how I feel.

10 DR. LISTGARTEN: But if you're comparing
11 it to a control and it's not significantly different,
12 you're showing that.

13 DR. WU: Oh, so you're doing that for both
14 criteria?

15 DR. GENCO: Right. Are you satisfied
16 then? In other words, the idea was that we wouldn't
17 be adding that at all, either component.

18 DR. BARNETT: Could I ask Max a question
19 then as to what he just said?

20 DR. GENCO: Yes.

21 DR. BARNETT: Supposing you have a test
22 then where the positive control barely killed and
23 there was no difference between the positive control
24 and your new formulation, that is, this question about
25 the validity of the test to start with. I'm wondering

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1 if that could happen and if so, if the rationale for
2 having a criteria like greater than three logs or some
3 similar criteria, would it be at least serve the same
4 purpose as the positive controls in the clinical test
5 and that is to validate the test as a whole.

6 DR. LISTGARTEN: Well, assuming that this
7 strain was still effective should reduce the number of
8 bacteria.

9 DR. BARNETT: Yeah, no. This is in a
10 product question. This is a laboratory question in
11 terms of whether actually as conducted the test was
12 valid, not whether -- in other words, you can have a
13 product that works. It's very effective, but by some
14 fluke in the laboratory it may not have worked, and
15 yet you showed no difference, no statistical
16 difference between your standard formulation, the
17 positive control and your new formulation and so to
18 pick up on Christine's point that I think it's now
19 coming back to me, the rationale then was for having
20 that criteria was just to establish a test that was
21 run, to validate the test itself, that is to say that
22 the test was actually run properly and that was the
23 point.

24 DR. LISTGARTEN: I can see your point. I
25 can see your point. I'm just not sure what, whether

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1 one should specify a particular reduction of so many
2 logs. Clearly, there should be a difference between
3 the negative control and the other two products that
4 are equivalent and that should be in the direction of
5 antimicrobial activity. What it should be, I'm not so
6 sure.

7 DR. BARNETT: Well, for example, if you
8 look at the kill kinetics data that have been
9 submitted in our various submissions, there's been
10 virtually complete kill with the Listerine formulation
11 of all organisms that were tested within 30 seconds.
12 So you have at least some feeling that that's the
13 result you would expect from the positive control in
14 these settings, that is, going from laboratory to
15 laboratory, these are tested in various sites, in
16 commercial labs, academic labs, etcetera and there's
17 an incredibly consistency of results among the
18 different labs in terms of the ability to the standard
19 to have that level kill within that time period.

20 DR. LISTGARTEN: I'm just not familiar
21 enough with the variability that exists between labs.
22 I really don't know.

23 DR. GENCO: What is the process? Let's
24 say somebody makes a new formulation with one of these
25 Class 1 products. They then have to submit the data

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1 to the FDA.

2 DR. LISTGARTEN: No.

3 DR. GENCO: So that nobody looks at this
4 data, nobody looks at these experiments, they have to
5 --

6 MR. CANCRO: It must be on record, Bob.

7 DR. GENCO: It's on record, so it could be
8 requested by the FDA.

9 MR. CANCRO: It could.

10 DR. GENCO: Effectively, it should be a
11 good experiment. So to be consistent we're
12 prescribing, describing the clinical study, but not
13 describing the microbiologic and I think the problem
14 here that we all have is these cut off points, but if
15 it was phrased as a good experiment with positive and
16 negative controls, positive controls showing
17 comparable activity which is published in the
18 literature, negative control, no activity, test
19 control, significantly substantially equivalent, then
20 I think we'd have no problem. I think it's cut off
21 points.

22 Does that need to be spelled out for the
23 microbiology or is that obvious?

24 DR. D'AGOSTINO: I think it is the cut off
25 points, where our discussion was from, but just to

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1 actually -- on page 43 when we did the formulation
2 changes, I hate to go pages, but maybe we should also
3 include in there a statement about the validation of
4 the experiment that the standard product must do
5 better than the negative control for validation of the
6 study. We don't say that. And then we have specific
7 general rules and whatever product you're looking at
8 has to meet these three. You have to have a valid
9 experiment. You have to be equivalent -- the new has
10 to be equivalent to the standard and the new has to do
11 better than the negative.

12 DR. GENCO: Bill?

13 DR. BOWEN: I think we do say it. If you
14 look at the bottom of page 43. For a product to be
15 considered effective it must demonstrate that it's
16 statistically substantially equivalent. Forget the
17 next part -- to the standard formulation and
18 statistically superior to the negative control as
19 assessed by reasonable statistical analysis.

20 DR. D'AGOSTINO: But we don't say that the
21 standard has to do better than the negative control.
22 I mean that's the particular test we're talking about
23 now. The new has to do better than the negative
24 control.

25 DR. LISTGARTEN: But it says it's

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1 substantially equivalent to the standard and
2 substantially better than the negative control. So if
3 it's equivalent to 1, it's superior to the other --

4 DR. D'AGOSTINO: But you usually make
5 three comparisons. This could imply only two
6 comparisons. I'm not trying to be a stickler on it,
7 but usually you say is it valid, so you get the
8 standard versus the negative. Then is the new versus
9 the negative and then is the new equivalent to the
10 standard. Those are the three steps you oftentimes
11 take. So this could be read as only two.

12 DR. GENCO: So how would you phrase that?

13 DR. D'AGOSTINO: Well, just add another
14 one for validation of the experiment. The standard
15 must be substantially better than the negative
16 control.

17 DR. GENCO: So that would be on top of
18 page 44?

19 DR. D'AGOSTINO: Right, very last line.

20 DR. GENCO: What would you suggest that
21 for, for validation?

22 DR. D'AGOSTINO: Right.

23 DR. GENCO: For validation of, why don't
24 you phrase that and maybe Bob can take that down, if
25 we agree to that. That's going to clarify.

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1 DR. D'AGOSTINO: For validation of the
2 study, the standard must be substantially better than
3 the negative control, statistically superior to the
4 negative control.

5 DR. GENCO: Okay, is the Panel clear on
6 that? I think that addresses also Warner's comment
7 about that issue too. So it's there in the generic
8 for all these tests, micro and others.

9 DR. LISTGARTEN: Does this paragraph on
10 page 43 and 44, can that -- that does not necessarily
11 extrapolate to the other section.

12 DR. GENCO: That's the general, those are
13 the general principles.

14 DR. LISTGARTEN: Okay.

15 DR. GENCO: Okay, concentration of oils in
16 the fixed combination, small errors, those will be
17 corrected.

18 Bob, need we discuss that?

19 MR. SHERMAN: No.

20 DR. GENCO: Okay. Okay, discussion of
21 alcohol.

22 MR. CANCRO: Excuse me, Bob, pertinent to
23 that issue of concentrations, in this header on page
24 44, I'm sorry, page 45, is it necessary to put in the
25 concentrations of each of the oils? You're only

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1 talking about a header and here unlike all the other
2 ingredients you're spelling out concentrations. I
3 think for consistency you may not want to do that at
4 this point.

5 You see, page 45, No. 3, where you have
6 percentages for each of the oils?

7 DR. GENCO: What's the Panel's feelings.
8 It is certainly given elsewhere. You're saying it's
9 redundant here?

10 MR. CANCRO: Well, I'm saying this is the
11 only one you're treating differently. You don't have
12 this for stannous fluoride. You don't have this for
13 CPC. You go on later to say what the concentration,
14 effective concentration should be. So as a header,
15 I'm recommending you take it out.

16 DR. GENCO: Okay, what's the Panel's
17 feeling on that?

18 DR. SAXE: I would agree for consistency.

19 DR. GENCO: For consistency. In other
20 words, on page 45, it's No. 3. Fixed combination of
21 eucalyptol, etcetera, leave out the percentages
22 because it's a header. The percentages are described
23 elsewhere.

24 MR. SHERMAN: I think it's specified there
25 in particular so that to clarify that it's this

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1 particular combination, at these concentrations,
2 exactly, just to further clarify that it's this and
3 only this fixed combination.

4 I think that was the rationale for putting
5 it in there.

6 DR. BARNETT: It doesn't -- we're not
7 wedded to having it in that particular place. I think
8 the only point is that it be somewhere and that just
9 to be sure that the concentrations are correct. It
10 could be deleted from this place if that's what people
11 desire.

12 DR. GENCO: So the correction of the
13 concentrations will be made. That's done. The issue
14 is to include it in the header and you don't feel
15 strongly whether it's in the header or not, as long as
16 it's in there someplace.

17 DR. BARNETT: The point is as long as it's
18 somewhere in here, then that would be correct.

19 DR. GENCO: Bob, your concern that this
20 would be confusing, that somebody reading this might
21 think about another fixed combination?

22 MR. SHERMAN: Possibly. I think that's
23 the rationale. I think it was done that way in
24 another oral health care.

25 DR. GENCO: I would say we could err on

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1 the side of being clear, even if it's not aesthetic.

2 DR. D'AGOSTINO: I think that we spent a
3 lot of time worrying over this combination, should we
4 do one at a time, two at a time and three at a time
5 and I think it was a long history of this combination
6 that made us comfortable. So I think the specifics
7 are probably appropriate.

8 DR. GENCO: So the feeling of the Panel is
9 to leave it in, leave the concentrations in and
10 correct them.

11 Max?

12 DR. LISTGARTEN: I just want a point of
13 clarification. If I came along and I wanted to use .1
14 percent eucalyptol instead of .092 percent, I would
15 have to come back with an IND?

16 DR. KATZ: If you deviate from what the
17 combination has specified, you would have to come back
18 in.

19 DR. LISTGARTEN: Okay.

20 DR. GENCO: Okay, now the big issue, a big
21 issue. The discussion of alcohol. This is
22 extensively also described by NDMA.

23 Mike, is this now a different issue?

24 DR. BARNETT: No. I think basically it's
25 the same and there was concern that there was a lot of

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1 information in that section.

2 DR. GENCO: Right.

3 DR. BARNETT: And then there was not a lot
4 of discussion, if any -- there was a lot of a previous
5 report that had been reviewed by this Panel. Within
6 that report, there were statements made about the
7 Subcommittee recommended were, in fact, they never
8 were voted on. I think actually in the penultimate
9 paragraph, I got that word from you, Bob, from the
10 last meeting. Those recommendations, which were, in
11 fact, never formal recommendations for this
12 Subcommittee, so I think the concern was No. 1, there
13 was some confusion about what were the real
14 recommendations and conclusions, what were not. And
15 also the fact that if you look at the very last
16 paragraph which summarizes the events and conclusions
17 at that June 1996 workshop, there almost appear to be
18 a disconnect with respect to everything that came
19 before and how those conclusions were arrived at, that
20 is, much of the material that was presented at that
21 June workshop, some of the work by Phil Cole and
22 others which really, I think, led to a lot of the
23 changes in outlook and the final decisions and
24 conclusions that were arrived at were really not
25 reflected in that section. And the feeling then was

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1 that it ought to be at least augmented to reflect the
2 additional materials and also to indicate what were
3 formal recommendations that were actual
4 recommendations and which were suggested, but never
5 really voted on and implemented. That was the intent.

6 It's very similar, I think, to the -- all
7 the other comments.

8 DR. GENCO: Okay, what I think we might do
9 then is to defer it to the -- when we discuss the NDMA
10 recommendations because there are some specific
11 recommendations to revise, reformat, etcetera. If you
12 would not mind, we could defer this until --

13 DR. BARNETT: Sure. I'd like to just make
14 two additional comments that weren't in here.

15 DR. GENCO: Okay.

16 DR. BARNETT: One is fairly specific for
17 this section on our ingredients. The other, I think,
18 is a more general comment.

19 With respect to the section on our
20 ingredient and I too would like to leave a legacy,
21 somewhere, somehow, but there was a lot of discussion
22 on the contribution of each of the ingredients to the
23 total formulation and the satisfying of the
24 culmination policy. I don't recall that there was any
25 statement about it in there. We would like to suggest

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1 that a statement be included and we would be glad to
2 at least furnish the outline or the verbiage, if you
3 wish, short couple of sentences, a short paragraph to
4 take that into account.

5 The second issue, I think is a more
6 general one that applies not only to ours, but all the
7 Category I. Toward the end of the section on the
8 essential oils, there was a paragraph added that
9 talked about some of those additional analyses that
10 you all had requested and which really formed the
11 basis of the judgment of clinical relevance or
12 clinical significance of the data and there's --
13 although there are percentages and odds ratios and all
14 that, nowhere in this whole document really is there
15 a discussion of the rationale as to how this was
16 arrived at and the significance of these things in
17 terms of indicating clinical relevance or clinical
18 significance. This really, I think, applies across
19 the board to all three ingredients where some of this
20 information is listed. So you may want to consider as
21 part of this whole question of documenting how -- the
22 reasoning leading to the final decisions, you may want
23 to consider adding a section on that as well. But
24 that's a more general comment.

25 DR. GENCO: So let me see if I understand

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1 that second comment. The intent was to get to
2 clinical significance and so we looked at data in
3 different ways, it was presented to us in different
4 ways.

5 DR. BARNETT: Right.

6 DR. GENCO: So you want a rationale for
7 the clinical significance, why we would request those
8 particular analyses or why they were presented and how
9 they get a little further to understanding clinical
10 significance.

11 DR. BARNETT: Yes, exactly. I think as
12 part of this whole rationale of the pathway between
13 the initial review, the final decision what came in
14 between.

15 DR. GENCO: Right.

16 DR. BARNETT: I think again, if someone
17 were to look at in future years and see these targets
18 of 33 percent or whatever, at least somebody could add
19 to the question by looking at it, what was arrived at,
20 how did that come about and what does it mean.

21 DR. GENCO: Does anybody on the Panel feel
22 interested to look at the document with that in mind?
23 I think that's an interesting point.

24 Stan, would you do that?

25 Okay, so Bob, Stan will look at that and

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1 he'll make some suggestions relative to the rationale
2 for these various analyses in our quest for clinical
3 significance.

4 Max?

5 DR. LISTGARTEN: I think obviously several
6 members of industry are concerned about this alcohol
7 section and mostly some of the things that were not
8 mentioned and I'm just wondering if it might be
9 appropriate to ask for an example of the type of
10 fleshing out they would like to see for consideration
11 by --

12 DR. GENCO: I think when we get to the
13 NDMA, there's quite a few very specific suggestions,
14 so we can maybe get into that.

15 DR. LISTGARTEN: Okay, because it might
16 make it easier for the FDA staff to actually do the
17 necessary changes if we had some suggestions.

18 DR. GENCO: Thank you. Mike, with respect
19 to your first comment, could you draft that material
20 up and maybe present it tomorrow morning?

21 DR. BARNETT: Yeah, we will, Bob.

22 DR. GENCO: Okay, thank you. So we've
23 dealt then with the Warner-Lambert submission. It's
24 a few minutes after 12. Perhaps this would be a good
25 time to stop for lunch.

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Bill?

DR. BOWEN: I have a point that I wanted to raise, Bob. It may not be of any consequence. We dealt primarily with the equivalence issue. What happens if the new formulation, in fact, is superior in all the profile tests? Are there any consequences for that? And how should it be handled?

DR. GENCO: That's a good question. What company might want to make a superiority claim? What is the FDA's advice on that? What are the guidance there?

DR. KATZ: Usually when things have been looked with regard to bioequivalence and they've been superior, then one needs to go back again and reanalyze the data and a determination needs to be made on what basis there is superiority because it's very clear in terms of the regulatory definition as to what is equivalent and if it's not equivalent, then it's not equivalent. It may be superior, but it would not be allowed a claim on the basis of one trial or one test that had been done and then the agency would need to make the determination as to whether or not it would be something that could be approved or not approved and in this case, whether it would have to come in through the route of an NDA if it's superior

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1 to what it's being looked or whether it would be an
2 NDA deviation to the monograph.

3 MR. CANCRO: Yeah.

4 DR. GENCO: Okay, is that clear?

5 MR. CANCRO: I would think there's a logic
6 here which says that if a laboratory test shows your
7 new formulation, your new Category I ingredient of the
8 same concentration as the old ingredient, comes out
9 statistically significant, then the issue is to make
10 the claim, you're obviously talking about its clinical
11 meaning. I mean it would seem to me that just seeing
12 a laboratory test, show a difference for superiority,
13 I don't think is relevant either to the advertising or
14 to the issue at hand. Is this formulation really
15 bringing anything new to the table? So probably your
16 suggestion is right, just redo the test to be sure
17 that this isn't some arbitrary thing, some artifact.

18 DR. GENCO: Superiority claim could not
19 come then from what's in the monograph. It would be
20 an additional activity with the FDA.

21 DR. KATZ: That's correct.

22 DR. GENCO: A very positive activity.
23 Certainly couldn't just, on the basis of your tests
24 showed superior and then go out and make the claim.
25 The company would have to do something with the FDA to

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1 be allowed to make a superiority claim. Is that true?

2 DR. KATZ: Right, and there are very
3 specific guidance as to what would be allowed for
4 superiority type of a claim.

5 DR. GENCO: Bill?

6 DR. BOWEN: But the data would be accepted
7 as being equivalent.

8 DR. KATZ: Well, not necessarily. It
9 would depend. And this is again where we would, as an
10 agency need to go back and review. Genetics, again,
11 and this is probably the easiest way to kind of go
12 back are very clear with regard to their guidance as
13 to what is acceptable and what can be approved on the
14 basis of clinical -- bioequivalence. And if things
15 are not bioequivalent, then one needs to go back and
16 ask for different things to approve the application.

17 So this may come out to be something in
18 that kind of a category, but this is something that
19 the Agency would then need to deal with, if in fact,
20 we end up with applications showing superiority to the
21 reference.

22 DR. GENCO: Okay, thank you. This will be
23 a good time to break for lunch. I'd like to thank
24 those on the program this morning for their help,
25 particularly Mike Barnett. I have another word for

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1 you. This is our finale, but it's also the pinnacle
2 of our activity, new word, "pinale."

3 We'll see you back here at 1:15. And the
4 Committee is going to be hosted by the FDA to a
5 gourmet lunch. Just follow Dr. Titus.

6 (Whereupon, at 12:08 p.m., the meeting was
7 recessed, to reconvene at 1:15 p.m., Wednesday,
8 December, 1, 1998.)

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1:22 P.M.

DR. GENCO: Welcome back. It's been pointed out to us that there's a distracting thumping that's going on at the tables and it makes noises on the microphones. I don't know where it's coming from, but it could very well be that when the tables move, does that do it? Maybe somebody is kicking. Okay.

MR. CANCRO: Somebody's chewing gum in this room, right?

DR. GENCO: Let's go for a while. When you hear it, maybe you could raise your hand and we'll see if we can identify the source.

(Laughter.)

And get rid of him or her.

(Laughter.)

That's it. I'll try not to do that. Okay, let's proceed now with the P & G comments and these occur, are presented to us as a letter of 11/23 and then the blue folder has the actual pages from the original draft with the revisions in them. So first of all let me read for the record a letter from Dr. White regarding the presentation last time by Dr. George Stookey. "Dear Colleague, The purpose of this note is to help clarify some possible misperceptions

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1 originating from the October meeting of the
2 Subcommittee and the presentation of Dr. George
3 Stookey, Indiana University, regarding safety and
4 effectiveness of cetyl pyridinium chloride containing
5 chewing gum. With P & G's well known and long
6 standing research collaborations at Indiana
7 University, some of you may have mistaken Dr.
8 Stookey's presentation to be representative of P & G
9 or contracted by ourselves. In fact, this is not
10 true. Proctor & Gamble had no role in the
11 presentation of Dr. Stookey to the Subcommittee
12 regarding the cetyl pyridinium chloride chewing gum.
13 We have no knowledge whether Dr. Stookey's
14 presentation was sponsored by another party and if so,
15 whom. I felt it was worthwhile to clarify this for
16 you. I'm looking forward to seeing you in December.
17 Dr. D.J. White."

18 Okay, let's proceed now with the letter of
19 11/23 from Procter & Gamble. First comment is on page
20 8 and that would -- these pages now refer to our
21 original draft. And the changes are actually
22 incorporated in the blue manual. Let's see, page 8 to
23 10, these are, I think, additions of middle initials,
24 so we'll take those as done.

25 Page 13, change Crest Tartar Control to

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1 Crest Gum Care Toothpaste. I think we can consider
2 that done.

3 Page 18, line 18, delete bacteria as
4 pellicle is derived from saliva only. Now this was
5 brought up also by NDMA. Page 18, line 18.

