

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

1 1982 NOV 19 P3

DENTAL PLAQUE SUBCOMMITTEE
OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

OPEN PUBLIC SESSION

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Thursday, October 22, 1998

8:45 a.m.

Town Center Hotel
8728 Colesville Road
Silver Spring, Maryland

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PARTICIPANTS

PANEL MEMBERS PRESENT:

ROBERT J. GENCO, D.D.S., PH.D., Chairperson

WILLIAM H. BOWEN, Ph.D., D.Sc.

EUGENE D. SAVITT, D.M.D.

STANLEY R. SAXE, D.M.D., M.S.D.

CHRISTINE D. WU, Ph.D.

LEWIS P. CANCRO

KATHLEEN REEDY

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P R O C E E D I N G S

1
2 DR. GENCO: Good morning. I'm Bob Genco, State
3 University of New York at Buffalo, School of Dental
4 Medicine, and I'm chairing the Dental Plaque Subcommittee of
5 the NDA and would like to open this what appears to be the
6 penultimate meeting of this Dental Plaque Subcommittee.

7 I'd like first to ask each of the members of the
8 panel to introduce themselves and we'll start with Dr. Katz.

9 DR. KATZ: I'm Linda Katz, Deputy Director of
10 Over-The-Counter Drug Products.

11 MR. SHERMAN: I'm Bob Sherman, CDER liaison,
12 Division of OTC Drug Products.

13 DR. HYMAN: Fred Hyman, dental officer, Division
14 of Dermatologic and Dental Products.

15 DR. SAXE: Stanley Saxe, professor of periodontics
16 and geriatric dentistry at the University of Kentucky.

17 MS. REEDY: Kathleen Reedy, executive secretary of
18 the Dental Plaque Subcommittee of Nonprescription Drugs
19 Advisory Committee with the FDA.

20 DR. SAVITT: Eugene Savitt, private practice and
21 staff affiliate Forsyth Dental Center.

22 DR. WU: Christine Wu, University of Illinois,
23 periodontics.

24 DR. BOWEN: Bill Bowen, University of Rochester,
25 Center for Oral Biology.

1 MR. CANCRO: Lew Cancro, ILR.

2 DR. GENCO: Thank you very much and welcome,
3 everyone. Next I'd like to ask Kathleen Reedy to read the
4 meeting statement. Kathleen?

5 MS. REEDY: This is the conflict of interest
6 statement for the Dental Plaque Subcommittee of the
7 Nonprescription Drugs Advisory Committee, October 22, 1998.
8 The following announcement addresses the issue of conflict
9 of interest with regard to this meeting and is made a part
10 of the record to preclude even the appearance of such at
11 this meeting.

12 Since the subcommittee's discussion of triclosan
13 and zinc citrate, zinc chloride, sodium citrate, hydrogen
14 peroxide, and sodium loralsulfite and the subcommittee's
15 recommendations concerning OTC anti-plaque, anti-gingivitis
16 drug products will not have a unique impact on any
17 particular firm or product, but rather have widespread
18 implications with respect to an entire class of products, in
19 accordance with 18 United States Code, Section 208, general
20 matters waivers have been granted to each member and
21 consultant participating in the subcommittee's discussions.

22 In addition, Dr. Robert Genco, Dr. Christine Wu,
23 Dr. William Bowen have been granted waivers in accordance
24 with 18 United States Code, Section 208(b)(3) which permits
25 them to participate in the discussions concerning

1 professional labeling for OTC anti-plaque, anti-gingivitis
2 drug products. A copy of these waiver statements may be
3 obtained by submitting a written request to the FDA's
4 Freedom of Information Office, Room 12(A)(30) of the
5 Parklawn Building.

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

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

16 Two things I'd like to mention. Each microphone
17 must be turned on each time you speak, and please do so for
18 the transcriber and the audience. And secondly, this
19 meeting originally was scheduled for the 22nd and 23rd, but
20 the agenda will be completed today. We will not meet
21 tomorrow -- and you'll hear that again.

22 DR. GENCO: Thank you, Kathleen. Do we have to
23 turn the microphones off when we're not talking? Would that
24 be convenient?

25 VOICE: They're all on right now. Let's go with

1 it.

2 DR. GENCO: Okay, we'll keep them on them. Thank
3 you.

4 I'd like now to ask Bob Sherman to make some
5 announcements.

6 MR. SHERMAN: I just want to announce again that
7 although the meeting was announced in the Federal Register
8 as a two-day meeting, it will be held today only. Also,
9 there were three ingredients announced that would be
10 reviewed and all of those will be reviewed in December.
11 That's all.

12 DR. GENCO: Thank you, Bob. We'll now Dr.
13 Stookey, George Stookey, to talk about chewing gum as a
14 permitted dosage form for cetylpyridinium chloride. Dr.
15 Stookey?

16 DR. STOOKEY: Good morning. I am George Stookey.
17 I'm an associate dean and a professor at Indiana University
18 School of Dentistry. I wish to thank the members of the
19 Dental Plaque Subcommittee and interested parties for this
20 opportunity to make some comments and some recommendations
21 to the subcommittee regarding your deliberations which will
22 soon result in a monograph covering OTC products for the
23 prevention and reduction of dental plaque and gingivitis.
24 Although I have not attended the previous meetings of your
25 subcommittee, I have reviewed the minutes and some of the

1 transcripts of your meetings, and in doing so, I've been
2 impressed with the thoroughness of your reviews and the
3 sound scientific basis for your decisions.

4 However, in reviewing the minutes of your May
5 meeting there appear to be some inconsistencies regarding
6 the possible inclusion of additional vehicles for the
7 delivery of an anti-plaque agent such as cetylpyridinium
8 chloride, or CPC. On the first day of your meeting it
9 appeared that additional vehicles would be permitted with
10 the appropriate testing. But on the third day, the vehicles
11 were restricted to traditional dosage forms, such as
12 mouthwashes not intended for ingestion.

13 I am requesting that the subcommittee clarify this
14 matter and am recommending that additional dosage forms,
15 particularly chewing gum, be permitted in the monograph for
16 scientific reasons. These reasons essentially involve the
17 issue of substantivity of the anti-plaque agent and the
18 overall safety. Of course, such a recommendation is
19 proposed with the understand that there would be finished
20 formulation performance testing comparable to mouth rinse
21 formulations to demonstrate efficacy in reducing dental
22 plaque and gingivitis.

23 The rationale for this proposal is that it is
24 generally recognized that the greater efficacy of some anti-
25 plaque agents and some anti-gingivitis agents, the

1 combination, at least in part is due to the greater
2 substantivity of the agent to the surface of the oral hard
3 and soft tissues. In other words, some agents, such as
4 chlorhexidine, become attached to the various oral soft
5 tissues and hard tissues during the treatment and are
6 therefore available to exert their anti-microbial activity
7 for a prolonged period of time.

8 It is also recognized that quaternary ammonium
9 salts, such as cetylpyridinium chloride or CPC, lack this
10 property and are not retained in the oral cavity for any
11 appreciable period. As a result, the effectiveness of CPC
12 for the reduction of dental p and gingivitis requires the
13 use of elevated concentrations, 0.025 to 0.1 percent in a
14 mouthwash to produce a sufficient intra-oral titer to exert
15 a therapeutic effect.

16 It is also recognized that the soluble components
17 of a chewing gum are released to the saliva over a prolonged
18 period of time. For example, the soluble sweeteners present
19 in chewing gum are still being released from the gum some 25
20 to 30 minutes after chewing. Thus, the incorporation of an
21 antiplaque agent such as CPC into a chewing gum would be
22 expected to result in the release of the agent to the oral
23 fluids over a period of 25 to 30 minutes.