6 MS. FEDER: Dr. Genco?

7 DR. GENCO: Yes.

8 MS. FEDER: If you -- those page numbers,
9 page 18, line 18 are in the original. Those refer to
10 the original page numbers that you received from FDA.
11 The page numbers that are on the document --

12 DR. GENCO: So they're in the original
13 draft.

14 MS. FEDER: Right. But the page numbers
15 that are on this document, you'll find are different.

16 DR. GENCO: Ah, that's the confusion.

17 MS. FEDER: Yes.

18 DR. GENCO: Okay, so --

19 MS. FEDER: So if you want to see
20 something in context, that's why we provided these,
21 but the page numbers and the cover letter, you're
22 better served referring to the original that you got
23 from the Agency.

24 DR. GENCO: Thank you for that
25 clarification. So let's go back -- let's use our

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1 original draft and as we've done before, let's try to
2 find those --

3 MR. SHERMAN: It's page 18 of the original
4 draft, No. 6.

5 DR. GENCO: Okay. Page 18 of the original
6 draft, suggestion is to delete bacteria as pellicle is
7 derived from saliva only.

8 DR. LISTGARTEN: I think it's very hard to
9 -- considering the oral environment to say that it's
10 strictly salivary and not bacterial.

11 DR. GENCO: Bill?

12 DR. BOWEN: I'm really surprised to see
13 this statement. It's being shown in the literature
14 now for close to 15 years that there are soluble
15 bacterial products in pellicle from within the first
16 minute of formation of pellicle. So while what's
17 written in our draft should be perhaps soluble
18 bacterial products, certainly not derived from saliva
19 only. The document shows that very clearly.

20 DR. GENCO: Okay, are we comfortable with
21 the way it is in the original? Derived from bacteria
22 and saliva?

23 DR. BOWEN: Bacterial products would be
24 more accurate.

25 DR. GENCO: Okay. Bacterial products.

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1 Okay, that's page 18, fifth line from the bottom, the
2 last word is bacterial products.

3 Okay, now page 21, line 1, suggestion
4 change to be more similar composition than plaque from
5 sites in different subjects or to be more similar in
6 composition to plaque from sites of differing clinical
7 health or even among different subjects.

8 Let's go back to page 20 and read that
9 whole sentence. "Plaque from sites of similar
10 clinical health within individual subjects tends to be
11 more similar in composition than plaque from sites in
12 different subjects."

13 Somebody from P & G, how does your
14 statement clarify that? It seems to be clear as is.
15 Does somebody want to address that?

16 DR. WHITE: Hold on a second, because --
17 Don White, Procter & Gamble. Because I didn't write
18 that, now I have to read it. Okay.

19 DR. LEUSCH: Mark Leusch, Procter &
20 Gamble. I just thought that by adding the phrase "of
21 differing clinical health or even among different
22 subjects" added some clarity to the statement.

23 DR. GENCO: It says -- as it's stated on
24 page 20, "plaque from sites of similar clinical health
25 within individual subjects tends to be more similar in

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1 composition than plaque from sites in different
2 subjects."

3 DR. LEUSCH: "Of differing clinical health
4 or even among differing subjects" just seemed more
5 clarifying. Not wed to it.

6 DR. GENCO: Okay, thank you. Max?

7 DR. LISTGARTEN: I think the intent here
8 was to demonstrate that if you sample different sites
9 in a particular subject and compare that to different
10 sites in different subjects, that the variation among
11 sites within subjects is less than the sites among
12 subjects.

13 We go on later on to describe how plaques
14 differ in composition between healthy and disease
15 sites, so we elaborate much more so about differences
16 between healthy and disease later on. I think the
17 intent of this statement is simply to point out that
18 differences within subjects are much less important
19 than differences among subjects.

20 DR. GENCO: So if you look at clinically
21 healthy sites --

22 DR. LISTGARTEN: Whether they're healthy
23 or diseased.

24 DR. GENCO: Or diseased.

25 DR. LISTGARTEN: Regardless of whether

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1 they're healthy or diseased, there's much more
2 similarity in the composition of plaque within sites
3 of the same mouth as there is between subjects.

4 DR. GENCO: Would you object to adding
5 sites of similar clinical health or disease?

6 DR. LISTGARTEN: Yes, because that's a
7 different matter which we address later on. I think
8 we should just leave it alone.

9 DR. GENCO: Okay, anybody else on the
10 Panel want to make a comment to the suggested change
11 or Max's suggestion to leave it alone?

12 So the idea is, the consensus is to leave
13 it as is? Okay.

14 Okay, page 22, line 3, replace Wolinella
15 recta with Campylobacter. That will do. That's okay.

16 Page 23, line 13, replace word plaque with
17 calculus. Line 13. It reads -- it's about in the
18 middle of that paragraph, "Both subgingival and
19 supragingival plaque are often stained." Yeah, that
20 should be calculus. Any objection to that?

21 Okay, page 23, line 13 and 24. And page
22 24, lines 1 to 11. To more clearly distinguish
23 supragingival calculus from subgingival calculus we
24 suggest replacing the information contained with the
25 following. Okay, then --

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1 DR. WHITE: Mr. Chairman, if I may, Donald
2 White, P & G.

3 DR. GENCO: Yes.

4 DR. WHITE: The intent here was, I think
5 what the Panel had in mind was to try to first of all
6 distinguish supragingival calculus from subgingival
7 calculus and then secondly make sure that it's clear
8 that when you partially provide definitions as to what
9 tartar control products do, how they may affect
10 supragingival calculus and provide a basis for why
11 that's a cosmetic and not a therapeutic benefit.

12 Now I'm not so sure after hearing the
13 conversation this morning where some of this
14 discussion would go because it conceivably could go in
15 -- hold on, it could conceivably go under the
16 definition of drug cosmetic status in the section on
17 tartar. The reason I bring that up is because if you
18 think about it, you have an expanded discussion of why
19 plaque claims are therapeutic or why the Panel
20 considered plaque claims to require gingivitis, okay?
21 And that some of this wording, the fact that
22 supragingival calculus reductions haven't been shown
23 to provide gingivitis reductions, some of that same
24 wording, you could imagine seeing in the drug versus
25 cosmetic status section, so I'm not so sure where

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1 you'd want to put it.

2 But the intent here was to clarify what
3 you folks had put down because we thought in some
4 areas it wasn't as clear as it might be. But we want
5 to make sure, obviously, it still contains your
6 original intent.

7 So where this would start is if you're on
8 page 23, and you go to the beginning of that
9 paragraph, I guess it's the first new paragraph in
10 that page where you say "calculus may form
11 subgingivally." This is page 23 of the --

12 DR. GENCO: Right, second paragraph.

13 DR. WHITE: Right. "Calculus may form
14 subgingivally and is often stained and tenaciously
15 attached to the crown or root. Calculus may also form
16 supragingivally coronal to the margin. Supragingival
17 calculus is found in greater amounts on surfaces
18 adjacent to the openings of the ducts of the major
19 salivary glands." Right after that we were suggesting
20 start with what we have suggested, if it's acceptable
21 to you and perhaps think about including that thought
22 process through to the end because we thought it might
23 read a touch clearer and you can read it and see if
24 you agree.

25 DR. GENCO: Okay, so what you're saying is

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1 -- you've actually done this on your page 18. You're
2 striking everything after major salivary glands and
3 substituting your paragraph.

4 DR. WHITE: Right.

5 DR. GENCO: All the way up to section 4,
6 gingivitis.

7 DR. WHITE: Right, and it contains
8 everything that you folks mentioned, it's just in a
9 little bit of a different order and you can decide
10 whether it's clear or not.

11 DR. GENCO: Perhaps we could take a minute
12 to read that. It's their page in the blue book 18-19.
13 It shows exactly what they're suggesting.

14 (Pause.)

15 I'm wondering, has anybody found any new
16 concepts here?

17 DR. WHITE: I guess the point, Mr.
18 Chairman, is if someone read page 23 to 24 the way it
19 is, and they wouldn't necessarily come away with the
20 conclusion that you would arrive at in the drug versus
21 cosmetic classification for tartar. You sort of list
22 the pluses and minuses, the supragingival calculus and
23 subgingival calculus, but you never describe for the
24 reader why it is that you make the conclusion that
25 supragingival calculus should be cosmetic. And all

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1 that is is providing the rest of that rationale.

2 DR. GENCO: Does anybody have any strong
3 thoughts? Yes.

4 DR. SAVITT: Just a specific comment.
5 Since we haven't reviewed the anti-calculus
6 ingredients, it would be inappropriate to include the
7 comment about the efficacy of those products.

8 DR. WHITE: Efficacy for tartar, you mean?

9 DR. SAVITT: Yes, for tartar.

10 DR. WHITE: Okay, or maybe we could
11 reference the literature that shows clinical --

12 DR. SAVITT: I'm not sure why that's even
13 relevant. We haven't reviewed it.

14 DR. GENCO: Max?

15 DR. LISTGARTEN: Well, for the same reason
16 that we didn't go along with the ADA recommendations
17 of using treatments to define the basic biology, I
18 think there is no reason to do this here. I think
19 we're basically just providing an overview of where a
20 sub and supragingival calculus fits into the
21 maintenance of periodontal health. I don't think we
22 want to get involved with treatment methods.

23 DR. GENCO: Okay, fine. Does anybody else
24 have any feelings?

25 Bill?

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1 DR. BOWEN: For completeness, I'd like to
2 see a couple of references included in that section.

3 DR. GENCO: In our -- in the original
4 section?

5 DR. BOWEN: Yes.

6 DR. GENCO: Specifically where? Or just
7 in general to go through that and reference it?

8 DR. BOWEN: Yes. We appear to have just
9 one reference right on the top of page 23. It would
10 be appropriate to have a couple more.

11 DR. GENCO: Bill, could I ask you to make
12 some suggestions and maybe you can transmit that to
13 Bob?

14 DR. BOWEN: I'd be happy to do that.

15 DR. GENCO: Thank you. So the general
16 feeling is to leave this alone, add some references to
17 it to strengthen it.

18 DR. WHITE: Okay, that's fine. Perhaps
19 one last comment. In a couple of cases then where the
20 language like on page 20 -- if you leave it the way it
21 is, page 24 --

22 DR. GENCO: Okay.

23 DR. WHITE: Right at the very top, when
24 you say "it interferes with the regeneration of lost
25 attachments", what is "it"? Supragingival -- I guess

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1 that was my problem with the section. I didn't always
2 know when the "its" were referring to supragingival
3 calculus and when they were referring to subgingival
4 calculus. I think that's where my difficulty was.

5 I would think that what was meant was
6 subgingival calculus interferes with the generation,
7 regeneration of lost attachment because I think that's
8 what the literature shows. I don't think that you are
9 talking about supragingival there. So maybe you could
10 qualify that with subgingival calculus. Is that okay?

11 DR. GENCO: Okay, the paragraph begins on
12 the previous page. It says "calculus facilitates" and
13 the two "its" refers to the calculus. You would like
14 us to consider the first "it" at the bottom of page 23
15 be supragingival calculus reduces the effectiveness of
16 oral hygiene -- overall hygiene and the second,
17 subgingival calculus interferes with regeneration of
18 loss attachment. Would that do it?

19 DR. WHITE: Now I need to see where we're
20 at.

21 DR. GENCO: Okay, bottom of page 23. The
22 sentence begins "calculus facilitates the retention of
23 dental plaque." Then there is an "it", the next
24 sentence.

25 DR. WHITE: Right.

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1 DR. GENCO: That should be supragingival
2 and then the next "it" should be subgingival.

3 DR. WHITE: Yes. Is that okay?

4 DR. LISTGARTEN: Well, doesn't any kind of
5 calculus interfere with -- I mean you could have
6 slightly subgingival calculus and that's -- that
7 interferes with oral hygiene. So "it" is appropriate.
8 It just refers to calculus in general.

9 DR. WHITE: You mean like flossing, yes.
10 Okay, sure.

11 DR. LISTGARTEN: But I'll buy subgingival
12 for the --

13 DR. WHITE: For the regeneration of
14 attachment, yes.

15 DR. GENCO: Okay, any other comments on
16 that from the Panel? All right.

17 So thank you. Page 24, the second line,
18 Bob, the sentence begins, "It interferes with
19 regeneration of loss attachment, subgingival
20 calculus." Thank you, for it.

21 Okay, page 27, line 21. Suggestion is to
22 insert, "however, it should be noted that the
23 relationship between the quantity of plaque present
24 and the degree of gingivitis is sufficient and complex
25 such that reductions in plaque mass alone are

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1 inadequate to conclude that a therapeutic effect of
2 gingivitis could be expected. As a result, gingivitis
3 reductions must be measured directly. Furthermore,
4 reductions in gingivitis are possible without obvious
5 reductions in plaque quantity."

6 So you're asking us to consider adding
7 that to line 21. Okay, so that's --

8 DR. WHITE: I guess that would be at the
9 end of the paragraph.

10 DR. GENCO: Okay. Add to the end of the
11 second paragraph that statement. Okay? And that
12 actually is the fourth line from the bottom of page
13 27. What's the Panel's feeling?

14 DR. LISTGARTEN: Can we just read it
15 quickly?

16 DR. GENCO: Surely.

17 (Pause.)

18 Max?

19 DR. LISTGARTEN: I'm okay with the
20 beginning of that paragraph. I'm a little bit worried
21 about the last sentence. I don't want to leave the
22 door open to substituting "anti-inflammatory agents"
23 for -- at the exclusion of agents designed to control
24 bacteria. And I think that even though the statement
25 is correct, that you could have a reduction in

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1 gingivitis without an obvious reduction in plaque, I
2 don't think that this should be the intent of the
3 monograph.

4 DR. GENCO: So you would --

5 DR. LISTGARTEN: I'd accept the first
6 part.

7 DR. GENCO: The first part --

8 DR. LISTGARTEN: And delete the last
9 sentence.

10 DR. GENCO: Okay, first of all, let me ask
11 if you'd be or anybody would be amenable to inserting
12 that at the very end of this section on page 28 just
13 before periodontitis. Because we go through a lot
14 more discussion of the development of gingivitis and
15 its association with plaque. And then we end up with
16 that middle paragraph on page 28, the Subcommittee
17 accepts that gingivitis is associated with
18 accumulation of plaque and there's a close association
19 between plaque and reduction of gingivitis and it
20 would seem then that this insert could be added there.
21 "However, it should be noted that this relationship is
22 complex."

23 That's a possibility. Okay. So two
24 issues. One is consider maybe adding it just before
25 periodontitis on page 28. The end of that paragraph

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1 beginning with "the Subcommittee." And second
2 suggestion is deleting the "Furthermore, reductions in
3 gingivitis are possible without obvious reductions in
4 plaque quantity."

5 DR. SAVITT: I'm in favor of both
6 suggestions.

7 DR. LISTGARTEN: What's the second
8 suggestion?

9 DR. GENCO: Well, the first -- deleting
10 your sentence. I think the anti-inflammatory
11 potential here, I think we all -- everybody has agreed
12 to that or there's a consensus. My point was just
13 instead of adding it where they suggested, line 21, to
14 add it on page 28 at the end of the whole section on
15 gingivitis. See where there's a 6 periodontitis on
16 page 28? Add it to that paragraph beginning "The
17 Subcommittee accepts that gingivitis is associated
18 with accumulation of plaque." And P & G would agree
19 to that. That's like the final statement on the
20 association between gingivitis and plaque before you
21 get into periodontitis.

22 DR. WHITE: I think it goes better there
23 as well.

24 DR. LISTGARTEN: I actually think it fits
25 better in the beginning. It's a little bit awkward

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1 putting it at the very end.

2 DR. GENCO: So you're thinking of the line
3 21 which is about four lines in at the end of the
4 middle paragraph on page 27?

5 DR. LISTGARTEN: Where P & G suggests we
6 put it I think it fits quite well there.

7 DR. GENCO: Okay. Gene?

8 DR. SAVITT: I just think it's -- I'm not
9 strongly opposed to either position. It just seems
10 like a useful summation sentence which seems a little
11 bit more appropriate at the end, but I'm not opposed
12 to either location.

13 DR. GENCO: Bill?

14 DR. BOWEN: I would agree with Gene.

15 DR. GENCO: Stan? Chris?

16 DR. SAXE: I agree.

17 DR. GENCO: Max?

18 DR. LISTGARTEN: It will have to be
19 reworded because the "however" is no longer
20 appropriate.

21 DR. GENCO: Just leave the "however" out.
22 "It should be noted" then.

23 Well, if the intent is to put it there,
24 then just before periodontitis, we can make sure it is
25 grammatically correct. So Bob, is that clear?

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1 MR. SHERMAN: Okay.

2 DR. GENCO: Page 28, just before
3 "periodontitis" to add the statement from P & G minus
4 the last sentence.

5 MR. SHERMAN: Yes, thanks.

6 DR. GENCO: Okay. Fine. Page 32, line 9.
7 Yes, oh yes, we've dealt with this. We're going to
8 look for a term. Okay.

9 Page 33, line 16. Same thing. All right.

10 Page 33, line 19. Okay, you were
11 suggesting deleting lines 19 to 24, on page 33.

12 DR. WHITE: I think only because we didn't
13 have a data base that one could argue, you know, if
14 you do surveys of consumers off the street and you
15 grade their plaque and you ask them how clean their
16 mouth feels, you can easily get a correlation between
17 how much tartar and plaque is on their teeth and how
18 clean their mouth feels. I'm not saying that products
19 that change surface tension don't -- can't change the
20 way your mouth feels, I'm just saying that we don't
21 necessarily have data -- they're more likely to --
22 that the feel is more likely to be affected by those
23 agents than the other variables in their mouth, I
24 think.

25 DR. GENCO: What if we considered just

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1 eliminating the last sentence? Outcome variables such
2 as taste and feel, but leave the first sentence in
3 that section? "It is also highly unlikely that
4 marginal control of bacterial deposits has a
5 significant relationship to most, if not all, cosmetic
6 claims."

7 What does the Panel feel about that,
8 striking the last sentence on page 33? That's
9 speculation. That's your point.

10 Anybody on the Panel have an opinion about
11 that? Like to do that?

12 DR. BOWEN: Bob, do you remember the
13 context of the discussion in which this was put in?

14 DR. GENCO: Yes. Agents which make your
15 teeth feel squeaky clean? But I think it's
16 speculation as to why, unless you know differently.

17 Do you think that leaving that sentence
18 out compromises that discussion that we had?

19 DR. BOWEN: Probably not.

20 MR. CANCRO: Bob?

21 DR. GENCO: Yes.

22 MR. CANCRO: I think you've really
23 captured the essence of what you want to say in the
24 first two sentences where you're talking about the
25 fact that some mouthwashes may be able to reduce

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1 plaque. They don't do it -- and do it to a
2 statistically significant degree. That's insufficient
3 to be considered therapeutic benefit. The following :
4 sentences after that are very speculative. They don't
5 add to your primary thrust here which is basically
6 that plaque reduction doesn't necessarily mean it's a
7 therapeutic effect. That's the point you're making
8 here.

9 DR. GENCO: What does the Panel feel?
10 Chris?

11 DR. WU: I don't mind leaving it out.

12 DR. GENCO: Stan?

13 DR. SAXE: It's a singular occasion that
14 I agree with Lew Cancro.

15 (Laughter.)

16 DR. GENCO: Gene?

17 DR. SAVITT: I definitely feel the last
18 sentence is speculative. The one before I could argue
19 either way.

20 DR. GENCO: Bill?

21 DR. BOWEN: Did this material come in as
22 a result of consumer surveys on certain products made
23 them feel good? And this was being used as a
24 rationale for making certain claims, the consumer felt
25 good as a result of using these products? I think

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1 that's the context in which it appeared and we were
2 attempting, as I recall it, to refute that they cite
3 any clinical significance whatsoever and that's why
4 it's in there.

5 I can't obviously rely on my memory for
6 certain, but that's my recollection. If that's the
7 case, if I am correct, then I think a case can be made
8 for retaining both sentences. If I'm wrong, then I
9 readily agree to their removal.

10 DR. D'AGOSTINO: Would we have a reference
11 for that?

12 DR. GENCO: Do you think that those
13 surveys can be referenced? They probably can be
14 referenced. They may not be published, but we could
15 reference the company.

16 DR. BOWEN: I believe they were submitted
17 to the FDA for our perusal.

18 DR. GENCO: Right. Well, maybe that's the
19 way to do it. If it's not speculative. If it's based
20 upon what's in the surveys, we could reference and
21 make sure that the statement reflects what's in the
22 survey.

23 Could we look into that then? Good. Bob,
24 maybe you could work with Bill on that. Good.

25 Gene?

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1 DR. SAVITT: I was going to say that the
2 last sentence, if my recollection and reading it, it's
3 likely that the last sentence is still going to be
4 somewhat speculative.

5 DR. GENCO: So they've been given the task
6 to make sure it reflects the study and put the
7 reference in.

8 MR. CANCRO: The problem I had with what
9 you're suggesting and requesting of Bob is that
10 companies would not have submitted any data that
11 substantiates what they believe to be cosmetic claims
12 to this Panel. So if you go to the record, I mean the
13 record isn't going to show any relationship of A to B
14 because if it's a cosmetic claim, this is not the
15 Panel to which those claims would have been submitted.

16 DR. GENCO: Now the suggestion was to go
17 back to those -- Bill brought up the point that this
18 may have been a distillation of a discussion of the
19 marketing surveys or the patient preference surveys.
20 If so, it should be referenced and the statement
21 should be reflective of what those surveys said.

22 MR. CANCRO: Yes, I think the marketing
23 surveys, the essence of what they said can be
24 captured. They seem to say different things. Perhaps
25 they didn't say different things, but the point is

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1 that if a specific cosmetic claim was supported in
2 some manufacturer's testing by presumably an
3 association with a plaque reduction, that would not
4 have made its way, that study would not have made its
5 way into this Panel. It would never appear.

6 DR. GENCO: Now the issue was, as I
7 recall, those surveys were carried out to determine if
8 patients or consumers equated plaque reduction, good
9 mouth feel, etcetera, with gingivitis, anti-gingivitis
10 or anti-periodontitis or saving teeth, remember the
11 domino concept --

12 MR. CANCRO: Yes.

13 DR. WHITE: Yes, Mr. Chairman, but
14 actually the surveys, I believe, were related to, if
15 you made a claim of, if a person saw an advertisement
16 or a claim and said that you reduce plaque what would
17 their take away be from the message and I don't think
18 there was any data in there that would help you with
19 respect to these two sentences at all. Because these
20 are essentially saying if they had a difference in
21 plaque in their mouth, then it wouldn't be of any
22 cosmetic import to them and of course it's a moot
23 point, claim-wise, because we've decided, you've
24 decided that a plaque -- then the question is do you
25 need the extra two sentences then if it's a moot

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1 point, claim-wise, then the last two sentences are --
2 may be the opinion of the Panel, but is it really
3 relevant a discussion of whether plaque is a
4 therapeutic endpoint or not and I think that's what
5 Lew Cancro is trying to say. He's trying to say that
6 it's really isn't germane to -- see, you wouldn't have
7 seen any of that data because people wouldn't have
8 come in and said with data like that because it was a
9 plaque and gingivitis Panel, not a cosmetic plaque.

10 DR. GENCO: Given that that took place
11 several years ago, I think it's still prudent for Bill
12 to look into that and make sure that those two
13 statements, if deleted, are perfectly deleted, or can
14 be reworded to reflect the consumer survey.

15 DR. WHITE: It seems reasonable, yes.

16 DR. GENCO: Good.

17 DR. WHITE: Could I ask one question at
18 this point, Mr. Chairman?

19 DR. GENCO: Sure.

20 DR. WHITE: In this, before we leave it,
21 on page 31 in this section on drug cosmetic status,
22 one of the things that occurred to me while you folks
23 were discussing it earlier, I mean what you may want
24 this section to -- because I know you're going to go
25 back to it, what you may want this section to look

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1 like is I think the way the section is structured is
2 that you're talking about drug cosmetics status of
3 oral products. In the first four or five paragraphs
4 you define what a cosmetic and a drug are. Then you
5 go into an explanation as to why anti-plaque is, in
6 your opinion, a drug status with gingivitis and then
7 you also have tartar.

8 You might want to contemplate just
9 reformatting this section a little bit and calling it
10 drug, cosmetic status of oral products. Have that
11 general introduction and then have three separate
12 sections. One is anti-gingivitis which is clearly
13 drug. One is plaque which includes all of your
14 descriptions, and then the last one is tartar which
15 you define as cosmetic. And then those three
16 subsections underneath that would be relatively clear.
17 Because see, you started out with anti-plaque products
18 right after the title, drug cosmetic status and you
19 immediately start in with anti-plaque. I think what
20 you're doing is you're establishing drug cosmetic
21 status for oral products, over-the-counter oral
22 products and then that includes gingivitis, plaque and
23 tartar are the three.

24 DR. GENCO: So the one anti-plaque product
25 on page 31 is misplaced?

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1 DR. WHITE: Yes, I was saying yes. If you
2 re-orient it, it may be clearer because the first five
3 or six paragraphs just speak to what the definition of
4 drug is and what the definition of cosmetic is. And
5 then later you get into what plaque is and what tartar
6 is and then you might even want to add a sentence
7 saying gingivitis is clearly a drug indication because
8 you never really mentioned gingivitis per se, only as
9 it's associated with plaque. It's just a thought.

10 DR. GENCO: We'll take that under
11 advisement. It looks like that could be added on page
12 32 before the third paragraph, that is the anti-plaque
13 products.

14 DR. WHITE: Yes, that's exactly what I'm
15 referring to. Then the only question is for
16 completeness, if you had that as the first section,
17 and you had tartar as the second section do you think
18 you need for completeness a section that just says
19 gingivitis and then say gingivitis is clearly a
20 therapeutic drug indication. Maybe you don't. Maybe
21 it's obvious.

22 DR. GENCO: I think it's probably dealt
23 with otherwise.

24 DR. WHITE: If it's obvious, that's all
25 right.

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1 DR. GENCO: What does the Panel feel about
2 that? Taking that subheading one, anti-plaque
3 products on page 31 and putting it on page 32 after
4 the second paragraph and then the second, number two
5 would be tartar and then the idea is that the
6 gingivitis, anti-gingivitis claim is discussed in
7 detail.

8 DR. WHITE: Maybe that will be clearer, I
9 don't know if it is or not. I'm asking.

10 DR. GENCO: We can check to make sure it
11 is.

12 DR. WHITE: Okay. Sorry to get you off
13 track. I guess you're on 37, line --

14 DR. GENCO: Okay, 34, line 17. Add
15 supragingival before the word tartar.

16 DR. WHITE: I think you did that.

17 DR. GENCO: Okay. 37, line 3. Delete the
18 word "dentifrice". Okay. I think we dealt with this
19 too, that we're going to use that generic term for
20 oral care products or whatever it is.

21 37, lines 3 to 9. Could you give us some
22 orientation as to what you want done here? What
23 you're suggesting.

24 DR. WHITE: The question is where it
25 should be located. Because you're talking about

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1 labeling here, because the last portion of the
2 sentence is your description of helps interfere with
3 harmful effects of plaque associated with gingivitis.
4 That was the sort of generic nonspecific plaque claim
5 associated with the effects of the stannous fluoride
6 toothpaste. The question should be where should that
7 section be because you're talking about labeling.
8 Should it be in the labeling section or should it be
9 in this section. I think that's all we're asking.

10 DR. GENCO: Okay, so we'll be advised to
11 look at the B section to determine if it's appropriate
12 here.

13 DR. WHITE: Yes. Marlene has an
14 additional point to raise.

15 DR. GENCO: Bob, is that clear? So we'll
16 look at page 37, B section to determine --

17 MR. SHERMAN: You're asking if it should
18 be just included after the ingredient review rather
19 than in the general labeling section?

20 MS. FEDER: Actually, what we're
21 suggesting in this labeling portion of the report,
22 this is the only place where you give some reasoning
23 as to why you gave up specific indication. And what
24 we're suggesting is just put in the wording for the
25 indication, for the limited plaque claim that you've

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1 allowed for stannous fluoride products and give the
2 rationale for why -- what the support is for giving us
3 that indication back in the safety and effectiveness
4 of stannous fluoride section.

5 So we're actually asking that you --

6 MR. SHERMAN: In other words, they're
7 saying delete this sentence that says "although the
8 Subcommittee concludes the available data, do not
9 provide evidence", in other words take out and just
10 put what the permitted indication is, put the
11 rationale in with the ingredient review.

12 DR. GENCO: Is that what you're asking?

13 MS. FEDER: That's what we're asking, yes.

14 DR. GENCO: Okay. Panel? Agree to look to
15 that and include that in the revision?

16 DR. D'AGOSTINO: I am not sure what
17 actually is going to be there, what will the section
18 now read?

19 MR. SHERMAN: So it would just start with
20 a permitted optional indication and just state what
21 the optional indication is without giving a reason for
22 it.

23 DR. SAVITT: Bob, we probably should
24 include without mentioning stannous fluoride
25 specifically include the concept that there are

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1 products that do not provide available data to show an
2 anti-plaque effect, but do show an anti-gingivitis
3 effect, if I'm reading this correctly. Because
4 otherwise it doesn't seem to make much sense to have
5 an anti-gingivitis effect just floating out there.

6 DR. WHITE: Well, the question would be
7 whether that should be in the section on the
8 ingredients specifically.

9 DR. SAVITT: I agree with your comment
10 that it doesn't make sense to have stannous fluoride
11 specifically named here.

12 MS. FEDER: Actually, based on the
13 discussions from the last Subcommittee meeting, we
14 think it is appropriate that it should be specific to
15 stannous fluoride, but what we don't want in this
16 section or we don't think is appropriate in this
17 section is the rationale for why that alternate
18 indication was given to stannous fluoride. We want
19 the scientific rationale to be put in the back in the
20 safety and effectiveness discussion. So what we're
21 suggesting is that subheading B would read as follows:
22 "For OTC anti-gingivitis drug products containing
23 stannous fluoride, a permitted optional indication is
24 'helps interfere with the harmful effects of plaque
25 associated with gingivitis.'"

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1 And then the explanation of the data that
2 we presented to the Panel to support that would be
3 summarized in the effectiveness section.

4 DR. GENCO: Okay, we could look into that.
5 I think that we have to think about the clarity and
6 the user-friendliness and it might be explained here
7 in a sentence why that decision was made and then more
8 extensively later.

9 DR. WHITE: As a suggestion, where it
10 might go is when you go to page 92 which is where
11 you're talking about stannous fluoride. There you
12 already have a sentence that says "the Subcommittee
13 concludes that" --

14 DR. GENCO: Right.

15 DR. WHITE: "Although it has little effect
16 on plaque formation, stannous fluoride is safe and
17 effective in a dentifrice." You might contemplate
18 putting that --

19 DR. GENCO: But that's 60 pages beyond
20 this. You're asking -- I think one could make an
21 argument for leaving it the way it is based upon it
22 being clearer to the reader why that was done and then
23 later, a more detailed description of that is given.

24 MS. FEDER: For consistency of the
25 section, Dr. Genco, if you look at subheader A, under

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1 "Indications" on page 36. For indications for the
2 other active ingredients, it merely states "this is
3 the recommended indication." Again, it doesn't give
4 a rationale for why the indication was given.

5 DR. GENCO: Okay.

6 MS. FEDER: And so one of the reasons we
7 suggested this was again for consistency within that
8 labeling section.

9 DR. GENCO: Okay, I think we hear you.
10 Thank you very much.

11 Okay, so we will take that into
12 consideration.

13 Page 42, line 10. Insert "anti-gingivitis
14 or" before "anti-gingivitis/anti-plaque agents." I
15 don't think that changes the meaning. It makes it
16 more clear. Is everybody looking at that page 42,
17 line 10. It's the second paragraph. "The
18 Subcommittee concludes that anti-gingivitis,
19 anti-plaque agents." Is this where we were thinking
20 about a slash, anti-gingivitis slash -- yes, not "or".

21 That's the construction, slash.

22 DR. WHITE: I think you want both because
23 stannous fluoride is anti-gingivitis and CPC and the
24 essential oils are anti-gingivitis/anti-plaque.

25 MR. SHERMAN: This implies that only an

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1 ingredient that was approved for both could be
2 combined with an anti-caries agent, so they're saying
3 you should be able to combine either an anti-plaque,
4 excuse me, either anti-gingivitis/anti-plaque agent or
5 an anti-gingivitis agent with an anticaries agent.

6 DR. GENCO: Okay, fine. So it would be
7 anti-gingivitis/anti-plaque or anti-gingivitis agents.

8 MR. SHERMAN: Right.

9 DR. GENCO: Thank you.

10 DR. LISTGARTEN: Could we just say
11 anti-gingivitis since that covers both?

12 DR. GENCO: What does the Panel feel about
13 that?

14 DR. SAVITT: Just for clarity, I would
15 suggest both.

16 DR. GENCO: We have that as a category.
17 Okay, "anti-gingivitis/anti-plaque or anti-gingivitis
18 agents may be combined with anti-caries agents."

19 Okay? Good. Page 43, novel formations to
20 new dose forms. I think we've dealt with that --I'm
21 sorry.

22 DR. SAXE: I was just going to say also
23 for clarity down on the following line, do you have it
24 inhere that the anti-gingivitis or anti-
25 gingivitis/anti-plaque agents may also be combined

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1 with a tooth desensitizing agent."

2 DR. WHITE: Yes.

3 DR. GENCO: Okay, fine. Does anybody
4 object to that? Good.

5 Okay, line 43, excuse me, page 43, line
6 16, "novel formations." I think we've dealt with
7 this. Okay.

8 Page 43, line 23, I think we've dealt with
9 this. Anything new here? Dr. White? Okay.

10 Line 44, excuse me, page 44, line 19, "ex
11 vivo." So that's item c, "demonstrated biologic
12 activity of the formation using a plaque glycolysis
13 and regrowth model that's an ex vivo?

14 DR. WHITE: Yes, it's just the way it's
15 described in the literature, so when you go to the
16 reference. It's just our definition that we use.

17 DR. GENCO: Any objection to that? An ex
18 vivo?

19 Okay, line 4, insert "or" before "30
20 second". That's page 45. Page 45, line 4. Any
21 objection? Okay. We'll incorporate that.

22 Line 56, excuse me, page 56, line 16.
23 Anybody object to that? We're substituting "active
24 ingredient" for "product."

25 Okay, hearing no objections, let's

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1 proceed. Page 56, line 21, toxicological studies,
2 alternatives to animal testing and they've suggested
3 a sentence to be added. Page 56, line 21. Bill?

4 DR. BOWEN: I don't think that's in our
5 remit. This is more a political statement than
6 anything to do with the development of
7 anti-plaque/anti-gingivitis products.

8 DR. GENCO: Further comments? Okay. So
9 we -- consensus is not to include that statement.

10 Page 63, line 11. Irritancy and
11 sensitivity studies in humans to be changed to
12 "irritation and delayed context sensitivity studies in
13 humans."

14 Were those indeed delayed context
15 sensitization? Is that accurate in describing these
16 studies?

17 MR. MERSKI: Jerry Merski with Procter &
18 Gamble, yes, it would be.

19 DR. GENCO: Okay. Any objection to
20 including that correction? Okay.

21 Insert -- excuse me, page 69, line 15,
22 insert "or accepted" before "techniques." Validated
23 or accepted techniques must be used. That's the --
24 any objection to that? Okay. We'll include that.

25 Page 69, line 22. Is there a mistake

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1 here? Should it be one study rather than two? Do you
2 see that?

3 We're talking here about --

4 MR. CANCRO: Would it be two times two is
5 four, is that what we're talking about?

6 DR. GENCO: We're talking about the
7 original clinical trial now for a new product, right?
8 Okay, so -- oh, I see, for a minimum of two studies
9 conducted by independent investigative groups each
10 conducted by an independent investigative group. That
11 would be absolutely clear then. Okay. Two studies,
12 each conducted by an independent investigative group.

13 MR. COLLIER: Greg Collier, Procter &
14 Gamble. What we were referring to there was the
15 Modernization Act where they no longer require two
16 studies.

17 DR. GENCO: Does somebody want to give us
18 --

19 DR. D'AGOSTINO: I don't think we should
20 get into that. I mean that's -- you're talking about
21 mortality studies for 20,000 people where you only
22 need one study. Here you're talking about six month
23 studies with 100 people. I don't think we want to get
24 into substituting with just one trial.

25 DR. GENCO: Okay. Lew?

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1 MR. CANCRO: Bob, I have a request. The
2 audience does not have this guideline so that when
3 we're going over this, if we could read just a little
4 bit more of the sentence so they get an appreciation
5 of what we're talking about.

6 DR. GENCO: Surely. They don't have the
7 Procter & Gamble?

8 MR. CANCRO: They don't have that, no.

9 DR. GENCO: It must be deadly out there.
10 Sorry.

11 (Laughter.)

12 DR. LISTGARTEN: It's even deadly when
13 you've got it.

14 DR. GENCO: Is it possible for them to get
15 a copy? Let's see if we can get some copies.

16 DR. WHITE: Procter & Gamble prefers that
17 the audience doesn't see copies.

18 DR. GENCO: All right. Okay, I will read
19 more of where we are and what we're doing.

20 Okay, the next is page 69, line 22.

21 DR. LISTGARTEN: What was the outcome of
22 that last discussion?

23 DR. GENCO: Two studies by at least two
24 independent investigative groups. Two studies each
25 conducted by an independent investigative group or

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1 some such phraseology.

2 Yes?

3 MR. CANCRO: Bob, I'm sorry, the industry
4 did have a comment on that, Bob, specifically to that.

5 DR. GENCO: Okay.

6 MR. CANCRO: And their suggestion was on
7 page 94 of the book, same sentence, "positive evidence
8 of drug effectiveness should be obtained from a
9 minimum of two studies, preferably conducted by at
10 least two independent investigative groups."

11 DR. LISTGARTEN: I think our sentence is
12 clearer.

13 DR. GENCO: "Preferably" allows then the
14 possibility for one group to do both studies.

15 MR. CANCRO: Yes, what the implication is
16 is that you could have one principal investigator who
17 may conduct two independent studies at different
18 sites. That's the issue, not at the same site. I
19 mean it's conceivable that you could have two
20 independent studies, but one man would run both of
21 them as the PI or something like that.

22 DR. GENCO: I think the intent is that
23 there would be two independent groups. I know that
24 sometimes they're run this way, one big study, ten
25 sites, five consist of one study and five consist of

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1 another, but generally they're made independent by
2 having two PIs, but maybe coordinated. I think there
3 are ways of doing this that are efficient, but still
4 represent two independent groups, the PIs being
5 independent, representing the independence of the
6 group. I think that's the intent.

7 I mean they could follow the same profile.
8 I think industry knows how to do these things so that
9 they're appropriate, still independent, represent two
10 studies.

11 DR. LISTGARTEN: Wouldn't it be a
12 multi-center study if one person coordinated several
13 centers to do a study? It would be a multi-center
14 study.

15 DR. GENCO: I don't think we'd get into
16 that. We'd say two studies. They could be
17 multi-center.

18 MR. CANCRO: Yes, but they have to be
19 independent.

20 DR. GENCO: But they have to be
21 independent.

22 MR. CANCRO: You can't have the same
23 investigator.

24 DR. GENCO: Right, so the PI would be
25 different. That would be a key difference,

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1 differentiating independent studies from two studies
2 that aren't independent.

3 My point was there are ways of doing this
4 using, efficiently, obviously. One way is to have a
5 ten center study, two different PIs, one for five and
6 one for the other five, but similar protocol. But the
7 independence is there because the PI would be
8 responsible for his five or her five centers.

9 DR. LISTGARTEN: But there would be
10 different PIs.

11 DR. GENCO: Different PIs would be the
12 key, I think.

13 DR. LISTGARTEN: That's the key.

14 DR. GENCO: Right. Okay, so you like the
15 wording that we have there.

16 Lew, are you unhappy with that? "Minimum
17 of two studies each conducted by an independent
18 investigative group." Okay, thank you.

19 All right, pages 70 to 210, really moving
20 along here.

21 (Laughter.)

22 Remove all references to labeling
23 requirements from the ingredient safety and
24 effectiveness discussions. This information is
25 covered on pages 34 to 39 of the Panel report. Okay,

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1 so we're referred to pages 30 to 39, excuse me, I'm
2 confused now. We're referred to page 70 of the draft
3 Panel report to 210.

4 MS. FEDER: Right. What we're suggesting
5 is you just finished reviewing a section on pages 34
6 to 39 which encompasses labeling for the ingredients
7 that are Category 1 under this rule making.

8 DR. GENCO: Okay.

9 MS. FEDER: And there also references to
10 labeling in each of the ingredient discussions and
11 we're suggesting that you delete it from the
12 ingredient discussions and keep it in front of the
13 Panel report.