24 This prolonged release would be expected to result
25 in an elevated titer of the agent in the oral fluids for a

1 much longer period of time than is possible with a
2 mouthwash.

3 In Dr. Genco's very thorough review of the safety
4 and efficacy of CPC presented at the August 1995 meeting of
5 the subcommittee, it was noted that CPC is effective against
6 some microorganisms at concentrations as low as 0.12
7 micrograms per milliliter. A mouth rinse containing 0.04
8 percent CPC contains a much greater concentration of 400
9 micrograms of CPC per milliliter. Considering the prolonged
10 release of an agent such as CPC from a chewing gum, it is
11 possible that therapeutic benefits could be achieved with
12 greatly reduced concentrations delivered from each stick of
13 gum.

14 Obviously, there are concerns about the safety.
15 In that regard, since the soluble ingredients in a chewing
16 gum are essentially ingested, safety considerations related
17 to this dosage must be considered. In approving the safety
18 of CPC in Category I in mouthwashes at concentrations up to
19 0.1 percent, it was noted that some of the CPC was likely to
20 be ingested. It was conservatively estimated that this
21 amount could be as much as 20 percent of the total dosage of
22 20 milliliters of mouthwash containing 0.038 percent CPC,
23 which was used in your discussion, used twice daily.

24 A calculation of this amount indicates that a
25 daily ingestion of 1,520 micrograms or 1.52 milligrams per

1 use is considered safe. Or if you use twice daily
2 ingestion, that amount becomes 3,040 micrograms or 3.04
3 milligrams.

4 The ingestion of CPC from the chewing of two
5 sticks of chewing gum, as an example, containing say 250
6 micrograms of CPC per stick would result in a daily
7 ingestion of some 500 micrograms of CPC or about one-third
8 of the single use of a mouthwash ingested daily, or one-
9 sixth of the amount if you use the rinse twice daily. This
10 was considered safe when the vehicle was a mouthwash.

11 In summary, the incorporation of CPC in a chewing
12 gum should be considered safe as long as the daily ingested
13 dosage is greater than that that has been shown to be safe
14 with existing data.

15 In view of the foregoing considerations, I am
16 proposing that the subcommittee permit the use of additional
17 vehicles or dosage forms, particularly chewing gum,
18 containing CPC included in the monogram as long as the daily
19 ingested dosage is shown to be safe and as long as the final
20 formulation performance testing demonstrates comparable
21 reductions in dental plaque and gingivitis.

22 Thank you.

23 DR. GENCO: Thank you, Dr. Stookey. Any comments
24 from the panel? Questions?

25 Clearly, we are being presented with chewing gum

1 as delivery of agents for oral use, Zylotol chewing gum with
2 baking soda is on the market with some claims being made, so
3 I think this is an important issue to discuss in general, as
4 well as in specific with respect to CPC.

5 I think the two main considerations, safety and
6 efficacy, you have addressed. I'd like to ask a question
7 with respect to safety. What do we know about the use of
8 chewing gum in the population? The average number of sticks
9 per day? The range, particularly the range. A quick
10 calculation here shows 3 milligrams of CPC you'd get in
11 about 12 sticks of gum. Are there people who chew 12 a day?
12 What's the upper range? What could we expect would be a
13 maximum dose? Are there people who chew 24 sticks a day?

14 Is there anything that you're aware of that could
15 help us understand that?

16 DR. STOOKEY: I'm honestly not aware of that range
17 of ingestion or use of the gum. However, I would imagine
18 that issues related to that could be handled by labeling and
19 so forth on a product.

20 DR. GENCO: With respect to efficacy, one of the
21 concerns that we had with respect to in particular CPC was
22 the formulation and there's ample evidence, both from the
23 data presented to us by Procter and Gamble, as well as data
24 in the literature showing that various preparations of even
25 mouth rinses on the market with CPC have varying efficacies

1 at comparable concentrations.

2 So obviously, it is reasonable that there is some
3 problems in formulation, that inactivation is a problem. Do
4 you have any data, or does anybody have any data on the
5 efficacy of CPC in a chewing gum with respect to
6 antigingivitis effect?

7 DR. STOOKEY: I'm not aware of data that would
8 suggest that, although it has been shown at least in
9 laboratory studies that you can have release of CPC from a
10 chewing gum. But I think that the inclusion of such a
11 vehicle in the monograph, along with the requirement for
12 performance testing, covers those kinds of issues of
13 efficacy because it would have to demonstrate that it was
14 effective for plaque and gingivitis.

15 DR. GENCO: Bill?

16 DR. BOWEN: I have a question for staff. How does
17 the FDA view the use of what I think is classified as a food
18 as a vehicle for the administration of therapeutic
19 substances?

20 MR. SHERMAN: Gums haven't been typically
21 considered a traditional dosage form. You do have products
22 out there of Zylotol, for example, in a gum making plaque
23 claims. Recently sodium bicarb has been marketed in a gum
24 making plaque claims.

25 The strict interpretation of that could be to

1 consider those new drugs and therefore not eligible for the
2 monograph. So that answer is not really clear right now,
3 but I guess what we're trying to get from the subcommittee
4 is would you consider this as a reasonable dosage form? Are
5 there any particular concerns that you might have about
6 availability of the ingredient in a gum form, about testing,
7 those types of issues? Just what your concerns are? Do you
8 think this is a reasonable prospect?

9 DR. GENCO: Do you want to ask a further question,
10 Bill, for follow up?

11 DR. BOWEN: Yes, a question for George. How,
12 George, would you envision controlling the dosage of any
13 therapeutic agent in gum, controlling it for the use of
14 children, for example, of among the primary users of chewing
15 gum?

16 DR. STOOKEY: I would imagine that this gum would
17 be primarily intended for adult consumers and I would
18 imagine that you would utilize labeling and so forth to
19 focus it, rather than the typical chewing gum for children.

20 DR. BOWEN: But as an over-the-counter proposal,
21 there would be nothing to stop a child from buying gum from
22 a counter that CPC or indeed any other ingredient?

23 DR. STOOKEY: That's true. That's true, but even
24 so, with the margin of safety that exists and the
25 demonstration of efficacy, I'm not so sure that that would

1 be a problem.

2 DR. GENCO: Lou and then Gene.

3 MR. CANCRO: I think this really identifies two
4 issues. One, of course, is any specific ingredient is
5 distributed by safety considerations and hence is
6 independent of any other ingredient in terms of somebody
7 reviewing it and saying it's safe or it isn't safe. So on
8 that basis, this is simply a case of knowing of the toxicity
9 issues relating to the ingredient.

10 But the second issue is really the dosage form.
11 And here, I think the panel has begin to come to grips with
12 that in that it was proposed, at least by one manufacturer,
13 and I kind of thing the panel accepted it, that when you go
14 for a change in the dosage form, then the burden of
15 establishing efficacy rests on completion of four and six
16 month clinical trial.

17 I think if we go back to the minutes we would find
18 that that was proposed. I'm not sure where it finally ended
19 out. So when you think about the availability of the drug
20 and its deliverance for the benefit, we have considered a
21 means to establish that. At least there was a proposal on
22 the table that changing dosage form would be one clinical
23 trial of six months would be adequate.

24 DR. SAVITT: For a point of clarification, I'm
25 somewhat uneasy about the idea of taking an efficacy study

1 which is based upon a single large exposure of the
2 microorganisms to a particular product such as CPC and then
3 try to convert this very large high concentration single
4 dose experience to these bacteria to a very slow much, much
5 lower dosage.

6 I think that following up on what Lou had to say
7 and he took my thunder from me, but I'm concerned that one
8 could not easily translate the efficacy studies based upon a
9 single, very large dosage experiment into something where
10 you're applying a very low dosage over time.

11 DR. STOOKEY: I think that the end result that
12 you're measuring in your six month clinical study or
13 whatever studies you select is the effect upon plaque and
14 gingivitis during that period of time. So it would have to
15 be able to demonstrate an equivalent clinical benefit.

16 Your review also indicated in 1995, Dr. Genco's
17 review, indicated that the bacteria, at least the important
18 organisms that were cited, would be affected by
19 concentrations of CPC ranging from 0.12 to 8 micrograms per
20 milliliter. Those concentrations are all very low. In
21 other words, the bacteria would be susceptible to even lower
22 concentrations but delivered over a prolonged period of
23 time.

24 But I really think the end result is that if you
25 see the clinical benefit, the performance testing that

1 you've talked about, that really answers the question that
2 you've raised, which is a very good one.

3 DR. HYMAN: I wanted to raise something to the
4 panelists about chewing gum that I believe is different than
5 other changes in dosage forms. That is, I think that we
6 need to keep in mind that chewing on gum without any
7 therapeutic agent in it stimulates saliva significantly.
8 There's a mechanical action, removal of plaque, et cetera.

9 I would propose that it would be very difficult to
10 demonstrate the effect of CPC above and beyond chewing with
11 any gum alone, and that may be what needs to be considered
12 in approving this dosage form.

13 DR. GENCO: Did I hear you correctly, Fred, saying
14 that if there is a substantial concern about the dosage form
15 being effective for a variety of reasons, that to approve a
16 dosage form as being reasonable in an OTC monograph would
17 not be appropriate? That is, there's no data that chewing
18 gum is effective at all, George, in reducing plaque and
19 gingivitis with such an agent. In other words, there's no
20 precedent for this, from the literature, as I understand.

21 DR. STOOKEY: There are not published studies
22 demonstrating that you can put CPC into a gum and get a
23 clinical benefit. However, the question that was raised
24 here was whether or not you could expect to see a benefit
25 from such a formulation over and beyond the benefit of just

1 chewing gum.

2 In fact, in the next issue of the ADA we will, in
3 fact, publish a report which indicates that the chewing of a
4 gum after meals will reduce caries some 10 percent. It
5 would be assumed that in performance testing it would be
6 versus a placebo.

7 In other words, there would be a similar panel of
8 patients who would be chewing a gum without the active
9 agent. Therefore, the performance testing should control
10 that concern because it would have to be able to demonstrate
11 a benefit over and above whatever might be there from just
12 chewing.

13 DR. GENCO: So we're asked to give an opinion on
14 whether a gum is a reasonable dosage form, and what I'm
15 hearing is that it may be difficult to show that it has an
16 effect, Fred's point; my point that with CPC there may be
17 formulation problems that may preclude it ever having an
18 effect. Like some of these agents will probably be
19 extremely difficult to put into dentifrices. That's why
20 they're used in mouth rinses.

21 So one could think that it's not reasonable,
22 absent some data showing that it would work in a gum, that
23 gum may just never, ever be a good vehicle for these drugs.
24 I'm just bringing that up to address the issue of
25 reasonableness as a dosage form.

1 DR. STOOKEY: That's a very legitimate question
2 but there are products that are on the market in Europe that
3 do contain chlorhexidine. They contain other kinds -- these
4 are chewing gums. And there have been some studies -- not
5 here, though, not in the states -- but there have been
6 studies in which they have demonstrated a benefit from those
7 kinds of gums.

8 So I think the potential is there. The question
9 is whether or not you would allow chewing gum as a possible
10 vehicle pending all of the various considerations, safety
11 and demonstrated efficacy. The failure to do that obviously
12 limits the potential for that type of vehicle ever being
13 considered because it would have to go an NDA route or some
14 other route.

15 Being included as a possible vehicle with
16 appropriate testing leaves that door open.

17 DR. GENCO: I guess the issue that I'm addressing
18 is the reasonableness. It would be very easy for all of us
19 to come up with a list of 10 different dosage forms that
20 might be theoretically possible. Some may never, ever see
21 the light of day, may ever be effective. Others may.

22 Is it appropriate to list all of these that have
23 any chance at all of being successful? Or do we need better
24 evidence that this is a reasonable form? I guess I'm asking
25 also the FDA personnel that question, too.

1 MR. SHERMAN: I think we need to focus in on the
2 gum in particular at this point. If you could give us your
3 concerns -- if it seems reasonable, are there any concerns
4 that it could be proven reasonable at this point, given that
5 we have no data at this point?

6 MR. CANCRO: I'm a little concerned that we would
7 shut this door on an approach, which is really what George
8 is asking. There are precedents. Aspirin obviously is one
9 that comes to my mind very quickly, being delivered in a gum
10 form.

11 But with respect to the difficulty of showing the
12 benefit of the chewing gum base, that's on the burden of the
13 manufacturer. The manufacturer must do that in a well-
14 controlled clinical trial. To deny him the ability to do
15 that seems wrong in principle. If he can't do it,
16 obviously, then he can't show that the active is deliverable
17 in that base.

18 But it seems to me that that's what the clinical
19 trial is all about. A well-controlled clinical trial should
20 or should not define the activity of the agent in the gum
21 base.

22 DR. BOWEN: I think I have a broader concern. I
23 don't think we can concern ourselves with anticipating the
24 outcome of any research that people would propose to do. I
25 would add, somewhat gratuitously, that the release of active

1 agents from chewing gum is not a trivial matter and I think
2 many people are aware of that.

3 The example that you gave, George, of
4 chlorhexidine being approved in Europe, as far as I recall
5 that is, in fact, a prescription item and is not available
6 over-the-counter. And Lou uses the example of aspirin. The
7 purpose of that, of course, is for systemic administration.

8 Here we want to deliver an agent all for topical
9 application, virtually all of which is going to be
10 swallowed. And we're going to use a vehicle that's
11 traditionally regarded as a confectionery; i.e., a
12 foodstuff. I realize that we would be dealing with
13 principles, that if we say well, CPC we are, in fact,
14 agreeing to lots of other agents, also.

15 So my concern is one primarily of restricting the
16 use. I might be a little less concerned if I knew the items
17 would be prescription items. But on the other hand, we're
18 not dealing with prescription items, we're dealing with OTC
19 agents. So that's my primary concern, is unrestricted
20 access.

21 DR. GENCO: George, do you want to comment?

22 DR. STOOKEY: If I might. I think that what I'm
23 suggesting is, though, that whatever that vehicle is, and
24 whatever the agent is, you would demonstrate safety at a
25 level which is already accepted. You've reviewed that in

1 other materials, other agents, and you've decided that this
2 level is safe.

3 And you're also requiring proof of efficacy. So
4 it seems to me that if you accept those criteria, safety and
5 efficacy, then the dosage, the traditional vehicle or
6 whatever, is of less concern.

7 But I hear your points.

8 DR. GENCO: Christine?

9 DR. WU: I have a question for FDA about gums.
10 When gums are used as vehicle, is it considered a dental
11 device?

12 MR. SHERMAN: If it has a drug ingredient, it is a
13 delivery system and it would be considered -- the overall
14 product would be considered a drug.

15 DR. GENCO: Stan?

16 DR. SAXE: I just want to add this, the difference
17 I think of use of chewing gum as a delivery system is quite
18 marked in that when a toothpaste or mouth rinse is used the
19 individual who uses it makes an active effort to see that
20 it's distributed throughout the mouth; i.e., brushing it on
21 the teeth, swishing it around. Much of the release of an
22 active agent into saliva in a chewing gum, I believe, once
23 that active agent is into saliva it's swallowed, it's
24 ingested.