14 DR. GENCO: Okay, I understand. Does
15 everybody understand that, first of all, and secondly
16 comments on it. In other words, we have already, on
17 pages 34 to 39 of the report gone over labeling
18 considerations. There are other labeling references
19 in subsequent pages of the report, pages 70 to 210,
20 and what they're asking is that we remove those
21 references to labeling because they're already covered
22 in 34 to 39.

23 DR. D'AGOSTINO: Are they all redundant or
24 is there anything specific? I don't remember.

25 DR. GENCO: This looks like it's going to

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1 take some time to do. We're probably not going to be
2 able to do that around the table.

3 MR. SHERMAN: I think that's basically a
4 format issue.

5 DR. GENCO: Okay, fine.

6 MR. SHERMAN: We'll note that and consider
7 doing that.

8 DR. GENCO: Thank you. In other words, to
9 remove those that are redundant. If some aren't, to
10 leave them. Or if some are -- there's a reason to
11 include them twice, to include them twice. Okay.

12 MR. CANCRO: Bob, on this issue --

13 DR. GENCO: Yes.

14 MR. CANCRO: I think one of the things
15 you're going to find as you go through it is that
16 there's been an attempt to label many of the Category
17 III ingredients and that's just unnecessary because
18 that hasn't happened, that labeling hasn't been the
19 result of the agent being effective. So that could
20 all be eliminated.

21 DR. GENCO: Is there any reason to label
22 the Category III ingredients?

23 MR. SHERMAN: No, those types of things
24 probably got in there from the original reports and
25 were never taken out.

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1 DR. GENCO: Okay, thank you. Excuse me,
2 some more comments on pages 70 to 210?

3 "While literature references are important
4 supportive data for substantiating the safety and
5 effectiveness of active ingredients, the pivotal
6 information in the safety and effectiveness
7 determinations is the data supplied by the sponsor.
8 Therefore, we recommend that for each active
9 ingredient, the literature review of the ingredient
10 safety and/or efficacy be summarized first, followed
11 by the sponsor's data and then directly to the Panel's
12 conclusion."

13 Is there a reason for that? If you're
14 talking about science, can't you mix what's in the
15 literature with what the companies have supplied to
16 us. We're assuming that they're legitimate and well
17 done, as well done as literature references.

18 MS. FEDER: And we agree that everything
19 should be included. It's just as we read through some
20 of the sections and again this is a formatting
21 suggestion --

22 DR. GENCO: Right.

23 MS. FEDER: It's based on the independent
24 reviewer and how each reviewer chose to deal with the
25 data and we're just making a suggestion that what we

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1 believe is most pivotal for our ingredients in making
2 the safety and efficacy decisions, where the clinical
3 studies that we conducted on our ingredients, so we're
4 recommending that literature is supportive of what's
5 really critical to the Panel's decision and what leads
6 most directly from a thought flow standpoint to the
7 Panel's conclusion is the data submitted by the
8 sponsor and so that's just a recommended order for
9 consistency throughout the ingredient review.

10 DR. GENCO: Okay, so consider this in the
11 formatting as appropriate.

12 MR. SHERMAN: Yes, and I just want to make
13 another point going back to what we talked about
14 before. Another reason that the Category III labeling
15 should be included is in case an ingredient is updated
16 in the future, that that information needs to be
17 somewhere in the report, otherwise, it could get lost.

18 DR. GENCO: Lew? I'm sorry, I didn't know
19 you were talking.

20 Bob Sherman said that Category III should
21 be labeled in case they're upgraded.

22 MR. SHERMAN: We lay out specific labeling
23 for the accepted ingredients, but we need somewhere to
24 have, to reflect labeling for Category III ingredients
25 that may be upgraded in the future. We don't want to

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1 lose those things.

2 DR. GENCO: I guess that make sense.

3 MR. SHERMAN: A different place would be
4 appropriate, but we need to have it there.

5 DR. GENCO: Certainly the safety is also
6 an issue where you've also looked at it and if there's
7 any labeling to that, that would be appropriate. But
8 the specific, these specifics of the label going into
9 what dose, you can't put that together until you have
10 that in terms of the effectiveness of the product, so
11 I don't know how to handle that. I mean what are you
12 suggesting?

13 DR. KATZ: In some of the other reports,
14 it has been there, to going back to use as reference
15 and either at some point in time when a monograph
16 becomes finalized, either it's been upgraded and it's
17 been added in or it's not been upgraded and then it's
18 been deleted.

19 Remember that this is still kind of, in a
20 sense, a preliminary type of report. We're not
21 talking about a final monograph at this point in time,
22 so that it's possible that by the time it gets
23 finalized it will no longer be relevant and will no
24 longer need to be there.

25 The only question would be from a

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1 formatting issue, in the past what we've done is kind
2 of put it at the back of after you've listed Category
3 I ingredients, then to Category III. I guess we could
4 just discuss where might be a best place to put it, in
5 essence, as a kind of a reference so that it doesn't,
6 someone doesn't get lost in looking at the Category
7 III, you get confused as to what's Category I versus
8 Category III.

9 Sort of more of a formatting type of an
10 issue.

11 DR. GENCO: Yes.

12 DR. WRIGHT: Yes, I think in order not to
13 lose it, it's probably okay in the Category III
14 sections to leave some of the discussion there, but I
15 think for the Category I ingredients, I think we have
16 a process issue here again where some things were
17 recommended in an initial reviewer's report that were
18 never necessarily voted on by the Committee and then
19 we went through some discussions where we talked about
20 what the labeling was and those issues are captured in
21 the beginning. So you have sections here that list
22 those preliminary conclusions and we don't think that
23 those are appropriate.

24 DR. KATZ: Actually, it sounds like then
25 we're talking about two different issues right. We're

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1 talking about one issue as to Category III and then
2 we're talking about one issue for Category I and what
3 to do with some of the things that may not have
4 necessarily been voted on in Category I.

5 DR. WRIGHT: Right, and I guess what I'm
6 saying is it's probably a good idea to leave it in the
7 scientific discussion for the Category III, but put it
8 in the front where we have all the labeling
9 discussions and delete it from the Category I.

10 DR. GENCO: Okay, thank you. That's very
11 helpful.

12 The next is page 70, line 16 -- yes?

13 DR. D'AGOSTINO: I'm sorry, what about the
14 request to have the literature, then the sponsor's
15 data and the conclusion that we --

16 DR. GENCO: I thought we were going to
17 consider that in the reformatting as appropriate. It
18 may be that for some products the literature is more
19 supportive than the sponsor's studies. It would seem
20 to me that would be appropriate for each -- we do that
21 in a reasonable way.

22 DR. D'AGOSTINO: I do think at times the
23 sponsored studies were really very important and mixed
24 the literature with the sponsor's studies or not have
25 that impact of what was really the basis of the

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1 conclusions of the Panel is probably a bad feature.
2 So I would support going through and just say
3 formatting so that the cases where the literature is
4 just sort of background, the sponsor's material was
5 essential, really comes through in the presentations.

6 DR. GENCO: Okay, I think we could do
7 that.

8 Bob, is that -- that's reasonable and
9 clear, good.

10 Matt?

11 DR. DOYLE: Like Michael, I'm here to make
12 sure we're getting your progress report. We're
13 getting into the next section which is my cue.

14 DR. GENCO: Okay.

15 DR. DOYLE: We're taking a WWF approach to
16 this.

17 DR. GENCO: Page 70, line 16. Add
18 "Minimally chemically available" before "72 to 77
19 percent" and delete "bioactive" after "percent." The
20 paragraph should now read, "Of 0.045 to 0.1 percent
21 minimally 72 percent chemically available
22 cetylpyridinium chloride." Sounds reasonable and is
23 an accurate representation of the studies. We have
24 looked at that. We're aware of that inaccuracy.

25 Any questions or problems with that?

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1 Okay, thank you.

2 Page 70, line 21. Change .025 percent to
3 .1 percent or .025 percent to .01 percent.

4 DR. DOYLE: Yes, that's basically a typo.

5 DR. GENCO: Okay, that will be done.
6 Cetylpyridinium misspelled. Okay, next. That will be
7 taken care of.

8 Page 72, line 14. We believe the
9 reference used to support the oral LD-50 as reported
10 by Nelson and Lister, 1946, if this is the reference,
11 the LD-50 is incorrectly listed as 20 milligrams per
12 ml. It should be 200 milligrams per kilogram. We'll
13 check that. Okay, good.

14 Page 75, line 1, change "systemically" to
15 "systematically." Does that change the -- page 75,
16 line 1. "The safety data were systemically" --
17 systematically, it should be.

18 DR. DOYLE: Correct. That's a typo.

19 DR. GENCO: Okay, that will be done. Page
20 75, line 21, change 0.12 to 8 milligrams or 0.12 to
21 0.82 micrograms from milligrams to micrograms. Okay.
22 That will be done.

23 Page 76, line 14. "The conclusion for the
24 safety section does not appear to follow logically
25 when presented directly after summarizing information

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1 from the FDA's spontaneous adverse reaction reports.
2 The conclusion would be more effectively presented in
3 a separate paragraph which more clearly supports the
4 conclusion that CPC is safe for use in mouth rinse
5 formulations. The following language is suggested to
6 replace lines 14 through 17 on page 76." Okay, that
7 line, as I take it, reads now, "Overall, it appears
8 that cetylpyridinium chloride is safe when used in a
9 concentration of .04 percent to 0.1 percent in
10 formulations such as mouth rinses." You want to
11 substitute, you're suggesting substituting that for
12 your statement.

13 MR. MERSKI: No, actually what we were
14 suggesting was to right before the sentence that
15 begins "overall, it appears" to insert that or tag
16 that, put our paragraph in there in front of that
17 sentence.

18 DR. GENCO: Okay --

19 MR. MERSKI: It's not actually a -- we're
20 not deleting anything. All we're doing is adding the
21 lines there.

22 DR. GENCO: First of all, I think for the
23 record, state your name?

24 MR. MERSKI: Jerry Merski with Procter &
25 Gamble.

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1 DR. GENCO: Okay, now would you -- we're
2 on page 76.

3 MR. MERSKI: We're on page 76.

4 DR. GENCO: There's the first paragraph.

5 MR. MERSKI: The first paragraph, just
6 before the second paragraph, you would end the first
7 paragraph with the sentence that ends "these severe
8 adverse events" and then go to the paragraph that
9 we're suggesting, to the next one that's in our text.

10 DR. GENCO: So --

11 MR. MERSKI: Rather than having the
12 conclusion follow the sentence that ends in "these
13 severe adverse events" you would insert "in summary,
14 the safety of CPC" and so forth.

15 DR. GENCO: I'm sorry, I don't see "these
16 severe."

17 We're on page 76. There's one paragraph
18 that begins, "The data" --

19 MR. SHERMAN: You see number two,
20 "effectiveness" -- it's three lines above that.

21 MR. MERSKI: Right.

22 DR. GENCO: Three lines above. Okay, so
23 it's the same sentence I said to take out. You're
24 trying to confuse me and you're doing it.

25 (Laughter.)

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1 Okay, okay. "Overall, it appears that
2 cetylpyridinium chloride is safe", etcetera. You want
3 to take that sentence out. No?

4 MR. MERSKI: Actually, it's in our
5 paragraph. All we're doing is adding some language in
6 front of that.

7 DR. GENCO: Okay, you want to add language
8 in front of that?

9 DR. LISTGARTEN: The language that is
10 added also contains that statement, so you --

11 MR. MERSKI: We didn't change the
12 conclusion, just added a few sentences.

13 DR. GENCO: I worked hard on that
14 sentence, thank you.

15 (Laughter.)

16 MR. MERSKI: Very good.

17 DR. GENCO: Okay, so what you're
18 suggesting then is after the sentence "It is not clear
19 to what extent other ingredients in the mouth rinse
20 contribute to these severe adverse events" you're
21 suggesting this sentence or two, "In summary, the
22 safety of cetylpyridinium chloride has been
23 extensively evaluated in a variety of controlled,
24 nonclinical and clinical studies. This information,
25 in addition to post-market adverse event data

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1 collected over a period of more than 50 years during
2 which mouth rinse products containing cetylpyridinium
3 chloride were sold in the United States, permits final
4 safety classification of cetylpyridinium chloride.
5 Overall, it appears that cetylpyridinium chloride is
6 safe when used at 0.04 to 0.1 percent concentrations
7 in formulations such as mouth rinses."

8 Okay, does the Panel have any problem with
9 that?

10 Bill?

11 DR. BOWEN: Final, it's a bit final, isn't
12 it?

13 DR. GENCO: Permits safety classification.

14 DR. BOWEN: That's fine.

15 DR. GENCO: Okay, Bob? The Panel seems to
16 agree.

17 Lew? In other words, to take that
18 paragraph or that -- those two sentences and add them
19 before "overall", after "adverse events."

20 MR. MERSKI: Grammatically, it may be
21 easier just to put that in as a separate paragraph,
22 that gives you kind of a -- where you'd actually begin
23 "In summary."

24 DR. GENCO: Good thought. Okay. Is that
25 clear, Bob?

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1 MR. SHERMAN: So we're not changing this
2 in any way, but we are inserting it there?

3 DR. GENCO: That's right. As a new
4 paragraph and omitting the word "final" from the
5 "permits final safety", about three lines from the
6 bottom of their -- from the end of their statement.

7 Fred?

8 DR. HYMAN: In that same paragraph, right
9 before all of that, I had commented on this at the
10 last meeting and I saw that a sentence was added. I'm
11 still troubled about the three deaths and six subjects
12 going into a coma and the sentence that was added that
13 was trying to alleviate that concern was "It is not
14 clear to what extent other ingredients in the mouth
15 rinse contributed to these severe adverse events."
16 I'm still not happy with that. I'm suggesting that
17 the Panel think about "the spontaneous reporting
18 adverse/reaction report" that they talk about I
19 haven't seen those, although with the references we
20 probably could get them. What I'm suggesting is maybe
21 it is not clear to what extent other circumstances
22 contributed to these severe adverse events to take it
23 away from the actual product, whether it be active or
24 inactive ingredients. So I'm wondering if we could,
25 the Panel could, think about changing that sentence.

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1 DR. GENCO: Comments on that?

2 MR. CANCRO: I think that's an appropriate
3 change, Fred. You can't say it's the ingredients.
4 You don't know what it is, but the circumstances are
5 suspicious. So it's --

6 DR. GENCO: I went over that data and I
7 would have no problem with that revision either.
8 Okay?

9 Okay, Bob, is that clear then? Take
10 Fred's suggestion and also take Procter & Gamble's
11 suggestion with the elimination of the word "final."

12 Okay, page 78, line 6 to 7. Change
13 "reduced plaque and gingivitis" to "reduced plaque" as
14 this was a four day plaque study. I agree completely
15 with that. I reviewed that and that's my mistake. So
16 let's do that.

17 Page 78, line 14. Change
18 "bioavailability" to "biologic effectiveness for
19 increased accuracy." That's page 78, line 14.

20 That sentence reads now, "Based on the
21 data presented, bioavailability and chemical
22 availability appear to be greatly affected by the
23 particular formulation of cetylpyridinium chloride
24 containing mouth rinse." So you're suggesting that
25 biologic effectiveness be substituted for

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1 bioavailability so the sentence would now read, "Based
2 on the data presented, biological effectiveness and
3 chemical availability appear to be greatly affected."

4 DR. DOYLE: That's correct.

5 DR. GENCO: Okay, thank you.

6 DR. DOYLE: Recall at our conversations
7 there bioavailability connotes something from a
8 pharmacokinetic standpoint. We didn't want to confuse
9 the issue, given that not we're doing anything
10 systemical here. So our consistent language
11 throughout is chemical availability and biological
12 effectiveness.

13 DR. GENCO: Anybody on the Panel object to
14 that? Okay. Seems reasonable. Thank you.

15 Cell to micelle. That's page 78, line 24.

16 DR. DOYLE: For the record keeper, I'm Dr.
17 Matt Doyle with Procter & Gamble.

18 DR. GENCO: That's the very last line on
19 page 78. Micelle formation.

20 DR. WU: Why is it bolded?

21 DR. GENCO: Why is it bolded? Maybe there
22 was some question about it. It shouldn't be bolded.

23 MR. SHERMAN: Could you repeat that?

24 DR. GENCO: Sure. Okay, on page 78, the
25 very last line, there's a bolded cell formation. That

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1 should be unbolded and it should be "micelle" M-I-C-E-
2 L-L-E formation.

3 MR. SHERMAN: Thank you.

4 DR. GENCO: Page 79, line 4. Seventy-six
5 percent to 77 percent. Okay.

6 DR. DOYLE: That's just a typo.

7 DR. GENCO: Right. Page 79, line 6,
8 change containing 72 to 76 percent available to
9 containing at least 72 percent chemically available
10 cetylpyridinium chloride at a nominal concentration of
11 .045 to .1 percent for increased accuracy.

12 DR. DOYLE: That's consistent with the
13 very first paragraph in this section that you started
14 out with.

15 DR. GENCO: Sounds reasonable. Anybody
16 comment on that? Okay.

17 All right, page 79, line 9.

18 MR. SHERMAN: Excuse me, can I interrupt
19 this? I'm just seeing a note that I had written here.
20 Under -- on page 79 of the draft, under No. 3 in
21 proposed dosage, it talks about .025 percent to .02 to
22 0.1 percent as a dosage, but at the beginning of the
23 report I think it was .045. It seems to be an
24 inconsistency there.

25 DR. DOYLE: That's the correction we made.

1 It should be .045. Sorry.

2 MR. SHERMAN: Thank you.

3 DR. GENCO: On line 9 of page 79, to
4 accurately reflect additional information submitted to
5 the Panel subsequent to our initial presentation
6 insert the following and place it at the paragraph
7 beginning "furthermore, based on analysis." So that
8 paragraph -- actually, it's the second paragraph on
9 page 79 begins, "Furthermore, based upon analysis"
10 they're suggesting that the paragraph read thus:
11 "Furthermore, at the request of the Subcommittee, the
12 sponsor conducted additional analysis demonstrating
13 cetylpyridinium chloride effectiveness on a site and
14 subject basis relative to other oral health care
15 practices and on the basis of odds, ratios,
16 calculations. Specifically, using a minimum 30
17 percent reduction in bleeding criteria, the results of
18 four long-term studies of cetylpyridinium chloride
19 were pooled to estimate an overall odds ratio for
20 improvement relative to a placebo. After three months
21 of product use, the odds ratio was 3.12 of the 95
22 percent confidence interval of 2.85 to 3.45. After
23 six months, the odds ratio was 3.1 with a 95 percent
24 confidence interval 2.75 to 3.45. Based upon the
25 totality of the data, the Subcommittee concludes that

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1 cetylpyridinium chloride is effective as an
2 anti-gingivitis/anti-plaque agent."

3 Stan?

4 DR. SAXE: I think that has merit. I
5 would concur.

6 DR. GENCO: Does this go far enough to
7 satisfy the rationale for doing this? In other words,
8 this is the clinical significance discussion that we
9 had this morning.

10 Stan, you were going to look into that.

11 DR. SAXE: Yes, I'm not saying that it
12 fulfills the request you made for developing a
13 rationale, but in terms of giving us some more
14 specific data that wasn't mentioned before and what
15 should be here I think this is appropriate.

16 DR. GENCO: Okay, any further comments on
17 this? I certainly would have no objection to it
18 either. Okay, let's include it then.

19 Just so we're clear, that's a substitute
20 for the entire second paragraph on page 79.

21 DR. DOYLE: Yes, Bob, that embodies your
22 opening and your closing line and he's just inserted
23 the relevant data at the appropriate place in
24 intermittent.

25 DR. GENCO: Okay, thank you. Now, page

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1 81, line 14, change tin to stannous. That's done.

2 DR. LISTGARTEN: Stannous what?

3 DR. GENCO: Fluoride. Page 81, line 14.

4 Studies conducted and human volunteers received 50
5 milligrams per day of tin revealed that about 3
6 percent of the dose is absorbed. Should that be
7 stannous ion? 50 milligrams per day of stannous ion
8 reveal that about 3 percent of the dose is absorbed?