25 So I think the concern is that a large amount of

1 any active agent that's released is swallowed. We like to
2 think that it's all being swished around the mouth, but
3 there's a high concentration that's swallowed. So that such
4 a delivery agent has to be carefully tested.

5 DR. STOOKEY: May I comment?

6 DR. GENCO: Yes.

7 DR. STOOKEY: The point is well made. However,
8 there have been, for more than 10 years, experiments with
9 devices that are attached to the tooth and release a small
10 amount of fluoride every day, and used these devices in
11 children as an experimental measure.

12 Studies with that approach, which again would be
13 the release of a low level fluoride in this case into the
14 saliva have demonstrated that a benefit is throughout the
15 mouth. So it gets into the oral fluids, the fluids are
16 interdispersed throughout the oral cavity.

17 So the point is well made, however there are at
18 least some data to suggest that other agents are distributed
19 thoroughly throughout the oral environment.

20 DR. GENCO: Fred?

21 DR. HYMAN: I just wanted to add one thing from a
22 regulatory standpoint because Lou, something you had said
23 led me to wonder if the panelists were unclear. But in
24 terms of saying that to adequately demonstrate efficacy it's
25 incumbent upon the sponsor or the manufacturer to provide

1 clinical data, that can be done at any time later. Even if
2 this panel does not believe there's sufficient evidence for
3 the gum dosage forum, a new drug application can be
4 submitted even for an OTC product. So that's certainly an
5 option.

6 DR. GENCO: An expensive one. Any comments from
7 the audience on this issue?

8 [No response.]

9 DR. GENCO: George, any further summary comments?

10 DR. STOOKEY: No, I've made my plea.

11 DR. GENCO: What does the FDA need from us? Do
12 you want a motion? Do you want a consensus?

13 MR. SHERMAN: An overall consensus. Do you think
14 that this is a reasonable dosage form that could be put in a
15 monograph?

16 DR. GENCO: What's the feeling? Does anybody not
17 have any concerns? I've only heard concerns. Is anybody
18 supportive of this? Anybody supportive of the gum as a --

19 MR. SHERMAN: And you could qualify this as given
20 the appropriate tests, unless you have serious concerns that
21 any testing would be a problem.

22 DR. GENCO: Okay, qualified. In other words,
23 supportive given the appropriate tests, the six-month trial
24 or what have you.

25 MR. CANCRO: Could you add to that, Bob, the issue

1 of appropriate safety and appropriate efficacy testing, I
2 think would make it complete, would limit it to the dosage
3 format?

4 DR. GENCO: I don't hear that statement, though.
5 I was trying to elicit it, but I don't hear it from the
6 panel. What I hear are concerns. Bill?

7 DR. BOWEN: I think you would, in my opinion, need
8 even more extensive testing than we would be asking for up
9 to now. I seem to recall that there was a penicillin
10 chewing gum on the market several years ago which led to
11 catastrophic effects on overgrowth by Canada and related
12 obnoxious organisms. And I think most of the antiseptic
13 agents that we would be looking at are selective, to some
14 extent. All of them are, to some extent.

15 So you're probably looking at really extensive
16 research on the persistent effect of these agents on the
17 microbial flora, something that I think none of the agents
18 has been really subjected to under the type of circumstances
19 under which these agents might be used by children.

20 So I have real concerns about this at this stage.
21 I would certainly not be opposed to look at it with a fresh
22 load of data along the concerns I've addressed. No way.

23 DR. GENCO: George, do you want to comment?

24 DR. STOOKEY: I think your point is well taken,
25 the concerns are there. But I think if you -- what I've

1 suggested to you is accepting this as a possible vehicle,
2 given that such a proposal would require evidence of safety
3 and certainly you would want to make sure there's been no
4 shifts or change in the oral flora. And also efficacy data,
5 which would be undoubtedly six month clinical trials of
6 plaque and gingivitis.

7 So I think if you -- what I've proposed is that
8 you consider gum as a vehicle, provided it has evidence of
9 safety using your current guidelines and proof of efficacy.

10 DR. WU: I have a question about the gum. If CPC
11 is formulated into a gum base, are you assuming that most of
12 the CPC is going to be released?

13 DR. STOOKEY: Yes, I would assume that you have to
14 be able to formulate a compatible system. There are any
15 ingredients of the gum. There are many ingredients of a
16 toothpaste, or whatever. It's up to the manufacturer, as
17 Mr. Cancro said, to demonstrate and to formulate and to
18 prove both safety and efficacy with such developments.

19 DR. GENCO: I think what I hear then from the
20 panel is considerable concern for both safety and efficacy
21 as an over-the-counter product in the absence of data, and
22 that the general view, what I'm hearing, is that gum is not
23 a reasonable dosage form for CPC. Anybody like to disagree
24 with that, or have I summarized what we've said? Given that
25 there is another mechanism to get this dosage form approved

1 through the NDA, it may not be appropriate at this time to
2 include this as a dosage form for over-the-counter use.

3 DR. STOOKEY: Is it unrealistic to at least have a
4 consideration for permitting additional dosage forms or
5 vehicles, provided they can demonstrate safety and efficacy?

6 DR. GENCO: Oh, I think that's been part of our
7 discussion all along, clearly. But we're talking about gum
8 and CPC now, and I don't hear any support for including it
9 as a dosage form for CPC in the monograph. As advisory to
10 the FDA, I think I've summarized what I've heard. That
11 doesn't preclude it being a dosage form, but there's another
12 mechanism to get it approved, the NDA.

13 MR. CANCRO: You were very clear with that
14 statement, Bob, but I simply wanted to ask you one
15 additional question. The topic here is CPC in a gum. Do
16 you feel that gum, with other ingredients, is again
17 precluded from this panel? I know no one is submitting it,
18 but the issue of the gum itself, that's what I'm trying to
19 get at.

20 DR. GENCO: It would seem that each ingredient
21 would have to be looked at on its own considerations in that
22 dosage form. Lou, I was trying to summarize what I heard
23 the panel say. I happen to agree with that, but it's not my
24 opinion. I'm trying to give Fred an consensus from the
25 panel, in lieu of a vote.

1 DR. SAVITT: I would just add that most of the
2 objections that we heard about this particular vehicle with
3 this particular ingredient, I think, would hold for any
4 particular ingredient that you would add to the gum. All of
5 the issues were not so much about CPC, although there were
6 some specific ingredient concerns, but many of them were
7 generalized about that type of vehicle which I think would
8 preclude inclusion in this monograph for any of the
9 ingredients, using the chewing gum as a vehicle.

10 DR. GENCO: Further comments?

11 [No response.]

12 DR. GENCO: Thank you very much, Dr. Stookey.

13 Let's now proceed to the discussion by Dr.
14 Barnett, the antibacterial mechanism of action for the fixed
15 combination of essential oils. Michael?

16 MR. SHERMAN: Excuse me, Bob. Just before Dr.
17 Barnett begins his talk, I just wanted to summarize the
18 events of the last meeting. During the discussion of
19 acceptable indications for anti-gingivitis, anti-plaque drug
20 products, one of the proposed indications was aids or helps
21 in the control or inhibition or killing of plaque bacteria
22 that contributes to the development of gingivitis or
23 gingivitis, an early form of gum disease.

24 After considerable discussion, the panel voted
25 five to three against that particular indication. And I

1 believe Warner-Lambert Company would like to present some
2 new data in support of that indication.