9 MR. MERSKI: That would probably be
10 accurate.

11 DR. GENCO: Okay.

12 DR. BOWEN: Stannous ion is what, Bob?
13 Stannous chloride, stannous fluoride?

14 MR. MERSKI: Wouldn't be given as a
15 stannous salt, so you would be looking at the stannous
16 ion content.

17 DR. GENCO: So that 50 milligrams per day
18 refers to the stannous ion content of whatever salt
19 was given.

20 MR. MERSKI: Given. If we want to say --

21 DR. BOWEN: Would it be stannous or
22 stannic?

23 MR. MERSKI: Stannous, probably stannous
24 chloride.

25 DR. BOWEN: Chloride.

1 DR. GENCO: Chloride.

2 MR. MERSKI: Chloride, not fluoride. No.
3 Definitely not fluoride.

4 DR. LISTGARTEN: Stannous chloride?

5 DR. GENCO: So 50 milligrams per day of
6 stannous chloride. Okay.

7 DR. BOWEN: That's not the same. Is it 50
8 milligrams of the stannous ion as stannous chloride?

9 MR. MERSKI: Right.

10 DR. GENCO: Okay. Are we happy with that
11 or should we check that? We're sure of that then?

12 MR. MERSKI: I don't have the reference
13 with me, so we can confirm it with a reference.

14 DR. GENCO: Probably a good idea. In
15 other words, these human studies, the humans were
16 given stannous chloride and you did a calculation and
17 it was 50 milligrams per day of stannous ion in that
18 stannous chloride. Okay, fine.

19 MR. MERSKI: We should check that.

20 DR. GENCO: Page 81, line 15 through 18.
21 The existing paragraph implies that NTP testing was
22 conducted on stannous fluoride dentifrice when it
23 actually was conducted on stannous chloride. For
24 accuracy, replace the existing paragraph with the
25 following, so line 15 is the paragraph we were

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1 discussing, isn't it?

2 MR. MERSKI: No, it's just below that.

3 DR. GENCO: Oh, it's the next paragraph.

4 MR. MERSKI: Yes.

5 DR. GENCO: Sorry.

6 MR. MERSKI: Begins "the safety factor of
7 5,000."

8 DR. GENCO: Okay, so page 81, if you look
9 at the third paragraph down, it begins a safety factor
10 of 5,000, etcetera. Suggestion is to replace that
11 paragraph with this paragraph. "Based on results from
12 a 13-week oral toxicity study on stannous chloride
13 conducted through the National Toxicology Program,
14 NTP, a safety factor of 5,000 exists for potential
15 exposure to stannous salts from use of a dentifrice
16 containing 0.454 percent stannous fluoride. The
17 safety factor is defined as the ratio between no
18 observed adverse effect level, NOAEL, in the NTP study
19 and the anticipated exposure to stannous salts from
20 twice daily use of stannous fluoride toothpaste." Any
21 comments to that?

22 Bill?

23 DR. BOWEN: No, it's okay.

24 DR. GENCO: Any other comments? Okay,
25 thank you.

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1 DR. SAXE: Is it clear that in the
2 original draft it says a study in rats. Is this clear
3 that this is an animal study?

4 DR. GENCO: In the reword, in the original
5 it was rats. In the reword, it isn't. It isn't
6 mentioned.

7 MR. MERSKI: The study was done in rats.

8 DR. GENCO: Should we add that? Results
9 based on a 13-week oral toxicity study on rats with
10 stannous chloride" or "conducted on rats". We can add
11 that, whatever.

12 Okay. So Bob we're going to add the rats
13 to that paragraph. Sorry.

14 MR. SHERMAN: Tell me how that reads
15 again.

16 DR. GENCO: The Procter & Gamble comment,
17 page 81, line 15 through 18. It's the third paragraph
18 on page 81. To be substituted with their paragraph,
19 "based on results of a 13-week oral toxicity study
20 carried out in rats." Add the phrase "carried out in
21 rats on stannous chloride".

22 MR. SHERMAN: Okay.

23 DR. GENCO: Revise that. Okay, next
24 section 80 to 81. That's, excuse me, pages 80 to 82,
25 this section does not provide an overview of the

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1 clinical and microbiologic data which helps support
2 the safety of stannous fluoride. The following
3 language is suggested to be inserted following line
4 18, page 81. So page 81 has line 18, must be the last
5 paragraph then. Beginning "stannous ion".

6 MR. MERSKI: Yes, this paragraph would be
7 inserted just in front of that.

8 DR. GENCO: Okay, so between the third and
9 fourth paragraph on page 81 to insert -- the
10 suggestion is to insert this paragraph. "The safety
11 of stannous fluoride in various dosage forms including
12 dentifrice, mouth rinse and gels has been evaluated
13 based on information from six controlled clinical
14 trials" and the trial numbers are listed here.
15 "Spontaneous adverse event data on previously marketed
16 stannous fluoride dentifrice products reported to the
17 sponsor, the FDA spontaneous reporting system and in
18 the literature. Overall, no clinically significant
19 health effects were noted for stannous fluoride
20 dentifrices compared to controls using the clinical
21 studies, other than tooth and tongue staining.
22 Spontaneous adverse report data indicate that the
23 stannous fluoride dentifrices were well tolerated with
24 a safety profile similar to that of the currently
25 marketed fluoride dentifrice products. Microbiologic

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1 analysis of plaque samples taken during clinical
2 trials indicate that the stannous fluoride dentifrices
3 do not affect plaque ecology or plaque susceptibility,
4 further supporting the overall safety of stannous
5 fluoride."

6 So that's an insert between the last two
7 paragraphs on page 81.

8 DR. BOWEN: Bob, may I draw your attention
9 to page 80 under safety. The opening sentence reads
10 "Stannous fluoride has been used as an OTC caries
11 preventive agent in toothpaste in the United States
12 since 1954. Since 1981, it's largely been replaced by
13 sodium chloride of monofluorophosphate." What I want
14 to draw your attention to is the next sentence.
15 "However, during it's 27 year marketing history, it's
16 estimated at least 70 billion doses of stannous
17 fluoride were sold in the United States." That's a
18 long market history pertaining to its safety. I don't
19 see that this paragraph adds anything of significance
20 to this.

21 DR. GENCO: Other comments from the Panel?

22 Yes.

23 DR. WHITE: Don White, Procter & Gamble.
24 The only issue would be is that the formulation that's
25 actually marketed today, you know the safety data was

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1 collected on that formulation as well and for
2 completeness it might be useful to have that included,
3 really. That's really the only rationale because the
4 material -- it's the same as stannous fluoride
5 toothpaste, obviously, but the toothpaste we sell
6 today is a silica abrasive and a few other things.

7 DR. BOWEN: But it's the safety of the
8 stannous fluoride we're concerned with.

9 DR. WHITE: I understand. I understand.

10 DR. LISTGARTEN: Some of the contents of
11 that paragraph also are found in the following
12 paragraph. It begins with stannous ion and stannous
13 fluoride also talks about staining and more
14 specifically refers to what was found in different
15 studies. So I that between what's at the beginning
16 and what's after, we kind of cover the waterfront.

17 DR. GENCO: Further comments? Okay, so
18 the feeling of the Panel is not to include that
19 paragraph.

20 Page 81, line 21. For accuracy replace
21 "in studies CC-191, CC-238 and CC-247", 2.1 percent of
22 subjects discontinued the trial early due to
23 self-perceived tooth staining. Okay now, they go on
24 to say, Procter & Gamble goes on to say "some of the
25 data Procter & Gamble submitted to the Subcommittee in

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1 support of the effectiveness of stannous fluoride have
2 been omitted from this section, pages 82 to 93, in the
3 interest of fair balance we recommended that this
4 additional information be noted as in the next several
5 comments." Excuse me, that's another issue.

6 Let's go back to the original issue of
7 adding the study numbers, page 81, line 21. Bill, do
8 you have any feeling on that.

9 DR. LEUSCH: Excuse me, Dr. Genco. Dr.
10 Mark Leusch from Procter & Gamble. What we've added
11 is the last few words there. I just lost my place.
12 After 2.1 percent, we've added "of subjects
13 discontinued the trial early due to self-perceived
14 tooth staining." That's what that 2.1 percent number
15 referred to.

16 DR. GENCO: Oh, I see. In the existing
17 next to the last line on page 81, it ends with 2 --

18 DR. LEUSCH: 2.1 percent.

19 DR. GENCO: There was an overall
20 prevalence of standing of 2.1 percent.

21 DR. LEUSCH: Right. It wasn't the overall
22 prevalence of the study. That was the percentage of
23 subjects who disenrolled from that trial early.

24 DR. GENCO: Okay. So it's not the
25 addition of the numbers of studies. I'm sorry.

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1 Bill?

2 DR. BOWEN: I can't remember exactly, so
3 I'll accept what P & G said.

4 DR. GENCO: Okay. Yes, Stan?

5 DR. SAXE: Mr. Chairman, another small
6 point. Go back to the top of this page, Procter &
7 Gamble's page. First line, fourth word, ration.
8 Should not that be ratio?

9 DR. GENCO: Yes, that's corrected, thank
10 you.

11 Okay, Bob, is it clear then that this
12 comment, page 81, line 21, is recommended to be
13 incorporated into the report.

14 Okay, now there's another -- see if I
15 understand this. You have underlined this statement
16 that I just read. Some of the data P & G submitted to
17 the Subcommittee in support of the effectiveness have
18 been omitted on pages 82 to 93. Are you saying the
19 rest of what's on -- how much of this -- the rest of
20 the report pretty much is on that?

21 MS. FEDER: Actually, Dr. Genco, that
22 statement is in the wrong place.

23 DR. GENCO: Okay, good.

24 MS. FEDER: It should be at the top of the
25 next page, before page 85, line 16.

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1 DR. GENCO: Okay, so that should be on top
2 of page --

3 MS. FEDER: On top of the next page of our
4 comments.

5 DR. GENCO: Right on top of the next page.

6 MS. FEDER: Yes. That's the information
7 that we think is missing and needs to be added to the
8 report in the interest of fair balance.

9 DR. GENCO: Okay, fine. I have a
10 suggestion. Why don't we finish up this page and then
11 we'll go to that. All right, good.

12 So we're on page 83, line 3 to 6. Remove
13 information regarding caries efficacy of stannous
14 fluoride as this is not pertinent to a plaque and
15 gingivitis rule making. That's page, lines 3 to 6.
16 It says stannous fluoride has a long and
17 well-established history as a caries preventive agent.
18 They want us to remove that.

19 Bill, do you have a feeling on that?

20 DR. BOWEN: I have no problem with
21 removing it, probably not as effective as the sodium
22 fluoride or monofluoride phosphate, but the remainder
23 of the sentence should stay.

24 DR. GENCO: Okay, so the strike "stannous
25 fluoride has a long and well-established history as a

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1 caries preventive agent, although it is probably not
2 as effective as sodium fluoride or monofluoride
3 phosphate. Stannous fluoride at a concentration of .4
4 percent results in a concentration of 970 parts per
5 million fluoride reference."

6 Strike all of that?

7 DR. BOWEN: No, just "probably not as
8 effective as sodium fluoride of monofluoride
9 phosphate." That part.

10 DR. GENCO: Okay, keep "stannous fluoride
11 has a long and well-established history as a caries
12 preventive agent."

13 Strike "although it is probably not as
14 effective as sodium fluoride or monofluoride
15 phosphate" with its reference.

16 DR. BOWEN: Right.

17 DR. GENCO: Then begin, "Stannous fluoride
18 at a concentration of .4 percent --

19 DR. BOWEN: Correct.

20 DR. GENCO: Okay. Did you get that, Bob?
21 I read it fast.

22 MR. SHERMAN: Was that striking the entire
23 first sentence.

24 DR. GENCO: No. Just from "although" --
25 just the "although" phrase.

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1 MR. SHERMAN: To after the 8 reference.

2 DR. GENCO: That's it.

3 MR. SHERMAN: Got it.

4 DR. GENCO: Okay. Now the rest of this
5 statement is if the Panel requires this information to
6 be included, it is suggested that the language be
7 modified and you had a modification. We felt that
8 it's not necessary, so therefore, Procter & Gamble is
9 recommending alternate wording to what we just struck,
10 since we struck it, it's irrelevant.

11 Okay, page 84, line 5. For added clarity,
12 insert Turesky modified Quigley Hein before plaque
13 index. Does anybody have a problem with that? Okay.

14 Page 84, line 15 through 17, change CC174,
15 demonstrated statistically significant differences in
16 the indices from the stannous fluoride group compared
17 to the negative control. Change that statement to
18 this one: Study CC174 demonstrated statistically
19 significant differences in the indices from the
20 stannous fluoride group compared with the negative
21 control at the 1.5 and 3 month grading periods.
22 However, all indices were not significant at the 7
23 month grading period. It sounds like there's more
24 specificity here relative to the time periods.

25 Bill, would you have any problem with

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1 that?

2 DR. BOWEN: It's okay.

3 DR. GENCO: Bob, is that clear?

4 MR. SHERMAN: Yes.

5 DR. GENCO: Page 85, line 12, change three
6 studies to two studies. Any problem with that,
7 anybody on the Panel?

8 I'm sorry, I'm going fast here. 85,
9 that's page 85, line 12. It looks like it's in the
10 middle of that paragraph in three of the six studies.
11 Should that be --

12 MR. CANCRO: Second paragraph.

13 DR. GENCO: Second paragraph in the
14 middle, should be in --

15 MR. CANCRO: Two of the six.

16 DR. GENCO: Two of the six studies, okay.
17 Do you see that?

18 DR. BOWEN: Yes.

19 DR. GENCO: Okay.

20 DR. BOWEN: Obviously, I don't remember,
21 but I thought I had it correct. I'll accept P & G's
22 word on it.

23 DR. GENCO: All right, the same page, the
24 same line -- how can it be the same line. Oh, oh,
25 excuse me. Insert. So it will read now, "In two of

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1 the six studies, i.e., 7 of 12 exams, there was a
2 reported statistically significant reduction in
3 bleeding scores."

4 Okay, any comments about that? So that
5 sentence would read now: "In two of the six studies,
6 i.e., 7 of 12 exams, there was a reported
7 statistically significant reduction in bleeding
8 scores. And in five of the six studies there was a
9 reduction in gingivitis scores associated with the use
10 of stannous fluoride gels."

11 Any objection? Any comments? Okay, we'll
12 go with that.

13 Page 85, line 16. Gels to dentifrices.
14 Any problems with changing gels?

15 DR. LISTGARTEN: Yes, because dentifrice
16 is already there. Just take gels out.

17 DR. GENCO: So the sentence now reads,
18 "Review of the cited literature indicates that a
19 number of studies have been conducted examining the
20 effects of stannous fluoride in mouth rinses and
21 dentifrices."

22 DR. LISTGARTEN: That's not accurate. We
23 were also examining gels, which I reviewed.

24 DR. GENCO: Yes, these are the gels and
25 mouth pieces and that sort of thing?

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1 DR. LISTGARTEN: Yes.

2 DR. GENCO: Separate from dentifrices.
3 "Fluoride containing gels." P & G, do you have some
4 comment to that?

5 DR. WHITE: Donald White, Procter &
6 Gamble. Where are we ending up on this now?

7 DR. GENCO: Leaving gels in there because
8 Bill feels that they were a separate category from
9 dentifrices.

10 DR. WHITE: That's true, but the specific
11 studies that we're talking about right here in this
12 paragraph happened to be dentifrices.

13 DR. BOWEN: The paragraph starts, Don,
14 "review of the cited literature." It indicates that
15 a number of studies --

16 DR. WHITE: No, we're the line above that.
17 It's the word "gels" in the last sentence of the prior
18 paragraph.

19 DR. GENCO: I'm sorry, that's my mistake.
20 Bill, do you see it now?

21 DR. BOWEN: Yes, okay. That's correct.

22 DR. GENCO: It's time to take a break.

23 (Laughter.)

24 DR. GENCO: I made a mistake. First one
25 since the early 1920s.

1 Shall we come back in 15 minutes? That
2 will be 20 minutes after 3. Okay, thank you.

3 (Off the record.)

4 DR. GENCO: I think we should start.
5 Thank you. Let's proceed now to the next to the last
6 page of the Procter & Gamble submission and let me
7 read the preface to what's on the next to the last
8 page. The preface is "some of the data Procter &
9 Gamble submitted to the Subcommittee in support of the
10 effectiveness of stannous fluoride have been omitted
11 from this discussion." That is pages 82 to 93,
12 essentially what we're coming to.

13 "In the interest of fair balance, we
14 recommended this additional material or information be
15 added as noted in the next several comments." So
16 those comments are on the next to the last page and
17 appear to go over to the last page.

18 So let's take -- okay, the first comment,
19 page 85, line 16. "At this stage of the report, the
20 Panel has completed its discussion on the initial
21 submitted material for stannous fluoride and turns to
22 consideration of literature studies on stannous
23 fluoride. Additional data were presented by the
24 sponsor to the Panel on three separate occasions,
25 providing further analysis and explanation supporting

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1 the safety and effectiveness of stannous fluoride for
2 anti-gingivitis efficacy. At this point of the report
3 it is our opinion that this additional information
4 should be summarized. We recommend the following
5 language be inserted following line 16 on page 85."

6 Now this language goes all th way over the
7 next page, is that what you mean, that entire five,
8 six, seven paragraph inclusion?

9 DR. WHITE: Yes, Donald White, Procter &
10 Gamble Company. Mr. Chairman, yes. The idea here is
11 that if we go back, I don't think, perhaps the word
12 omitted is the wrong word. Perhaps we should be
13 saying this type of information wasn't necessarily
14 reincluded or put into the final Panel report.

15 The point is that when we first submitted
16 a review of our studies with you, we went back and
17 forth on three separate occasions as you'll recall
18 doing subanalyses of site specificity of gingivitis
19 reduction, percent of subjects which received a
20 benefit, so on and so forth. For the later
21 ingredients, they also had similar data showing what
22 the clinical relevance of the benefit was, so on and
23 so forth.

24 If you look at the sections where the
25 other ingredients are reviewed, those additional types

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1 of analyses are included in the report and yet in the
2 stannous fluoride section we haven't had a chance to
3 get those, that type of information into the report.
4 So what this is is a summary of those studies which
5 presented to you.

6 Now I don't know the format that you might
7 use to review this and see if it's appropriate. I'm
8 not suggesting we try to all agree today. I don't
9 know what format you want to use.

10 DR. GENCO: What I'd like to do is just
11 maybe have the Panel just quickly browse this and one
12 suggestion would be to have maybe a couple of Panel
13 members to look at this in some detail and then
14 advise, work with Bob Sherman to determine just to
15 what extent how this might be incorporate, if
16 appropriate.

17 DR. WHITE: That would be excellent if you
18 could do that. We'd really appreciate that.

19 DR. GENCO: Has anybody had time to review
20 it enough to volunteer?

21 Bill?

22 DR. BOWEN: I agree that this -- the
23 subject of this material should be included because it
24 certainly was omitted and it's a pertinent part of the
25 discussion. I'll certainly volunteer to review the

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1 material and come up with an appropriate material with
2 anybody else you want to nominate and I'll get back to
3 Bob about. It should be included.

4 DR. GENCO: This does get to the issue of
5 clinical relevance too, doesn't it?

6 DR. BOWEN: Yes.

7 DR. GENCO: Stan, you've already been
8 asked to look at that. Do you want to work with Bill
9 on this?

10 DR. SAXE: I would like to. I'm also
11 working on triclosan and zinc citrate which is of
12 considerable length.

13 DR. GENCO: Okay. Max or Gene, do you
14 want to --

15 DR. SAVITT: I'm going to be fussing with
16 the hydrogen peroxide.

17 DR. GENCO: Right.

18 DR. LISTGARTEN: I'll do it.

19 DR. GENCO: So Max and Bill then will look
20 at the P & G, page 85, line 16 addition or revisions.

21 Okay, thank you.

22 Page 86, line 1. In order to distinguish
23 the literature from the sponsor's studies insert "with
24 the exception of studies presented by the sponsor"
25 before there appear to be few studies. Okay, so

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1 that's the very first line that says, "There appear to
2 be few studies" and what you would like us to consider
3 is "With the exception of studies presented by the
4 sponsor, there appear to be few studies."

5 Bill, do you have --

6 DR. BOWEN: I have no problem with that.

7 DR. GENCO: Okay. Bob, are you clear on
8 that? It's the very first line on page 86 and what
9 they're suggesting is that that sentence begin with
10 "With the exception of studies presented by the
11 sponsor, there appear to be few studies involving the
12 use of dentifrices, etcetera."

13 Page 92, line 14. For increased accuracy
14 insert "mass" before "formation." Do you have that
15 line 14? Let's see, page 92, line 14.

16 Something is wrong with that. Does anybody
17 see it. Line 14 does not have "mass" in it.

18 MS. FEDER: Formation.

19 DR. GENCO: Oh, formation. I'm sorry.
20 Yeah, plaque formation, plaque mass formation. Does
21 anybody have a problem with that? Okay.

22 Page 150.

23 DR. BOWEN: If it's plaque mass, Bob, is
24 formation really needed?

25 DR. GENCO: Probably not. So plaque mass?

1 Anybody else have a comment on that? Okay.

2 Fred, you look like you're quizzical?

3 DR. HYMAN: I was just wondering why there
4 were no comments from page 90 to 150.

5 DR. GENCO: I'm not even going to ask that
6 question.

7 (Laughter.)

8 DR. WHITE: I have an additional -- no.

9 (Laughter.)

10 It's just a threat.

11 DR. GENCO: I didn't even make a comment.
12 Okay, page 150, move all Category I ingredients or
13 ingredient combinations to the same section of the
14 report. Okay.

15 Do you want to explain that a bit?

16 MS. FEDER: This is again a formatting
17 suggestion for the Agency that all the Category I
18 ingredients, whether they're single ingredients to
19 fixed ingredient combinations be moved to the same
20 section of the report.

21 DR. GENCO: And which section would you
22 think that makes sense to --

23 MS. FEDER: The essential oils combination
24 is -- starts back on page 150 and so from a
25 readability standpoint I would just suggest you move

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1 that up, either before or after stannous fluoride and
2 cetylpyridinium chloride such that they're all
3 together.

4 DR. GENCO: Okay, Bob, did you hear that?
5 In other words, the suggestion is to take this section
6 which begins on 150 and move it up to the -- where the
7 stannous fluoride is being discussed, put all Category
8 I --

9 MR. SHERMAN: Again, that's a format. I
10 think that might have been standard procedure in the
11 past and we'll have to look at that.

12 DR. GENCO: Okay, fine.

13 MR. SHERMAN: Put them all up front.

14 DR. GENCO: Okay. Is this the time to
15 talk about this insert on the four essential oil
16 combination? Is it --

17 DR. WHITE: We are going to.

18 DR. GENCO: We're not finished, but I
19 thought -- excuse me, P & G is not finished. I just
20 thought is this relevant to their last comment? No.
21 Okay. Sorry.

22 All right. Let's through the P & G. I
23 just thought it was relevant to that last comment.

24 DR. WHITE: We are finished, I think.

25 (Laughter.)

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1 DR. GENCO: Oh, you just thanked us. All
2 right.

3 (Laughter.)

4 DR. WHITE: But on behalf of P & G
5 personally I'd like to thank the Panel again for their
6 patience in going through these suggested revisions.
7 So thank you very much.

8 DR. GENCO: And we thank you for pointing
9 out all of those numbers and also helping us with the
10 concept of clinical relevance. Thank you very much.

11 Okay, so we are finished with P & G.
12 Good, thank you.

13 Okay, well, why don't we finish the
14 Warner-Lambert then. We have been given an insert on
15 the four essential oils/combination drug policy.

16 Peter, do you want to help us with
17 understanding where this might go and why we should
18 include it?

19 MR. HUTT: Peter Hutt with Warner-Lambert.
20 First, we should make sure everyone has a copy of
21 this. It's -- on the Committee it's handwritten and
22 thus probably distinguishable from anything else you
23 have in front of you.

24 I think it would be helpful, Bob, if we
25 began by pointing out where the combination policy

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1 itself is in your report. In the version you're
2 looking at, the FDA version, it's on page 40. If
3 you're looking at the NDMA blue book, it's on page 57.
4 It doesn't make any difference which version you look
5 at. But basically, you set out in that report on page
6 40 going over to page 41 the -- you refer to the OTC
7 drug review regulation itself and then you say "the
8 Committee believes that it is rational to combine
9 ingredients that meet the regulatory requirements and
10 then lay out A, B, C, D, etcetera."

11 Now what we did over the lunch break was
12 to write a document that attempts to reflect your
13 earlier discussion about the four essential oils
14 meeting the regulatory requirements for a combination
15 drug. Please recall that there are two types of
16 combination drugs. Those that combine active
17 ingredients from the same pharmacologic class and
18 that's what we're dealing with here and those that
19 combine them from different pharmacologic classes,
20 we're not dealing with that here.

21 Thus, basically, if I may summarize this,
22 it simply says "The Subcommittee concludes that the
23 fixed combination of four essential oils meets the
24 requirements of both the FDA and the Subcommittee
25 policy" which again you laid out "on fixed

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1 combinations of active ingredients with the same
2 pharmacological action. Data presented to the
3 Subcommittee demonstrate that each of the four active
4 ingredients makes a contribution. Each is safe and
5 effective and the combination does not decrease the
6 effect of any individual active ingredient and
7 combining the four active ingredients does not
8 decrease the safety of the combination." Those are
9 basically the criteria, the regulatory criteria. And
10 the last two sentences simply refer in broad terms to
11 the data that were presented to the Committee to
12 support your conclusion -- and which led to your
13 conclusion.

14 You asked, Bob, where should that be
15 inserted or something of this type be inserted.
16 Again, if you look at your document on page 168 of
17 your document which is the very end of the discussion
18 of effectiveness of the fixed combination of four
19 essential oils, after the first two complete
20 paragraphs and before the paragraph starting "based on
21 the evidence" our judgment is that this statement
22 about the fixed combination would logically go at that
23 point. Quite honestly, it could go in any number of
24 different places, but that seemed to us to be the most
25 logical place to put it.

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1 DR. GENCO: Okay, thank you. Any comments
2 from the Committee? You're clear on what the
3 suggestion is and where the placement is.

4 Stan?

5 DR. SAXE: I have -- looking at the, looks
6 to be second sentence, but the last five lines on page
7 1, "data presented to the Subcommittee demonstrate
8 that each of the four active ingredients" and here's
9 where I have a question, "make a contribution to the
10 effectiveness of the product, each is safe and
11 effective and the combination, etcetera, does not
12 decrease." Effectiveness, does this imply clinical
13 effectiveness or is this talking about bactericidal
14 effectiveness?

15 MR. HUTT: Well, this basically refers to
16 the overall effectiveness of the product which was
17 based, as you know, both upon bactericidal activity
18 and upon clinical data.

19 The thought here was not go through a
20 recitation of all of the background data and
21 information that contributed to your decision, but
22 rather to refer to it broadly. These are actually,
23 Stan, these are taken straight from the FDA policy
24 itself, the requirements to satisfy the total FDA
25 policy and Subcommittee policy on combination drugs.

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1 DR. SAXE: I cannot pinpoint at this time,
2 I have before me that specific data that showed that
3 the clinical effect, that there was a study and the
4 clinical effectiveness of one agent, two agents, three
5 agents --

6 MR. HUTT: That's because --

7 DR. SAXE: There's only the four agents,
8 that there were other studies done to show --

9 MR. HUTT: That is correct.

10 DR. SAXE: -- there are in vitro studies
11 that were done and killing effectiveness of the
12 various agents.

13 MR. HUTT: That is correct.

14 DR. SAXE: But in terms of clinical
15 effectiveness, I don't see -- well, I don't recall
16 that.

17 MR. HUTT: Stan, there were -- I think it
18 was discussed at the time. There were no studies done
19 in sort of in tandem with deleting each one of the
20 active ingredients to show a reduction because of the
21 extreme difficulty of doing those. Instead, they were
22 done in vitro studies with subtracting each one
23 showing a significant decrease in bactericidal
24 activity.

25 And it was based on those studies that

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1 this Committee decided that the criteria had been met.
2 If you'll recall, additional data were presented to
3 the Panel, specifically with representative oral
4 bacteria which the Panel had requested be done.

5 DR. SAXE: Right, and the antibacterial
6 effects of each of the agents was presented. Just
7 this statement to me seems kind of a little bit of a
8 leap of faith that it infers to me there would be an
9 inference if I were to read it that an inference that
10 clinical studies have been done or clinical trials
11 have been done to document the clinical effectiveness
12 and perhaps this could be re-worded slightly.

13 MR. HUTT: If you take a look on page 2,
14 the fifth line down, the third sentence, it starts
15 with experiments conducted by the sponsor show that
16 removal of any one of the four active ingredients from
17 the product results in a statistically significant
18 reduction in bactericidal activity against
19 representative oral and micro organisms.

20 DR. SAXE: Right, and I certainly agree
21 with that statement.

22 MR. HUTT: Yes. If you want, we could
23 somehow work that into the second sentence.

24 DR. SAXE: That would be helpful.

25 MR. HUTT: Very good.

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1 DR. GENCO: Something like each of the
2 four ingredients makes a significant contribution to
3 the antibacterial activity?

4 MR. HUTT: That would be absolutely fine.

5 DR. GENCO: And it's reasonable that or
6 likely that --

7 MR. HUTT: Yes.

8 DR. GENCO: -- this would be reflected in
9 the contribution to the clinical study, although this
10 wasn't specifically shown. Okay, yes.

11 DR. SAXE: That would be helpful.

12 DR. GENCO: Okay.

13 MR. HUTT: Thank you.

14 DR. GENCO: So work on that and maybe
15 present it to us tomorrow? Good. thank you.

16 MR. SHERMAN: Could just clarify? The
17 word experiments conducted by the sponsor, is that
18 meant to be synonymous with study or -- okay.

19 MR. HUTT: Yes.

20 DR. GENCO: Yes?

21 DR. KATZ: I guess I'm still kind of a
22 little confused as to what we really mean by the term
23 "experiments". Can you define what you mean by
24 "experiments"? Are we talking clinical, laboratory,
25 in vivo, in vitro? What exactly are we talking about

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1 when we say the word experiments?

2 DR. BARNETT: It's sort of
3 self-explanatory by the nature of what the results
4 were, but very specifically, these were the data that
5 we had presented based on a series of in vitro
6 experiments in the -- excuse me, in vitro studies in
7 the laboratory.

8 DR. GENCO: And you could actually leave
9 that phrase out, experiments show. You can simply say
10 the sponsor showed that and the rest of the sentence
11 is antibacterial.

12 Okay, let's now proceed -- we are finished
13 with P & G, Warner-Lambert.

14 MR. SHERMAN: Just -- so what was the
15 outcome of this? Are we going to --

16 DR. GENCO: Okay, what they're going to
17 do, Bob, is to revise this, taking into consideration
18 Stan's concern about the possible misinterpretation of
19 the combined effect as a clinical effect when it
20 wasn't really tested, to revise it with respect to
21 that and give it to us tomorrow. And then we will
22 consider adding it to page 160 between the second and
23 third paragraph. But we can go over that again
24 tomorrow, the placement.

25 So the only leftover issue then from what

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1 we've done so far, leftover issues are the clinical
2 significance which Stan is going to look at, the
3 marketing survey which Bill Bowen is going to look at
4 to make sure that that item on page 33, those two
5 sentences make sense relative to that, and then Bill
6 Bowen and Max are going to look into the issue of the
7 large addition submitted by Procter & Gamble to talk
8 a little more about the additional information they
9 submitted. And then Warner is going to give us a
10 revision of this. So those are the four items left
11 over from ADA, Warner, Procter & Gamble. Okay?

12 So let's proceed then to the NDMA/CTFA
13 Joint Oral Care Task Group comments. Patricia has
14 very kindly given me a list now of the comments with
15 those comments that we've already discussed and I see
16 a lot of Xs which brings a smile to all of our faces.

17 So let's proceed to the dark blue book and
18 the comments of NDMA. Does everybody have a copy of
19 this in the audience? I know we do as a Panel. This
20 is the November 20th letter from NDMA to Bob Sherman.
21 It's approximately 20 pages long. Does everybody in
22 the audience have it? Should they?

23 MR. SHERMAN: I have some extra ones. Is
24 there any objection?

25 DR. GENCO: Should they, Bill?

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1 MR. SHERMAN: I have a few more with me.
2 Is there any objection to passing those out?

3 (Pause.)

4 DR. GENCO: Now the pages refer to in the
5 NDMA document, are those pages on the draft report?
6 Okay, the original pages in the draft report of FDA --
7 no. They refer to the pages in the NDMA revision.

8 MR. SHERMAN: Right, Bob.

9 DR. GENCO: Which everybody doesn't have.
10 But everybody has the FDA report.

11 MR. CANCRO: What you're looking at on the
12 NDMA sheet are pages within the document they
13 prepared. They will not match up with the original
14 report. We will try to, where needed, where
15 discussion is needed to get you to the original
16 report.

17 DR. GENCO: Okay, fine, I appreciate that.

18 MR. CANCRO: We'll make that attempt.

19 DR. GENCO: Because that would help the
20 audience too. All right.

21 MR. CANCRO: I would like to preface
22 before we start this and there really are three
23 points. Obviously, this is a response from the Joint
24 Trade Groups, NDMA and CTFA. It doesn't really
25 reflect in totality all of the ingredients in this

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1 review. The point has been made that three weeks time
2 was given, so we have taken into consideration several
3 of the ingredients, but not all of them.
4 Additionally, there's particularly when you get to
5 alcohol section, there is extensive material that is
6 missing and we can discuss that more as we approach
7 that. Certainly, the workshop isn't reflected. The
8 comments of Dr. Williams, Dr. Shapiro, Dr. Cole and
9 the -- one of the offices who did the original
10 epidemiological survey, I think Lott. So all of that
11 is -- we haven't had time to grasp and put in a form
12 which reflects that discussion.

13 Additionally, as you know today,
14 individual companies have put forth their own
15 viewpoints. Our document doesn't supersede their
16 viewpoints, nor does it reflect all of the companies
17 out there. And finally, I think, the issue is that we
18 have attempted to move things around for the sake of
19 clarity and we'll try to point out where we've done
20 that as well as capturing some of the thinking that
21 went to reach a conclusion.

22 So with those three caveats, I think we're
23 prepared to start.

24 DR. GENCO: Okay. It looks like the first
25 comment refers to page 1. The comment period be

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1 extended to 180 days. Can we have some discussion by
2 FDA staff on that?

3 MR. SHERMAN: I think that should have
4 been 90 days. That should be 90 days and a 30-day
5 reply comment period. So that's incorrect.

6 MR. CANCRO: So the 60 should be --

7 MR. SHERMAN: The 60 should be 90.

8 MR. CANCRO: And we are requesting 180.

9 MR. SHERMAN: That's something that you'd
10 have to -- I think you'd have to request that in a
11 letter or petition.

12 MR. CANCRO: Okay. We believe the 180 is
13 needed because there are many issues here that really
14 have opposing views. Some by individual companies,
15 some by the trade association and we haven't had an
16 opportunity to collect our thoughts so that we think
17 it's going to be an extensive time period required to
18 do that.

19 MR. SHERMAN: I understand. But anything
20 other than the standard --

21 MR. CANCRO: You need a formal request.

22 MR. SHERMAN: You need a formal request.

23 MR. CANCRO: Done.

24 MR. SHERMAN: Then we would respond to
25 that.

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1 DR. KATZ: I'd like to make one suggestion
2 because since you have an idea of where the comments
3 are, it may behoove you to start now to get together
4 some of the comments knowing that the dates are 90
5 days and 30, so that gives you ample time to get
6 started to think about some of the comments that you'd
7 like to put forth, while requesting as well a longer
8 time period.

9 MR. CANCRO: Yes, I think there are
10 periods in question, Linda. One is we believe an
11 extension is needed to rework this document and to get
12 all of the formatting in which the industry document
13 does not reflect. It reflects some of it, but not all
14 of it.

15 The second issue is that following public
16 review and publication of that, then you have the
17 traditional comment period to what you've published
18 and that is a different perspective to industry.
19 That, we're looking at from an entirely different view
20 in terms of agreements and disagreements, etcetera
21 with conclusions and recommendations.

22 This presentation deals only with trying
23 to get the report in the totality of what you did and
24 what the thinking was and get it in shape. That's the
25 effort we're making today.

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1 DR. GENCO: Okay.

2 MR. CANCRO: Okay? I think we can go
3 through much of this very quickly, Bob.

4 DR. GENCO: Page 11, all claims included
5 and the call for data be reported.

6 MR. CANCRO: That's on page 5 of your
7 report and what we're requesting is that you simply
8 take out from the original call for information
9 exactly what the FDA proposed. And you can see we've
10 inserted that by way of example.

11 DR. GENCO: Yes.

12 MR. CANCRO: Line 22.

13 DR. GENCO: Anybody have a problem with
14 that? Okay.

15 Bob, this is going to be very confusing.

16 MR. SHERMAN: Okay, run that by me again.

17 MR. CANCRO: On page 11 of the industry
18 submission, we have put in the exact information that
19 was requested in 1990 by the FDA. We simply lifted
20 that from your call for information and inserted it in
21 this report. That's all that's been done.

22 MR. SHERMAN: Okay.

23 DR. GENCO: Perhaps, we're not going to
24 finish this today, but perhaps I can ask the -- Lew,
25 maybe you can get together with the NDMA and -- maybe

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1 relabel --

2 MR. CANCRO: Relabel these with your page
3 numbers.

4 DR. GENCO: That would help tremendously.

5 MR. CANCRO: I totally agree.

6 DR. GENCO: Patrice Wright was very kind
7 to give me a list here with those overlaps. Maybe that
8 list with the pages from the revised pages in the
9 original. Actually, you can keep your pages but maybe
10 just a bracket with the original because then we can
11 refer back and forth.

12 MR. CANCRO: What I'm prefer to do today
13 and I can't do it for all 300 pages, I can get you
14 back up to page 59. So I can refer you back to your
15 document.

16 DR. GENCO: Okay, good.

17 MR. CANCRO: Beyond that I haven't had
18 time to --

19 DR. GENCO: Great.

20 MR. CANCRO: To line them up.

21 DR. GENCO: We probably won't get that
22 far. All right, so the -- we'll call this the page 11
23 comment, the second comment.

24 MR. CANCRO: Page 11 is your page 5. Page
25 12 is your page 6.

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1 DR. GENCO: Okay, now the page 11, our
2 page 5, we're going to add those claims. Does anybody
3 on the Panel --

4 MR. SHERMAN: Yes, it's really outside the
5 Panel. We'll do that. We can add that. It shouldn't
6 be any problem.

7 DR. GENCO: Good. Your page 12, our page
8 6, it's called PW3. As the text of this paragraph
9 stands, it is unclear which members were able to vote
10 on which committee. Again, that's technical, can be
11 dealt with by the FDA. Good.

12 Page 14 which is our page -- Dr. Altman's
13 name, no problem.

14 Page 15, full history of the Plaque
15 Committee. We can do that. Done.

16 Page 15, presenters missing, titles
17 included and you've added those.

18 MR. CANCRO: We've added them.

19 DR. GENCO: Okay. Page 22, P & G
20 submission, that name change. Okay.

21 MR. SHERMAN: Excuse me, was that the name
22 of the product that was submitted in 1991 or is that
23 a new name? That's fine.

24 DR. GENCO: Page 24, your PW8.
25 Subcommittee did not review all of the submitted

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1 ingredients for inclusion report and suggested
2 revision to changing the title clarifies this. That's
3 -- okay, Bob.

4 MR. SHERMAN: Sorry.

5 DR. GENCO: Which page is in our report?

6 MR. CANCRO: On your report that is page
7 14, Bob. And on page 24 of the NDMA submission is how
8 you can correct that, the suggested change. It's
9 underlined.

10 MR. SHERMAN: What page?

11 DR. GENCO: Okay, it's in the FDA, it's
12 document, page 14. And it's underlined, the title is
13 active ingredients reviewed by the Subcommittee. That
14 sounds like a formatting change, yes.

15 DR. WRIGHT: I just want to say that the
16 blue document is the exact Panel report that FDA had
17 issued. So unless you're keeping a master document,
18 this flows exactly as the initial document did.

19 DR. GENCO: It's the page numbers that are
20 different. So we're having trouble finding the page
21 numbers. If you read it through from page 1 through
22 whatever, that's not a problem, but we're skipping
23 pages.

24 DR. WRIGHT: And I guess the point is if
25 you just go to the blue document, unless you're

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1 keeping a master document, you don't need to refer
2 back because it is the entire document.

3 DR. D'AGOSTINO: But we have other
4 changes.

5 DR. KATZ: Patrice, we are keeping a
6 master document here to try to go along, line for line
7 and that's where the problem is.

8 DR. D'AGOSTINO: But I think as Members,
9 also, we have made changes all day and we want to see
10 how these changes fit in.

11 DR. GENCO: Is that clear then?

12 MR. CANCRO: Page 26 is your 16.

13 DR. GENCO: Okay, page 26, our 16. DWS10.

14 MR. CANCRO: And that's simply the outline
15 was misreferenced. It should be C instead of D. If
16 you look on our page 26.