3 DR. GENCO: That was specifically for the fixed
4 combination of essential oils, that vote?

5 MR. SHERMAN: Correct.

6 DR. GENCO: Thank you.

7 DR. BARNETT: Good morning, and I just want to
8 say, Bob, that the word penultimate never sounded as sweet
9 as it did in the context of your opening statement, so thank
10 you.

11 For the record, my name is Michael Barnett. I am
12 senior director of dental affairs in the consumer health
13 care research and development division of the Warner-Lambert
14 Company. I would, at the outset, like to thank this
15 subcommittee for the opportunity to make this presentation
16 which, as Bob Sherman just mentioned, is an outcome of a
17 discussion held at the last meeting of this group in May,
18 concerning our request for the indication, as Bob mentioned
19 but I'll quote it again: aids or helps in the control,
20 killing, inhibition of plaque bacteria that contribute to
21 gingivitis.

22 It was the intent that this indication be used in
23 conjunction with the previously approved indications
24 concerning plaque and gingivitis.

25 Some members of the panel agreed that the existing

1 data and scientific rationale were supportive of the
2 requested indication. Others sought specific information to
3 demonstrate that Listerine actually killed plaque bacteria
4 in vivo, and that it was this killing activity, rather than
5 an alternative mechanism -- for example, one relating to an
6 anti-inflammatory effect -- that was the primary mechanism
7 underlying the well documented effectiveness of the fixed
8 combination of essential oils against gingivitis.

9 Our presentation this morning will consist of two
10 parts. First, a presentation which I will make. And then
11 we had asked three experts in the consultant status to
12 review our data and our conclusions, as sort of a reality
13 check. And we will ask them, after I'm finished, to give
14 their comments and opinions of the results of the review.

15 The purpose of my presentation is two-fold, first
16 to consolidate and provide an overview of the data that had
17 been included in our previous submissions to this panel.
18 And second, to present new data in support of the
19 indication. For details about these studies, I refer you to
20 the appendices in the submission which we forwarded to you
21 recently, and I see is piled high on the tables.

22 The effectiveness of Listerine Antiseptic in
23 killing oral microorganisms has long been recognized. As
24 early as 1890 W.D. Miller, in his classic work
25 Microorganisms of the Human Mouth, noted that Listerine had

1 provided to be a "very useful and active antiseptic."

2 In 1929, an independent assessment of Listerine's
3 activity was carried out and published in the British
4 journal The Lancet. This study demonstrated Listerine to
5 have significant bactericidal activity against a variety of
6 microorganisms, and it was concluded that the formulation
7 was both safe and effective.

8 Numerous studies over the years have expanded upon
9 these early observations and have confirmed not only the
10 ability of Listerine to kill a broad spectrum of
11 microorganisms, both in vitro and in vivo, but also
12 demonstrated the significant clinical outcomes associated
13 with this cidal activity, including the prevention and
14 reduction of supragingival plaque and gingivitis, reduction
15 and control of intrinsic oral malodor, and the significant
16 reduction in viable bacteria contained in aerosols generated
17 during dental procedures.

18 Of course, many of these studies are certainly
19 familiar to members of this subcommittee.

20 The process of supragingival plaque formation has
21 been well documented. Initially, the pellicle-covered tooth
22 surface is colonized through the selective adherence of
23 bacteria from saliva. Then the growth of plaque mass occurs
24 as the result of the multiplication of these pioneer plaque
25 bacteria, the elaboration of an extracellular matrix, and

1 the interbacterial coaggregation of additional species from
2 saliva with those in the existing plaque. The latter
3 process is also responsible for the maturation of plaque to
4 a stage at which it becomes pathogenic.

5 The etiologic relationship between supragingival
6 plaque accumulation and the development of gingivitis
7 constitutes one of the fundamental tenets of periodontology.
8 The relationship was demonstrated by the landmark study
9 conducted by Loe and co-workers and reported in their
10 publication Experimental Gingivitis in Man. This study
11 showed the temporal relationship between plaque accumulation
12 and maturation and the development of gingivitis.

13 Additionally, it showed that when plaque is
14 removed gingivitis resolves. Since, in this study, plaque
15 levels were reduced entirely through mechanical methods, it
16 was clear that the resolution of gingivitis resulted solely
17 from the decrease of the bacterial load on the adjacent
18 tooth surface.

19 The effectiveness of Listerine Antiseptic in
20 preventing and reducing both supragingival plaque and
21 gingivitis has been confirmed by this subcommittee in its
22 recommendation of a Category I classification for the fixed
23 combination of essential oils.

24 We believe that the overwhelming preponderance of
25 the evidence leads to the conclusion that antibacterial

1 activity constitutes the primary, if not the sole, mechanism
2 by which Listerine produces its clinical effects. In all
3 the clinical trials reviewed by the Plaque Product
4 Subcommittee, there was a concurrent reduction in plaque and
5 gingivitis, with the six month reductions compared to the
6 negative control all statistically significant and
7 clinically meaningful according to criteria established by
8 this subcommittee.

9 The parallel changes in plaque and gingivitis
10 levels seen in the Listerine clinical trials are consistent
11 with those reported by Loe and co-workers in the above-
12 referenced publication.

13 Listerine has been shown to kill a broad spectrum
14 of oral microorganisms in vitro, including pathogens
15 associated with gingivitis. Evidence also exists which
16 demonstrates that Listerine is effective in killing bacteria
17 in a variety of intraoral sites, including saliva, the
18 dorsum of the tongue, and bacterial plaque. I will be
19 reviewing these data very shortly.

20 There is no evidence to support an alternative
21 mechanism of action by which Listerine produces a reduction
22 of plaque. For example, exposure of artificial biofilms to
23 Listerine in vitro results in a killing of bacteria but no
24 observable disaggregating or disrupting effect on the
25 biofilm, per se.

1 There is no evidence to support an alternative
2 mechanism for gingivitis reduction. For example, it is
3 extremely unlikely that the essential oils at the low
4 concentrations in Listerine exerted an anti-inflammatory
5 effect on the gingiva, especially in view of the numerous
6 clinical studies in which high doses of potent non-steroidal
7 anti-inflammatory agents failed to significantly reduce the
8 level of gingivitis, even in instances in which they
9 produced a significant reduction of alveolar bone loss in
10 patients with periodontitis.

11 I'd now like to provide an overview of data in the
12 following areas: first, laboratory studies demonstrating
13 Listerine's microbicidal activity. Then clinical studies
14 demonstrating the effectiveness of Listerine in killing
15 bacteria in saliva on oral mucosal surfaces and in bacterial
16 plaque. And last, a consideration of the possibility that
17 Listerine can affect gingivitis primarily through an anti-
18 inflammatory mechanism.

19 The kill time determination, also referred to as
20 the kill kinetics or assay or Bahn test, is a recognized
21 method by which to assess the effectiveness of oral
22 antimicrobial formulations. This assay evaluates the extent
23 to which an antimicrobial mouth rinse formulation kills
24 standard cultures of microorganisms under defined conditions
25 of time and temperature and can be used to demonstrate the

1 spectrum of activity of a given antimicrobial agent.

2 Numerous kill kinetic studies have demonstrated
3 that Listerine mouth rinse formulations kill a wide range of
4 oral microorganisms within 30 seconds, both in the presence
5 and absence of serum. The panel of widely accepted
6 representative microorganisms used in these studies included
7 *Actinomyces viscosus*, *Prevotella intermedia*, *Candida*
8 *albicans*, *Lactobacillus casei*, *Fusobacterium nucleatum*,
9 *Pseudomonas aeruginosa*, *Streptococcus sanguis*, *Strep mutans*,
10 *Actinobacillus actinomycetemcomitans*, *Eikenella corrodens*,
11 and *Campylobacter rectus*.