17 DR. GENCO: All right. That's format.

18 MR. CANCRO: Page 27 is your page 17 and
19 the issue here is we would like on line 21 of page 27
20 to insert the type of classification and you're
21 talking about a clinical classification as opposed to
22 any other of several classifications for calculus,
23 mineral, organic, etcetera, inorganic. Are you with
24 me, page 27, line 21.

25 That is -- your page 17.

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1 DR. GENCO: Okay, any problems on the
2 Panel? Everybody find that?

3 Page 28, your page 28.

4 MR. CANCRO: Page 28 is also page 17 and
5 we've covered this before. Bill, you handled this
6 before.

7 DR. GENCO: Okay. Page 29.

8 MR. CANCRO: 29, I think this has also
9 been addressed before.

10 DR. GENCO: Right.

11 MR. CANCRO: Page 30 --

12 DR. GENCO: No, there's another 29.

13 MR. CANCRO: Sorry, page 29, again, I
14 think you've handled this, bacteria will adhere to
15 pellicle. Is that correct, Bill?

16 DR. LISTGARTEN: You have some additions
17 which we don't have.

18 DR. GENCO: Yes. All right, so let's go
19 back to page 29, DWS13 which is on our page 18.

20 Your page 29 and it's the item 6 pellicle.
21 Is that where we are?

22 MR. CANCRO: Correct.

23 DR. BOWEN: I think our description is
24 adequate and should remain unaltered.

25 DR. GENCO: Okay.

1 DR. BOWEN: Other than what we discussed
2 earlier.

3 DR. GENCO: Yes, we discussed bacterial
4 products and saliva, right.

5 Bob, we've revised this before. It stays
6 as is. So that takes care of comments DWS13 to DWS14.

7 Now PW15, page -- your page 30, our page

8 --

9 MR. CANCRO: 19.

10 DR. GENCO: 19. You suggest the first
11 paragraph as not needed.

12 MR. CANCRO: Right.

13 DR. GENCO: Under background. Background
14 and general discussion of the terms?

15 MR. CANCRO: The issue here is that you
16 really capture what you were charged to do in the
17 paragraph when commences on line 16. It's the second
18 paragraph.

19 DR. GENCO: Anybody have any problems with
20 that? Omit? Strike the first paragraph beginning
21 "the Subcommittee was convened." On page 19, it's
22 under B1 background, first paragraph.

23 Okay, Panel agrees to strike that.

24 MR. CANCRO: And then there are some word
25 changes for -- on the same page, page 30, regarding

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1 increasing the clarity of the mission. And that's
2 underlined. If you look on line 18.

3 DR. GENCO: Okay, so that would be in the
4 next paragraph, that is under background, the
5 Subcommittee was charged with the evaluation of the
6 safety and effectiveness of individual ingredients for
7 -- now here's the addition. "Reduction and prevention
8 of gingivitis and plaque indications" for add
9 "reduction and prevention of gingivitis and plaque" --
10 right, I added it. "Reduction and prevention of
11 gingivitis and plaque." What does the Panel think of
12 that, clarifying the omission?

13 Leave out indications for English? Okay.

14 Okay, so that paragraph reads, "The
15 Subcommittee was charged with the evaluation of the
16 safety and effectiveness of individual ingredients for
17 reduction and prevention of gingivitis and plaque
18 claimed in the labeling of OTC products in light of
19 present day knowledge, etcetera."

20 DR. SAVITT: What about "combination of
21 ingredients"?

22 MR. SHERMAN: Or combinations?

23 DR. SAVITT: Or combinations of individual
24 -- that's good.

25 DR. GENCO: Okay. Everybody agree to

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1 that? All right.

2 Now the next three --

3 MR. HUTT: Just take individual out.

4 DR. GENCO: Okay. That sounds reasonable.

5 MR. CANCRO: Next three are typos and name
6 changes.

7 DR. GENCO: Next three have been taken
8 care of. Yes. The top one on the next page, page 36
9 PW20 has been taken care of.

10 MR. CANCRO: Right.

11 DR. GENCO: Okay, page 36, DWS21 which is
12 our page what, Lew?

13 MR. CANCRO: This is the issue that I
14 raised a bit prematurely, the issue of visible
15 detection and I think if you turn to page 36 you'll
16 find the issue is temperature. Page 36.

17 DR. GENCO: It's your 36, what is our
18 page?

19 MR. CANCRO: We're suggesting you
20 eliminate --

21 DR. GENCO: 24?

22 MR. CANCRO: -- this is your page 24.

23 DR. GENCO: Thank you, Lew. Okay, so the
24 suggestion is what now?

25 MR. CANCRO: You're characterizing

1 gingivitis and one of your characterizations is
2 increased tissue temperature, but you tart off by
3 saying the visible signs of gingivitis and temperature
4 wouldn't be a visible sign. So we're recommending you
5 drop visible.

6 DR. GENCO: And "characterized by"?

7 MR. CANCRO: Right.

8 DR. GENCO: Any objection to that revision
9 of the second sentence under gingivitis? Would read
10 now "The signs" -- strike visible -- "of gingivitis
11 are" -- strike characterized by -- "tissue swelling
12 and redness, loss of stippling, etcetera."

13 Okay? Next.

14 MR. CANCRO: Next is the same page, 24,
15 page 37 of the submission, the NDMA submission. And
16 prior to the word "injury" we'd like you to insert
17 "bacteria injury" to make it very specific.

18 DR. GENCO: Any problem with that?

19 DR. LISTGARTEN: Well, it's not the true
20 definition of gingivitis.

21 DR. SAXE: Yes.

22 DR. LISTGARTEN: Gingivitis is an
23 inflammation to any kind of injury.

24 DR. SAXE: I would not include the word.

25 DR. GENCO: Okay, so as is. Next?

1 MR. CANCRO: Okay, page 37 -- again, page
2 37, page 25 of your report. And the issue here is --
3 the issue is we think these changes more clearly
4 defined it as an OTC condition.

5 DR. GENCO: Okay, that's the second
6 paragraph on page 25, beginning "gingivitis especially
7 when severe", you're suggesting to change it to
8 "gingivitis, especially when" -- now strike severe
9 with a tendency -- add accompanied by bleeding.
10 Strike to bleeding. May be self-diagnosable.

11 MR. CANCRO: Is.

12 DR. GENCO: Is.

13 MR. CANCRO: The recommended change is
14 "gingivitis, especially when accompanied by bleeding,
15 is self-diagnosable."

16 DR. GENCO: Panel?

17 DR. LISTGARTEN: I think just large gums
18 that are not bleeding are also self-diagnosable.

19 MR. CANCRO: Sorry, Max, I couldn't hear
20 you. Would you repeat that?

21 DR. LISTGARTEN: I said that you could
22 have gingival enlargements that are not necessarily
23 accompanied by bleeding that could also be self-
24 diagnosable. I think just keeping it the way we have
25 it is okay. I don't see that you gain anything by

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1 changing the wording, unless you had a special concern
2 that I'm unaware of.

3 DR. GENCO: In fact, the second sentence
4 actually goes beyond just bleeding. It says it's
5 self-diagnosable as swelling and discoloration too.
6 So I think your approach was to make it more --
7 consistent with self-diagnosable makes it less.

8 MR. CANCRO: I look at just slightly
9 different, Bob. I mean you have the may be which is
10 maybe part of the issue here. Bleeding may be
11 self-diagnosable. We're saying that it is
12 self-diagnosable.

13 DR. GENCO: So that's the issue. The may
14 be. You want to change the may be to "is."

15 DR. LISTGARTEN: I think the way we could
16 solve this since we're going into details in the
17 following sentence is to change the first sentence to
18 read, "gingivitis, especially when severe, is
19 self-diagnosable" and just leave out the tendency to
20 bleeding because that's not the only concern, there
21 are others and we go into them later.

22 DR. GENCO: Stan.

23 DR. SAXE: I would like to leave -- I
24 disagree with you, Lew, respectfully, but I disagree
25 with you. The word "may be" because if you say it is

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1 it means that it is not only possible, but I think
2 there's an inference here that people can indeed and
3 do, an individual can diagnose one's own gingivitis
4 which is not true. And that's why I like the word
5 "may be" that has been inserted here. In some
6 instances, individuals can do it and then one explains
7 why it is possible to have self-diagnosis.

8 DR. GENCO: So leave it as is?

9 DR. LISTGARTEN: Take out "with a tendency
10 to bleeding."

11 DR. GENCO: Okay. Panel? So it reads now
12 "gingivitis, especially when severe," -- strike "with
13 a tendency to bleeding" -- "may be self-diagnosable."
14 And the rest remains as is.

15 Okay, page 38. Your PW24. Which page is

16 --

17 MR. CANCRO: Page 25, Bob.

18 DR. GENCO: Thank you.

19 MR. CANCRO: Okay, I think the issue here
20 is gingivitis is really the endpoint as you've defined
21 it. So that we are recommending the changes you see
22 on lines 4 and 5. OTC drug products for prevention
23 and control of plaque associated gingivitis are used,
24 etcetera.

25 Here, you basically have two classes of

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1 products, plaque and you've eliminated that.

2 DR. GENCO: Any problem with that Panel?
3 The new sentence would read, "When OTC products for.
4 the prevention and control of plaque associated
5 gingivitis are used as a part of a program of good
6 oral hygiene." Okay?

7 So Bob, we're taking their suggestion in
8 toto, their suggestion PW24. It's on page 25.

9 MR. CANCRO: Okay, staying with page 38,
10 the comment is No. 25 on our part. The page in your
11 book is again 26. And the suggestion here is being
12 made to reflect the fact that gingivitis is not a
13 homogenous condition in the mouth but may go from mild
14 to severe, depending on location, site, etcetera.

15 DR. GENCO: Okay, their comment PW --

16 MR. CANCRO: DW25.

17 DR. GENCO: Oh, sorry.

18 MR. CANCRO: On line 12.

19 DR. GENCO: Okay, so it's the paragraph
20 that reads "The most common form of gingivitis"
21 actually wraps around to the next page. So the
22 sentence begins at the bottom of page 25, goes up to
23 page 26 and begins on the bottom of page 25, "However"
24 and what they would like it to read, "Sites with mild
25 gingivitis are seldom easily detected by patients

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1 because they may not be associated with pain or
2 bleeding."

3 Any problem with that, Panel? You see .
4 it's the last word on page 25, "however" and then it
5 wraps around to page 26, "Sites with mild gingivitis
6 are seldom easily detected by patients because they
7 may not be associated with pain or bleeding."

8 Okay? So we take that comment, take
9 comment DWS25 in toto.

10 Page 39?

11 MR. CANCRO: Let's stick with 38-39, Bob.
12 Because 26 commences on line 23 at 38. And concludes
13 on line 1 of 39 and again that's page 26 of your
14 report, still the same page 26. And I think the issue
15 here is having established at least three ingredients
16 that are safe and effective, you no longer need the
17 "may". If you read the end of the sentence on page
18 39, first line.

19 DR. GENCO: Okay, if you look on page 26
20 the second paragraph begins "Readily available OTC
21 drug products for the prevention of control of plaque"
22 and what the suggestion is that that sentence read now
23 "Readily available OTC products for the prevention
24 and" -- strike "control of plaque and plaque
25 associated" -- "control of plaque associated

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1 gingivitis play a significant public health role."

2 Again, "Readily available OTC products for
3 the prevention and control of plaque associated
4 gingivitis play a significant public health role."

5 DR. SAXE: I'm not so sure that's a true
6 statement, yet, it might be in the near future, but in
7 the United States today --

8 MR. CANCRO: These products are there.

9 DR. SAXE: In the United States today, the
10 products are there, but are they really at this point
11 playing a major role? They may play a major role.
12 Hopefully, they will.

13 The product is sold and it's marketed, but
14 is it being used often enough and correctly enough and
15 appropriately enough to really have made changes in
16 the status of the health of the U.S. population. We
17 know that changes in selected study populations, a
18 relatively small group of people and hopefully it
19 would play a major role. But at the moment, is it
20 really a factor in the United States? You know, for
21 us to say it is, I'm coming from that point of view.
22 It may be and that's why we're here. Hopefully, this
23 will make a contribution to the oral health of the
24 America public.

25 MR. CANCRO: I think the fact that you say

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1 they are working and you've seen enough evidence to
2 say that that is representative of the effect that
3 could be seen in the general public leads you to the
4 loop which says they play a role. I mean if you have
5 confirmed that these populations are representative of
6 the populations out there and concluded that the
7 agents are safe and effective, then they play a role.

8 DR. SAXE: They're not representative of
9 the populations out there. They're representative of
10 human beings and what can be done in a subject, in a
11 human, what one expects.

12 The public health role, what the actual
13 health status is and we've had surveys every few years
14 for us to try to describe what the existing oral
15 health status is of the American public and hopefully
16 we can improve it with these products that these
17 active ingredients will play a role.

18 MR. CANCRO: Would you accept the word
19 "can", "can play a role."

20 DR. SAXE: They're intended to, yes. We
21 have no data saying that they play a role, have
22 affected the health of the American public.

23 MR. CANCRO: How about the "are intended
24 to" or "can play" --

25 DR. SAXE: That's fine, sure. Of course.

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1 DR. GENCO: Okay, so that sentence on page
2 26 would read, "Readily available OTC drug products
3 for the prevention plaque associated gingivitis are
4 intended to play a significant public health role."

5 Is everybody comfortable with that?

6 Okay, Bob, that's the middle paragraph on
7 page 26. Okay, good.

8 MR. SHERMAN: "Are intended to" rather
9 than "may."

10 DR. GENCO: "Are intended to" but actually
11 also strike "and control of plaque." So the sentence
12 would read, "Readily available OTC drug products for
13 the prevention and control of plaque associated
14 gingivitis" -- excuse me, strike "of plaque" -- just
15 "control of plaque associated gingivitis" not "and
16 plaque associated." Thank you.

17 MR. CANCRO: Okay, jumping to page 45.

18 DR. GENCO: Our page 31?

19 MR. CANCRO: That's your page 31.

20 DR. GENCO: Thank you.

21 MR. CANCRO: Again, if you look on line
22 22, it's simply trying to clarify the issue of
23 antibiotic use here. The discussion begins on line
24 20.

25 On page 44, line 20 and concludes at the

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1 top of page 45, line 1. The sentence reads,
2 "Antibiotics may be used as adjuncts to oral hygiene
3 to suppress or eliminate specific segments of the
4 bacterial population" and then we are suggesting "not
5 readily accessible to mechanical cleaning."

6 DR. GENCO: So that's page 31, it's the
7 first paragraph, last sentence that's under
8 discussion. Add the phrase, "not readily accessible
9 to mechanical removal"? What does the Panel think of
10 that?

11 There's another issue going on. That's
12 the biofilm issue that we may not have discussed
13 before. Is that covered by not amenable to
14 mechanical? I guess it is. Because mechanical would
15 disrupt the biofilm. And anything left over might be
16 nonbiofilm. Okay.

17 Okay. So Bob, are you clear on that?
18 Thank you.

19 MR. CANCRO: The next comment I think
20 you've handled where the general discussion should not
21 be related to mouth washes, but to oral care products
22 or however you're going to phrase that.

23 DR. GENCO: The next two, actually.

24 MR. CANCRO: Yes.

25 DR. GENCO: Thank you.

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1 MR. CANCRO: Now you've handled the next
2 two that we have listed on 48 and 49.

3 DR. GENCO: Actually, the next three,
4 right?

5 MR. CANCRO: The next three.

6 DR. GENCO: So we're on page 48, your
7 PW31.

8 MR. CANCRO: Yes, you've dispensed with
9 that, I think.

10 DR. GENCO: Oh, we have?

11 MR. CANCRO: I think so, yes.

12 DR. GENCO: Okay. Then we're on page 49,
13 your PW32.

14 MR. CANCRO: Yes, 32 is if you look on
15 line 7, 8 and 9, page 49 of our submission, page 34 of
16 yours, we're recommending that the sentence be
17 clarified in terms of plaque equivalent claims. Thus,
18 plaque and plaque equivalent claims should not stand
19 alone.

20 DR. GENCO: Lew, I missed our page
21 reference there.

22 MR. CANCRO: Your page is 34, Bob.

23 DR. GENCO: Thank you.

24 DR. SAXE: May I ask a question?

25 DR. GENCO: Surely.

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1 DR. SAXE: I understand, I believe, plaque
2 related, but can you help me, Lew, with plaque
3 equivalent?

4 MR. CANCRO: Well, I think the thinking
5 was, Stan, that plaque related could really embrace
6 lots of non-plaque issues where plaque equivalent,
7 however you describe it, it is equivalent to the
8 pathogenicity of the plaque. So the -- in the one
9 case you're saying plaque related which implies that
10 several other things could happen.

11 DR. SAXE: Could you give me an example of
12 what a plaque equivalent might be? What sort of a
13 claim?

14 MR. CANCRO: Well, let's look at plaque
15 equivalent. That's kind of easy. It may be noxious
16 films. That might be an equivalent to plaque related.
17 It could be maybe bacterial mass.

18 DR. SAXE: So it's in the wording of the
19 claim?

20 MR. CANCRO: Yes. What we're suggesting
21 here is that whatever the language is, if it is
22 intended to be a substitute for plaque, that's what
23 you mean, as opposed to something that happens as a
24 result of the plaque.

25 DR. SAXE: Okay. Thank you.

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1 DR. GENCO: So the middle paragraph on
2 page 34, the last sentence they're proposing reads,
3 "Thus, plaque and plaque equivalent claims should not
4 stand alone."

5 Panel?

6 DR. LISTGARTEN: Couldn't we just replace
7 this by anti-plaque claims?

8 Anti-plaque claims should not stand alone.

9 DR. GENCO: Does that embody your concern
10 about alternative terms?

11 MR. CANCRO: Yes.

12 DR. GENCO: Sounds like it would allow the
13 claim for --

14 MR. CANCRO: Yes.

15 DR. GENCO: Bacterial mass, sticky film,
16 noxious film. You're not concerned about that?

17 MR. CANCRO: I think it captures it, yes.

18 DR. GENCO: I think it goes the other
19 direction. It allows for those other claims.

20 DR. LISTGARTEN: What other claims?

21 DR. GENCO: Plaque equivalent. Like
22 noxious film, bacterial mass.

23 DR. LISTGARTEN: Anti-plaque takes care of
24 mass. That's how you -- anti-plaque suggests reducing
25 the mass of plaque. It indicates killing of plaque,

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1 reducing the mass of plaque, reducing plaque scores.

2 DR. GENCO: No, I meant the term bacterial
3 mass which would be a plaque -- you brought the point
4 up.

5 (Laughter.)

6 I hadn't really thought about it before.
7 You must be concerned about that, so -- you would not
8 like a noxious film claim to stand alone?

9 MR. CANCRO: Well, you wanted examples and
10 I'm just creating them. I don't know how realistic
11 they are.

12 DR. LISTGARTEN: Do you know of any
13 noxious films?

14 (Laughter.)

15 DR. GENCO: Outside of the X rated ones?

16 DR. LISTGARTEN: Okay, all right.

17 DR. GENCO: All right, what does the Panel
18 think? Plaque or anti-plaque claims. In other words,
19 "Thus, anti-plaque claims should not stand alone."

20 DR. SAVITT: We did define plaque on page
21 17 to include gel like and mucoid masses, etcetera,
22 etcetera. So by saying anti-plaque, we're including
23 all the various definitions and synonyms.

24 DR. GENCO: Okay.

25 DR. SAVITT: I agree with Lew though. I

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1 think it does make it a little easier for the reader
2 if you were confronted by a statement such as "fights
3 the soft sticky stuff on teeth" this makes it easier.
4 for the reader, it's just a plaque equivalent claim.
5 And so my feeling is that costs us little to add to
6 this legacy the word "plaque equivalent."

7 DR. GENCO: Max?

8 DR. LISTGARTEN: When we come a little bit
9 further down the page, under indications, we talk
10 about anti-plaque ingredients and that just simply
11 keeps the whole thing coherent.

12 MR. CANCRO: I don't have an objection to
13 anti-plaque.

14 DR. GENCO: Okay.

15 MR. CANCRO: I always get worried when
16 Stan agrees with me twice in the same day.

17 (Laughter.)

18 DR. GENCO: Okay, so it will read, "Thus,
19 anti-plaque claims should not stand alone." Any
20 objection. Okay, thank you.

21 Next?

22 MR. SHERMAN: Excuse me, Bob. Can I just
23 back up one. PW31, the first one on that page. How
24 was that resolved?

25 DR. GENCO: Apparently we had resolved

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1 that formerly, previously.

2 MR. SHERMAN: Because I don't have any
3 notation in my copy of our original draft where
4 they're talking about the claim that a product
5 significantly reduces dental plaque, may easily
6 mislead consumers. They say this statement is not
7 documented.

8 MR. CANCRO: Remember the discussion on
9 mouth feel and cosmetic claims associated with plaque.
10 We had this discussion --

11 MR. SHERMAN: Right, okay.

12 MR. CANCRO: -- earlier today.

13 DR. GENCO: Excuse me, it was in the
14 context of another two sentences somewhere I think on
15 page 33, but Bill has been asked to look at that.

16 MR. SHERMAN: Thanks.

17 DR. GENCO: And Bill, maybe you can make
18 a note. It would be page 34 here where you'd want to
19 look at that again. I guess that's --

20 DR. SAVITT: It's the following sentence.

21 DR. GENCO: Oh, it's the following
22 sentence to the one that he's going to look at. Okay,
23 fine.

24 Yes, that's more relevant, maybe, to those
25 studies, really. So that's where the reference might

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1 likely be as compared to the previous two sentences.

2 I have now that we have dealt with DWS 33,
3 34 and 35.

4 MR. CANCRO: Right.

5 DR. GENCO: Okay.

6 MR. CANCRO: That's correct.

7 DR. GENCO: So now we're on page 53, PW36
8 and which page is that in our version?

9 MR. CANCRO: It's 37, Bob.

10 DR. GENCO: Okay.

11 MR. CANCRO: It's 53 in our submission,
12 it's 37 in yours.

13 Now this is on lines 2, 3 and 4, page 53.
14 And -- I'm sorry, this discussion seems to deal with
15 --

16 MR. HUTT: It's the same one about oral
17 rinse.

18 MR. CANCRO: That's what I -- okay. The
19 issue is oral rinse, Bob, as opposed to the whole
20 category, the whole --

21 DR. GENCO: Okay, so we could deal with
22 here by taking your suggestion. That would be page
23 37, item D, for OTC anti-gingivitis, anti-plaque
24 products containing the fixed combination of essential
25 oils. Here it's products. Strike "oral rinse drug."

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1 MR. CANCRO: Right.

2 DR. GENCO: Anti-plaque products. Leave
3 drug in?

4 MR. CANCRO: Right. Anti-plaque drug
5 products.

6 DR. GENCO: Strike "oral rinse" here.

7 MR. SHERMAN: But wasn't that indication
8 referring specifically to Listerine as it exists, the
9 rinse product?

10 DR. GENCO: Good point.

11 DR. SOLLER: Bill Soller, NDMA. You're
12 already addressing the formulation issues and the
13 equivalents or new novel formulations as we've talked
14 about before. You have that final formulation testing
15 already built in. So you can write this in the
16 general way because in another part of the document
17 you're saying what is Category I.

18 So this part you can write as it would
19 relate to any drug product that might have that
20 mixture.

21 DR. GENCO: Okay, so the suggestion is to
22 strike "oral rinse" from the lien for OTC
23 anti-gingivitis, anti-plaque drug products.

24 MR. CANCRO: On page 54, the 38 comment is
25 of a similar nature, that you're talking about a broad

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1 recommendation. It's not specific to stannous
2 fluoride. It's just a general requirement.

3 DR. GENCO: Okay, this would be our page
4 38 under A.

5 MR. CANCRO: This is your page 38, that's
6 right.

7 DR. GENCO: It would read, "For
8 anti-gingivitis/anti-plaque dentifrice drug products
9 containing" -- strike "containing stannous fluoride".
10 "For anti-gingivitis/anti-plaque dentifrice drug
11 products."

12 MR. CANCRO: If for anti-gingivitis,
13 anti-plaque, dentifrice drug product they must be
14 consistent with the anti-caries monograph independent
15 of whether or not they're a stannous fluoride product.

16 DR. GENCO: Panel, any problem with that?
17 To take their suggestion PW37. Okay.

18 Max?

19 DR. LISTGARTEN: We may want to modify
20 this to read "for anti-gingivitis or
21 anti-gingivitis/anti-plaque products."

22 MR. CANCRO: Right.

23 DR. GENCO: Yes, that's more inclusive.
24 Good. Any objection to that? Okay, Bob, for page 38,
25 item A, "for anti-gingivitis or

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1 anti-gingivitis/anti-plaque dentifrice drug products."

2 DR. LISTGARTEN: How about just "drug
3 products"?

4 MR. CANCRO: I'm sorry, what?

5 DR. GENCO: Just "drug products" not
6 "dentifrice."

7 MR. CANCRO: But you are talking --

8 DR. GENCO: We're talking about
9 dentifrices here.

10 MR. CANCRO: It's direction for use.

11 DR. GENCO: Then it would be ", the
12 Subcommittee recommends." Okay, so that would be a
13 phrase. Convert the first sentence to a phrase
14 introducing the next idea.

15 Okay.

16 MR. CANCRO: Page 55 and that's your page
17 38.

18 DR. GENCO: Did you miss one, DWS38? Did
19 we deal with that? Your page 54. DWS38. That was
20 discussed?

21 MR. CANCRO: It's the same issue.

22 DR. GENCO: Okay, all right. Next is page
23 55, your PW39.

24 MR. CANCRO: 39, that's your page 38.

25 DR. GENCO: Okay.

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1 MR. CANCRO: And again, just to broaden
2 that.

3 DR. LISTGARTEN: Can we just come back? .
4 I think we're not finished the previous one.

5 DR. GENCO: Okay.

6 DR. LISTGARTEN: It's not just the title.
7 I think there's also a change to be made in the body
8 of that paragraph to be consistent with anti-
9 gingivitis, anti-gingivitis/anti-plaque.

10 MR. SHERMAN: Right and there's also
11 another reference to stannous fluoride which we can
12 also remove.

13 DR. LISTGARTEN: Which has to be removed.

14 DR. GENCO: Okay. So we're going to take
15 those comments in toto then? Or is there more to your
16 suggestion than what's suggested here by Lew?

17 DR. LISTGARTEN: Just the indication in
18 the text itself for the paragraph of anti-gingivitis
19 and anti-gingivitis/anti-plaque.

20 DR. GENCO: Okay, fine.

21 MR. SHERMAN: I've got that.

22 DR. GENCO: We've got that. And then
23 strike stannous fluoride twice.

24 MR. SHERMAN: Right.

25 DR. GENCO: Okay, we're on to the B

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1 paragraph on page 38, the last paragraph and the title
2 or the first sentence to be changed to read, "for
3 anti-gingivitis/anti-plaque oral rinse drug products,
4 adults and children under 12 years of age or older,
5 vigorous swishing, etcetera." Oh no, I see what
6 you've done, "for anti-gingivitis/anti-plaque oral
7 drug products" -- that's the title.

8 MR. CANCRO: Correct.

9 DR. GENCO: Good. Then the new sentence,
10 "Adults or children."

11 MR. CANCRO: Yes, it's your general
12 labeling for that group of products.

13 DR. GENCO: Okay, any problem with that?
14 That sounds like format.

15 All right.

16 MR. CANCRO: Then if you drop down to the
17 bottom of page 55, Bob, it's the last word, line 22,
18 just a correction.

19 DR. GENCO: Okay. I'm sorry, I don't --

20 MR. CANCRO: On page 55, it's loose teeth
21 or increasing, instead of increased.

22 DR. GENCO: I see it on yours. What page?

23 MR. CANCRO: Page 55.

24 DR. GENCO: Page 39?

25 MR. CANCRO: Your page 39.

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1 DR. GENCO: That's what I'm looking for,
2 sorry.

3 MR. CANCRO: It's PW40 which is really
4 identified on the next page and it's line 22 on page
5 55, the last word. Line 22, the last --

6 DR. GENCO: Okay, so Bob, it's on page 39.
7 It's paragraph A, beginning "For all OTC gingivitis,
8 anti-gingivitis products", drop down to the next to
9 the last line in that paragraph, "increasing" rather
10 than "increased" spacing between the teeth. Do you see
11 that?

12 "Increasing space."

13 MR. CANCRO: "Increasing space."

14 DR. GENCO: Right.

15 DR. SAXE: These are not all symptoms. It
16 says "These symptoms may be a sign of periodontitis."
17 Some indeed are signs. Loose teeth is not a symptom.
18 Increase in space is not a symptom.

19 DR. GENCO: Okay, these are signs and
20 symptoms of periodontitis. How is that? Okay, the
21 last sentence then, "These are signs and symptoms".

22 MR. SHERMAN: These may be might be more
23 accurate.

24 DR. GENCO: Okay, Bob. In that paragraph
25 A, in the middle of page 39, the last sentence now

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1 reads, "These may be signs and symptoms" or "signs or
2 symptoms of periodontitis, a serious form of gum
3 disease."

4 MR. SHERMAN: These may be signs or
5 symptoms.

6 DR. GENCO: Or symptoms of periodontitis,
7 a serious form of gum disease.

8 Where are we?

9 MR. CANCRO: Page 56.

10 DR. GENCO: PW40?

11 MR. CANCRO: This is 41. This is DW41.
12 It's on lines 9, 10 and 11 and the issue here is to
13 bring your warnings in harmony with your above
14 statement on line 5.

15 DR. GENCO: Which pages is that?

16 MR. CANCRO: In your text, this is 39, 40.

17 DR. LISTGARTEN: That's at the end of our
18 page 39.

19 DR. GENCO: Yes. Didn't we discuss this
20 before? Is this language that's already in use, Bob?
21 Linda?

22 MR. SHERMAN: Which one is this now?

23 DR. GENCO: If you look at the last line
24 on page 39, the quote begins, "Do not administer to
25 children under age 6, supervise use for children

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1 between the ages of 6 and 12."

2 MR. SHERMAN: I think it's language that's
3 presently used on rinses and the Subcommittee has
4 carried over.

5 DR. GENCO: What they're suggesting we do
6 is change that to "Children under 6 years of age:
7 consult a dentist or physician." Strike, "Donot
8 administer to children under age 6."

9 What's the Panel's feeling on that?
10 Linda? Does the FDA have a position on that?

11 DR. KATZ: The meaning is very different,
12 so it's basically the intent of what the Panel means.
13 And then we can come back and deal with what the
14 regulatory language should say.

15 DR. GENCO: Does the Panel mean do not
16 administer to children under age 6 for the fixed
17 combination and for cetylpyridinium chloride?

18 DR. SAXE: I think the question was can
19 children -- this is used as a rinse and then spit this
20 stuff out on command or not. And the feeling may have
21 been that this is not a process that kids under the
22 age of 6 can carry out.

23 DR. LISTGARTEN: I think children under
24 the 6 years of age will spit it out before they use
25 it.

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1 (Laughter.)

2 MR. CANCRO: Bob, I think the issue here
3 is only consistency. If you go back to page 55, turn
4 back to 55, and look at what you're recommending on
5 lines 9, 10 and 11, children under six years of age:
6 consult a dentist or" -- I guess we should say
7 physician. "This rinse is not intended to replace
8 brushing or flossing."

9 So the industry comment is keep your
10 consistency. If that's what you're saying,

11 DR. GENCO: Bill?

12 DR. BOWEN: Wasn't there a concern at the
13 time this matter was discussed about the high level of
14 alcohol in Listerine and people expressed concern that
15 six year olds would be exposed to this level of
16 alcohol?

17 I believe that's what the essence of these
18 discussions were.

19 DR. GENCO: So the feeling is that we
20 would change both to "do not administer to children
21 under age 6 and supervise use for children between the
22 ages of 6 and 12." So go back to -- first of all,
23 page 39, that last sentence, the suggestion is --
24 leave it as is. 39 and 40 as is. But change -- go
25 back to page 38. It's the last -- excuse me, it's the

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1 top of page 39. "Children under 6 years of age
2 consult a dentist." Change that to the same terms as
3 "do not administer to children under age 6."

4 DR. LISTGARTEN: I'm not sure that I
5 understand what we're doing.

6 DR. GENCO: Yes, I know. Let me sort it
7 out. We're leaving the statement at the bottom of
8 page 39 and 40 as is. "Do not administer to children
9 under age 6," as it reads on page 39 and 40. To be
10 consistent, go back to page 38, again at the bottom of
11 the page it begins, "Instruct children under age 12
12 good rinse habits" and then "supervise children as
13 necessary." And then another sentence on page 39,
14 "children under 6 years of age consult a dentist."
15 Change that to "Do not administer to children under 6
16 years of age." To be consistent.

17 DR. SAVITT: And change the first line
18 that you read, "Instruct children under 12" should be
19 "Instruct children between the ages of 6 and 12."

20 DR. GENCO: Okay, so the comments on 40,
21 41 should be consistent with the comments on 39.
22 Okay, Bob?

23 And the comments -- the Panel is in favor
24 of the comments on 39, 40. That wording is what the
25 Panel is recommending.

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1 MR. SHERMAN: "Do not administer to
2 children under age 6. Supervise use for children
3 between the ages of 6 and 12."

4 DR. GENCO: Right, so back to page 39 and
5 let's use that terminology, top of 39.

6 MR. CANCRO: Bob, just a question for you.
7 If a parent came in and some reason the condition was
8 severe gingivitis in the child, the -- I mean the
9 thing is that you would want her to go to somebody to
10 get control over this situation. So if you bluntly
11 say "not for children under 6", how do you cover that
12 period if somebody needs something? Shouldn't they
13 see a doctor or a physician, dentist or physician to
14 make a determination?

15 DR. LISTGARTEN: I think we've left that
16 in there.

17 MR. CANCRO: I don't know what the
18 "consult a dentist or a doctor" does because you've
19 now eliminated the use of the product for children
20 under age 6.

21 DR. GENCO: Okay, let's go back to page
22 39B. "For active gingivitis, drug products containing
23 stannous fluoride, keep out of the reach of children
24 under age 6." "C. For anti-gingivitis, anti-plaque
25 drug products containing cetylpyridinium chloride or

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1 the fixed combination of thymol, menthol, eucalyptol
2 and methyl salicylate, do not administer to children
3 under age 6. Supervise use for children between the
4 ages of 6 and 12."

5 DR. LISTGARTEN: I think Lew's concern is
6 answered in paragraph A, in Section A. "If
7 gingivitis, bleeding or redness persists for more than
8 two weeks, see your dentist."

9 DR. GENCO: Right. What we're saying is
10 the Panel likes B and C on 39, 40.

11 MR. CANCRO: Okay.

12 DR. GENCO: And we're asking, Bob, if he
13 would please go back to the top of page 39, bottom of
14 page 38 and make that consistent which would mean
15 taking out the "consult a dentist or physician."

16 MR. CANCRO: Okay, so that's what you --

17 DR. GENCO: Harmonize it, your term.

18 MR. CANCRO: Okay.

19 DR. GENCO: Now the issue of what to do
20 with children with gingivitis, I agree with Max. It
21 seems that that's dealt with in A on page 39.

22 "See your dentist."

23 Is that the Panel's intent?

24 DR. BOWEN: Yes.

25 DR. GENCO: Okay, fine. Bob, is that

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1 clear?

2 MR. SHERMAN: I think so.

3 DR. GENCO: Thank you. He thinks so.

4 DR. SOLLER: Dr. Genco?

5 DR. GENCO: Yes.

6 DR. SOLLER: Bill Soller. When the final
7 labeling formatting rule comes out, the warnings are
8 going to be set up with absolute contraindications and
9 relative contraindications. The absolute being do not
10 use and the relative ones ask a dentist or a physician
11 in this case before using. And I think you need to
12 construct how you do these warnings and directions in
13 the context of whether you want it to be an absolute
14 contraindication or a relative one.

15 If you think in one section of the label
16 that it's going to be relative, vis-a-vis the two
17 weeks and you have this gingivitis, then consult a
18 dentist and then elsewhere it says "do not use". If
19 I'm following it right, it's really not a connect for
20 the consumer because even if we had this discussion
21 with the Agency it came out in different ways, but our
22 view is that if you -- if it is your intent that it's
23 an absolute -- if it's your intent that it's a
24 relative contraindication, i.e., you must ask a health
25 professional before using, then you should put that at

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1 the point where you have the warning.

2 DR. GENCO: Okay, on page 39, the middle
3 paragraph says "for all OTC anti-gingivitis/anti-
4 plaque drug products, if you accidentally swallow more
5 than used for brushing or rinsing, contact a Poison
6 Control Center immediately or seek assistance." Okay,
7 new thought. "If gingivitis, bleeding or redness
8 persists for two weeks, see your dentist." Now that's
9 for everybody. Children, I mean everybody. So that's
10 the see your dentist comment. It's only related to
11 ineffectiveness of the agent.

12 Okay, then we get to B, "for
13 anti-gingivitis drug products containing stannous
14 fluoride, keep out of reach of children under age 6."
15 That's a do not? That's a contraindication?

16 Warning. Okay. All right, so that's the
17 warning.

18 And then C, for the anti-gingivitis, "Do
19 not administer to children under 6." That's absolute
20 contraindication.

21 And then the next segment, "Supervise use
22 for children between the ages of 6 and 12" is a
23 warning?

24 MR. HUTT: Direction for use.

25 DR. GENCO: It's a direction for use.

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1 DR. SOLLER: But my --

2 DR. GENCO: But you don't need a dentist's
3 opinion on that use in the 6 to 12.

4 DR. SOLLER: Right, and what I was
5 suggesting is that if you intend that once a person
6 has taken the child under 6 to see a dentist for
7 gingivitis, that this product could be used in that
8 instance. Having a warning that says "do not
9 administer" on the label is not consumer-friendly.

10 DR. GENCO: Okay. So it could be.

11 DR. SOLLER: So it could be "ask a dentist
12 or physician before using in children under 6",
13 something like that.

14 DR. GENCO: Okay, is that the intent of
15 the Committee? I mean would the Committee feel
16 comfortable with that? Or is the Committee
17 uncomfortable even if a dentist or physician says to
18 use it, that under age 6 a child would swallow it or
19 whatever, not use it appropriately. I think that's
20 the issue.

21 DR. SAVITT: A dentist can still suggest
22 it and it's off label use. I mean it's our intention
23 that it shouldn't be used.

24 DR. GENCO: That's what you feel. WE
25 can't deal with off-label use. What we're dealing

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1 with is the issue here are we comfortable saying if
2 your children under 6 has gingivitis, bring them to
3 the dentist and if the dentist recommends to use it,
4 use it, versus do not use under age 6. Those are the
5 options that Bill Soller has presented.

6 What's your feelings?

7 DR. LISTGARTEN: I'm uncomfortable because
8 you're recommending the usage of the product in a
9 population under 6 years of age without any clinicals
10 to back up the safety and effectiveness in that
11 population.

12 DR. SOLLER: Then it's do not use.

13 DR. GENCO: Then it's do not use. I think
14 we had this discussion before and I think the
15 swallowing versus the lack of study are the concerns
16 and I think we all know that gingivitis is pretty rare
17 in little kids, fortunately.

18 Okay. Bob? Are you clear?

19 MR. SHERMAN: I think so.

20 DR. GENCO: Good.

21 MR. SHERMAN: Do you think this might be
22 a good breaking point?

23 DR. GENCO: I'm sure it is.

24 MR. SHERMAN: We've all reached our
25 breaking points?

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1 DR. GENCO: Yes.

2 MR. SHERMAN: We'll have all day tomorrow
3 to deal with the remainder of the NDMA comments.

4 DR. GENCO: Good. Great.

5 MS. REEDY: This is Kathleen Reedy,
6 Executive Secretary here and you are in our new
7 building, in our new facility and I hope you enjoy it.
8 However, if it an office building, not a public
9 facility and the janitorial service went home at 3:30
10 and don't return until 9. So I would ask if you would
11 please pick up your trash around your area and put it
12 in the cans or the receptacles, but the books and
13 everything else can be left exactly where they are and
14 they'll be right th way they are in the morning.

15 DR. GENCO: I'd like to announce before we
16 leave that there's been a dinner arranged for the
17 Panel at Copeland's which is 1584 Rockville Pike at
18 6:30. I'd like to suggest that we meet some place and
19 either walk over or take transportation. What's your
20 pleasure?

21 MS. REEDY: It's walking distance from
22 your hotel.

23 DR. GENCO: So do we want to meet at what,
24 6:15? Is that enough time?

25 Or we can meet at the restaurant.

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1 (Whereupon, at 5:03 p.m., the meeting was
2 recessed to reconvene tomorrow, Thursday, December 3,
3 1998.)
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C E R T I F I C A T E

This is to certify that the foregoing transcript in
the matter of: MEETING

Before: DENTAL PLAQUE SUBCOMMITTEE

Date: DECEMBER 3, 1998

Place: ROCKVILLE, MD

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.