12 This group of microorganisms includes bacterial
13 species that have been associated with plaque and
14 gingivitis. These studies, therefore, provide irrefutable
15 evidence of Listerine's effectiveness in killing oral
16 bacteria.

17 A considerable body of data exists to demonstrate
18 that Listerine has significant antimicrobial activity in the
19 mouth as well, and I'll review these data at this point.

20 Numerous studies have demonstrated that a single
21 30 second rinse with 20 milliliters of Listerine produces
22 significant reductions in salivary bacteria. These findings
23 are of particular interest and clinical relevance, since
24 saliva is a source of bacteria which colonize teeth and lead
25 to plaque formation.

1 In two separate studies conducted at the
2 University of Maryland, unstimulated salivary samples were
3 collected just before and at two, 15, 30 and 60 minutes
4 after subjects rinsed with either Listerine or a negative
5 control rinse. The salivary counts of total recoverable
6 aerobic bacteria, total recoverable anaerobic bacteria,
7 streptococci, and Veillonella species were determined at
8 each sampling period.

9 At two minutes following a single 30 second rinse,
10 Listerine had produced statistically significant reductions
11 from baseline in all four groups of bacteria, ranging from
12 60 to 65 percent in one study and 72 to 81 percent in the
13 second study. Reductions in total bacterial counts of
14 approximately 50 percent were seen at 60 minutes.

15 In a separate study conducted at the Universities
16 of Wales and Bristol, and published in the Journal of
17 Clinical Periodontology, a single rinse with Listerine was
18 shown to significantly reduce salivary bacterial counts
19 compared to a control rinse for five hours.

20 In addition, a series of controlled clinical
21 studies has been reported which investigated the effects of
22 a single rinse with Listerine Antiseptic on levels of Gram-
23 negative odorgenic bacteria in the gingival crevicular
24 region and dorsum of the tongue.

25 These studies also evaluated oral malodor.

1 Results demonstrated significant reductions in crevicular
2 and tongue organisms for up to three hours, which correlated
3 with a simultaneous reduction in oral malorder. Appropriate
4 controls were included to demonstrate that the significant
5 reduction in bacterial levels was a result of bactericidal
6 activity and not the physical removal of bacteria by
7 rinsing. These studies have been reported in a series of
8 three publications in the Journal of Dental Research.

9 Studies on the effect of preprocedural rinsing
10 with Listerine on the level of viable bacteria in dental
11 aerosols provide additional, albeit indirect, evidence of
12 the antibacterial activity of Listerine in the mouth. In
13 these controlled studies, preprocedural rinsing with
14 Listerine produced statistically significant reductions in
15 viable bacteria compared to baseline, irrespective of
16 whether the aerosol was sampled immediately after or 40
17 minutes after rinsing. The reductions in the Listerine
18 group were on the order of 90 percent and were statistically
19 significantly greater than those found following use of the
20 negative control rinse.

21 The next studies present compelling demonstrations
22 of the cidal activity of Listerine on plaque bacteria in
23 situ. The first study determined the effect of rinsing with
24 Listerine on recoverable counts of Streptococcus mutans as
25 well as total Streptococci in dental plaque and saliva.

1 Although this organism is not associated with gingivitis, it
2 is an organism which contributes to plaque formation and
3 thus, is an indicator of in vivo bactericidal activity
4 relevant to plaque.

5 29 subjects with qualifying levels of baseline
6 plaque and salivary S. mutans were randomly assigned either
7 Listerine Antiseptic or a negative control rinse and began
8 rinsing with 20 milliliters for 30 seconds twice daily for
9 11 days and once on the 12th day. One hour after the final
10 rinsing, plaque and saliva samples were obtained. Total
11 recoverable Strep mutans and total recoverable streptococci
12 were enumerated by culture on appropriate selective media.
13 After a one-week washout period, the procedures were
14 repeated with the alternative rinse.

15 In this study, when compared to the control,
16 Listerine Antiseptic significantly reduced total recoverable
17 interproximal plaque Streptococcus mutans by 75.4 percent
18 and total recoverable plaque streptococci by 69.9 percent.
19 Additionally, Listerine significantly reduced salivary total
20 recoverable Strep mutans by 39.2 percent and total
21 recoverable salivary streptococci by 50.8 percent.

22 The final study utilized a vital staining method
23 to demonstrate the killing of plaque bacteria in situ. In a
24 crossover study design, subjects who refrained from all oral
25 hygiene procedures for 24 hours had baseline plaque sampled,

1 and then rinsed with 20 milliliters of either Listerine or a
2 negative control for 30 seconds, and had plaque from
3 contralateral quadrants sampled 30 minutes later. The
4 procedures were repeated with the alternate rinse after a
5 seven day washout period.

6 The plaque samples were treated with a
7 commercially available fluorescent staining solution which
8 fluoresces live and dead bacteria green and red,
9 respectively. For each sample, the percentage of dead and
10 live bacteria was determined using a Leitz Quantimet 500MC
11 image analysis instrument, with total red/green areas of
12 each plaque sample recorded as pixels per sample. Results
13 from each mouth rinse group were compared statistically.

14 The relevance of percent red per plaque specimen
15 to actual bactericidal activity was demonstrated in a
16 separate in vitro study, which showed an inverse
17 relationship between percentage of red staining and
18 recoverable colony forming units from standardized biofilms.

19 Data obtained from 12 subjects completing both
20 arms of the crossover demonstrated that rinsing with
21 Listerine produced a statistically significant 74.6 percent
22 kill of plaque bacteria compared to the control rinse kill
23 of 29.8 percent. This study provides direct, visual
24 evidence of the in situ killing activity of Listerine
25 against supragingival plaque organisms.

1 I just brought the three representative photo
2 micrographs to give you some idea what these look like.
3 This is a pre-rinse control in which the vast majority of
4 the specimen is stained in green, indicating the
5 overwhelming vitality of the bacteria in this plaque
6 specimen.

7 The next photo micrograph is an example of the
8 extreme at the opposite end. This is a post-Listerine rinse
9 specimen which is virtually all red, indicating the
10 virtually complete kill of bacteria. In fact, this was
11 obviously not seen in every case, so in many cases therefore
12 there was a situation such as this, where the majority was
13 red but certainly not the whole thing. This accounts for
14 the mean kill reduction of approximately 75 percent.

15 Again, these were analyzed not by I but by an
16 image analysis system which looked pixel-to-pixel, so it
17 eliminated this kind of impression that one has by looking
18 at it visually.

19 In summary, the clinical studies presented in this
20 section which utilized a variety of protocol designs and
21 were conducted by investigators at a number of different
22 locations, provide clear evidence that the fixed combination
23 of essential oils has significant bactericidal activity in
24 the mouth at sites which include supragingival dental
25 plaque. When these studies are considered in combination

1 with the microbicidal studies presented just previously, it
2 is clear that the totality of the evidence supports an anti-
3 microbial claim for Listerine Antiseptic.

4 Finally, I'd like to turn to the subject of a
5 possible anti-inflammatory activity of the methyl salicylate
6 in the fixed combination of essential oils. At the May
7 28th, 1998 meeting of the subcommittee, the intriguing
8 suggestion was made that the primary mechanism by which
9 Listerine prevents and reduces gingivitis may not be through
10 its demonstrated antiplaque and antibacterial activity but
11 rather by virtue of anti-inflammatory activity exerted by
12 methyl salicylate.

13 This suggestion was no doubt based on the fact
14 that some salicylates, such as magnesium salicylate, have
15 been demonstrated to have anti-inflammatory activity and
16 have been used systemically.

17 In the interim, we have followed up this
18 suggestion in a number of ways. First, we conducted a
19 search of the literature and a number of data bases to
20 investigate the evidence supporting an anti-inflammatory
21 activity by methyl salicylate in general. In the course of
22 this exercise, we're unable to find methyl salicylate listed
23 among anti-inflammatory agents or to identify published
24 studies that demonstrated to have anti-inflammatory
25 activity. Thus, any anti-inflammatory activity which methyl

1 salicylate might have would appear not to be potent enough
2 to be of therapeutic interest.

3 The Merck Index, for example, classifies methyl
4 salicylate as a counter-irritant and not as an anti-
5 inflammatory compound.

6 We then explored the possibility of an anti-
7 inflammatory activity by methyl salicylate as the primary
8 mechanism by which Listerine reduces gingivitis in the
9 context of studies on the periodontal effects of quite
10 potent non-steroidal anti-inflammatory drugs which have been
11 reported in the literature.

12 These studies consist of human clinical trials and
13 animal studies in which therapeutic doses of non-steroidal
14 anti-inflammatories were delivered either systemically or
15 topically. Although, in some studies, therapeutic levels of
16 a potent non-steroidal anti-inflammatory such as
17 flurbiprofen were shown to have an effects on gingivitis,
18 most studies demonstrated these drugs to have a modest or no
19 effect on gingival inflammation. Even in instances where
20 they produces a significant inhibition of periodontal bone
21 resorption.

22 In this regard, it is interesting to note that a
23 study by Heasman and Seymour comparing 50 patients on long-
24 term non-steroidal anti-inflammatory therapy for rheumatoid
25 arthritis with a group of age and sex-matched controls found

1 no significant different between the groups for a number of
2 periodontal parameters including gingival index.

3 When we compared the doses of the potent non-
4 steroidal anti-inflammatory drugs used in these studies to
5 the level of methyl salicylate in the daily dose of
6 Listerine, the difference in magnitude of doses suggested
7 that it is unlikely that methyl salicylate could be exerting
8 an anti-inflammatory effect.

9 Specifically, the level of methyl salicylate in
10 the Listerine formulations is 0.06 percent, which
11 corresponds to a 12 milligram dose per 20 milliliter rinse
12 volume or a daily topical dose of 24 milligrams. In
13 contrast, the daily systemic non-steroidal anti-inflammatory
14 drug doses used in the published clinical studies were 1,000
15 milligrams for acetylsalicylic acid, 50 to 100 milligrams
16 for flurbiprofen and Meclomen and 800 milligrams for
17 ibuprofen. While topical non-steroidal doses in toothpaste
18 were 1 percent for flurbiprofen, 8 percent for ibuprofen,
19 and 5 percent for Meclomen.

20 Since the dose of methyl salicylate contained in
21 Listerine is considerably smaller than the doses of quite
22 potent non-steroidal anti-inflammatory drugs which have
23 failed to demonstrate anti-gingivitis activity or have
24 inconsistently demonstrated anti-gingivitis activity, you
25 would have to conclude that it is unlikely that an anti-

1 inflammatory activity by the methyl salicylate in Listerine
2 could represent the primary mechanism for Listerine's effect
3 on gingivitis.

4 Therefore, although the suggestion was an
5 interesting one which led to further investigation, we
6 believe that the data presented in this section clearly
7 support the conclusion that the methyl salicylate at the
8 level in Listerine mouth rinses does not contribute to
9 gingivitis reduction by virtue of anti-inflammatory
10 activity; and moreover, that there is little likelihood that
11 Listerine can affect gingivitis primarily by an anti-
12 inflammatory mechanism of action.

13 In summary, the significant bactericidal activity
14 of Listerine has been generally recognized since its
15 development as an antiseptic solution. In fact, the cidal
16 activity of Listerine as an oral care product is recognized
17 as early as the turn of the century. In the interim, the
18 safe and effective adjunctive use of Listerine for the
19 prevention and control of supragingival plaque and
20 gingivitis has been recognized by numerous dental
21 professional organizations as well as advisory panels,
22 including this subcommittee.

23 The etiologic relationship between plaque
24 formation and the development of gingivitis is one of the
25 bedrock tenets of periodontology. The data presented today

1 provide clear evidence in support of Listerine's killing
2 activity against plaque bacteria as the primary mechanism
3 underlying its anti-gingivitis effectiveness.

4 Listerine rapidly kills a broad spectrum of oral
5 microorganisms in vitro, including bacteria that have been
6 associated with plaque and gingivitis. In clinical studies
7 using a variety of protocol designs mouth rinsing with
8 Listerine has been unequivocally shown to have cidal
9 activity against oral microorganisms in supragingival
10 plaque, as well as in other sites from which bacteria
11 colonize tooth surfaces. There is no evidence or scientific
12 basis to support the hypothesis that the primary mechanism
13 by which Listerine affects gingivitis is based on anything
14 other than antimicrobial activity.

15 We believe that the overwhelming weight of the
16 evidence supports the requested indication for Listerine.
17 In light of the material presented today and included in our
18 submission, we respectfully request the Plaque Subcommittee
19 to reconsider its previous decision and approve the
20 indication proposed at the May, 1998 meeting, namely "aids
21 helps in the control, inhibition, killing of plaque bacteria
22 that contribute to gingivitis."

23 I would now, as I mentioned, like to call upon our
24 expert consultants and just ask for their comments and
25 review. I should mention that we had requested these well-

1 respected experts to review our data and Warner-Lambert has
2 paid to their travel expenses to attend this meeting and is
3 providing an honorarium for their services.

4 The first of our panelists, essentially, is Dr.
5 Clay Walker. Dr. Walker is a professor of oral biology at
6 the University of Florida College of Dentistry. He is known
7 to most people in the field of periodontology as perhaps one
8 of the premier periodontal microbiologists. He got his
9 Ph.D. at the Virginia Polytechnic Institute, which was a
10 hotbed of anaerobic microbiologic studies, and subsequently
11 did a post-doc in the laboratory of Sid Sakransky at the
12 Forsyth Dental Institute.

13 DR. WALKER: Thank you, Michael.

14 As Dr. Barnett said, he asked me if I would read
15 over the Listerine data. I did so essentially, I think,
16 pretty much the same publications and the same reports
17 that's been forwarded to the committee. I guess I'm
18 considered an outside consultant because none of this work
19 submitted to the committee is my own work, so I was
20 reviewing other work pretty much unbiased.

21 I was very impressed with this data. In looking
22 at totally the microbial effect compared to other products
23 that I'm familiar with, other products I have tested,
24 including bactericidal antibiotics.

25 From the data presented, I would have to conclude

1 that Listerine Antiseptic does have a bactericidal effect
2 against a wide range of microorganisms. From the data
3 presented, I would have to conclude that the effect was only
4 bactericide, that when we have a kill, by definition, that
5 is a cidal effect.

6 I would be happy, if I could, to answer any
7 questions that you might have concerning my interpretation
8 of these reports.

9 DR. GENCO: Thank you, Dr. Walker.

10 Any comments or questions from the panel?

11 [No response.]

12 DR. GENCO: Thank you.

13 DR. BARNETT: Incidentally, each of the persons
14 we've asked to review the data, we asked to do so from a
15 slightly different perspective and based on the different
16 experiences of the individuals. And so the next individual
17 is Dr. Daniel Fine, who is currently a professor of oral
18 biology and director of the dental research center at the
19 University of Dentistry of New Jersey. Dr. Fine was
20 previously director of the division of oral infectious
21 diseases at Columbia University and comes to us both as a
22 periodontal researcher and as a practicing periodontist.

23 DR. FINE: Thank you, Michael.

24 I, unlike Clay, was personally involved in design
25 and performance testing in several of the studies that have

1 been submitted for Mike's report. In addition, I thoroughly
2 reviewed the report and all of the references that have been
3 submitted to the panel. And I, like Clay, fully support the
4 concept that Listerine Antiseptic is an effective
5 bactericidal agent against bacteria that are related and
6 associated to plaque and gingivitis.

7 DR. BARNETT: And the last individual probably
8 needs no introduction, but for the record I have to, and
9 that is Dr. Irwin Mandel, who is professor emeritus of
10 dentistry at Columbia University. Irwin, I think, is well
11 known in the field of plaque research. Some say he may have
12 invented plaque initially.

13 DR. MANDEL: Don't blame me.

14 DR. BARNETT: But we asked him to look at it from
15 his historical perspective, as well.

16 DR. MANDEL: Thank you very much. Thank you,
17 panel members, for the opportunity to comment on this
18 product because it relates to so much of what I have been
19 involved in through most of my professional life.

20 As Dr. Barnett indicated, they asked me to serve
21 as a consultant to review the data, essentially the material
22 that has been presented to this panel. Much of it had been
23 familiar to me because I had written a number of review
24 articles over the years on the mouth rinses, and so in a
25 sense, was a student of these studies. But there is an

1 advantage when all of these data are put together.

2 And that does supply, for us, a perspective, a
3 totality. I must say that in viewing that totality, I was
4 impressed with the amount of work that had been done in
5 considerable depth over the years, plus some recent
6 additional studies using the fluorescent eye system with the
7 red and green contrast. It's sort of like traffic lights.

8 In any event, I think the totality was very
9 supportive. And of course, when one reviews a body of data,
10 one not only has the perspective of the data itself and in
11 its totality, but one brings his own perspective to the
12 situation. In my case, I look back on more than 40 years of
13 involvement in the development biology of the plaque and the
14 sequential steps involved in the development and the
15 quantitative measurements that enabled us finally to go
16 beyond just the suggested value of antiseptic mouth rinses,
17 but to be able to actually demonstrate a quantitative
18 relationship between plaque and gingivitis.

19 As I put it, on occasion, it provided the
20 mechanism where we could finally find in mouth rinses a
21 solution that finally found its problem, as it were. And
22 also the opportunity to be involved as a director of a
23 clinical research center in clinical studies, I certainly do
24 appreciate the depth of how these were conducted. And
25 indeed, also acting as a consultant for the American Dental

1 Association, that had been involved in the promulgation of
2 the standards by which these mouth rinses evolved.

3 So it seems to me that from all of these
4 perspectives, I have viewed this data and plain and simply I
5 think they're impressive. I think that they've been able to
6 demonstrate the validity of the proposal and I think the
7 proposal is scientifically valid. I think it fairly
8 describes the situation. I think it's circumspect and I
9 would urge the panel to be supportive.

10 DR. BARNETT: Before we get into questions, I'd
11 just like to make one additional comment. And that is I
12 think it's important to emphasize to the subcommittee that
13 the claim, this killing bacterial claim, that we're
14 requesting is not intended to be used in any unqualified
15 way, but rather is intended to be used in a mechanism of
16 action claim in the context of the other two clinical claims
17 that had been previously, or indications that had been
18 previously approved by this subcommittee. I think that's an
19 important point that we need to keep in mind.

20 So if anybody has any questions that I or my
21 colleagues can answer, I'd be happy to entertain them.

22 DR. GENCO: I'd like to thank you, Dr. Barnett,
23 and Drs. Walker, Fine and Mandel for their opinions. You've
24 all been very helpful.

25 Any comments or questions of Dr. Barnett or any of

1 the consultants?

2 DR. WU: I notice that in your study you tried
3 standardized biofilm in a laboratory and you used the Strep
4 mutans biofilm. Have you ever tried a mixed biofilm model
5 for testing your mouth rinse? I'm just curious?

6 DR. BARNETT: Yes, we had the most experience with
7 the Strep mutans, and so that was used to establish the
8 relationship of the fluorescent dye findings to what it
9 actually meant in terms of bacterial kill. It was the most
10 standardized way we had available to do that.

11 DR. WU: Thanks

12 DR. GENCO: Bill?

13 DR. BOWEN: I would agree to the preponderance of
14 evidence of supports what you're claiming, but I do have a
15 few questions on parts of the preponderance.

16 First of all, I want to commend you for getting
17 into the effect of the agents on biofilm, because I think
18 that's the way things are going to have to be tested in the
19 future, but for the moment we have to deal with the way
20 things are.

21 In Dr. Fine's study, I may have missed this, but I
22 can't see any standardization of the plaque amounts. And I
23 see a huge reduction in total population of Streps and Strep
24 mutans and what he may possibly have been looking at is a
25 reduction in plaque, which of course obviously is not a bad

1 thing, but you may not be getting the type of killing that
2 is noted. I just would like some clarification on that
3 issue.

4 DR. BARNETT: Why don't we go to the horse's
5 mouth, Bill.

6 DR. FINE: Thank you, Bill. The plaque was
7 collected, as usual it's very difficult to document
8 quantities of plaque when they're collected. So the
9 standardized way of collecting plaque was, in this case, the
10 use of a stimudent to be inserted interproximally and then
11 placed into a standard amount of collection fluid. Then the
12 quantitation was done based on total Strep versus Strep
13 mutans within that standardized method.

14 I mean, obviously, we couldn't weigh the plaque
15 and do other methods because of the fragility of the plaque,
16 et cetera. But in each case, the same method was used. It
17 was a short interval, I believe 10 seconds, of collection
18 and insertion of a stimudent interproximally placed in a
19 standardized amount of reduced transport medium.

20 Does that answer your question?

21 DR. BOWEN: It does, but I'm still a little
22 worried that if you were basing the amount of plaque on the
23 total number of Streps, in fact you saw a reduction in total
24 Streps, which kind of supports my supposition that you had a
25 reduction in plaque as a result of using the mouth rinse,

1 which of course, as I've indicated already is no bad thing.

2 DR. FINE: Yes, exactly. And I think if you look
3 at the data you will see that there was a greater reduction
4 in Strep mutans interproximally versus the reduction in
5 saliva. And in fact, we have done some in vitro testing
6 which may suggest, this is preliminary, that there may be a
7 selective effect on Strep mutans versus other streptococcal
8 microorganisms.

9 DR. BOWEN: I think your data showed that the
10 proportion in reduction of mutans roughly paralleled the
11 reduction in total Streps in the plaque.

12 DR. FINE: In the plaque, exactly, but not in the
13 saliva.

14 DR. BOWEN: I don't get very excited about saliva
15 because all it represents are washings from various
16 surfaces.

17 DR. FINE: Yes, that's true.

18 DR. BOWEN: That's my opinion.

19 I'm also, if I may proceed Bob?

20 DR. GENCO: Please do.

21 DR. BOWEN: A question on the fluorescent dye
22 technique. Based on the magnifications, I would have
23 expected to be able to see individual microorganisms. And
24 what I'm seeing is a blur. As we all know, as much as 40
25 percent of the plaque can be made up of matrix. So in

1 reality, I don't really know what I'm looking at, so I'd
2 like a little clarification of that.

3 And also, could we have some information on the
4 effect of Listerine on the fluorescence of the dye? Have I
5 made myself clear? Does the Listerine itself interfere with
6 fluorescence, as opposed to killing microorganisms?

7 DR. BARNETT: I'll ask Dr. Pauline Pan to respond
8 to that.

9 DR. PAN: Bill, in response to your question, yes,
10 we did check the effect of the Listerine formulation and
11 dilutions of the Listerine formulation on the dye and there
12 was insignificant effect.

13 I think that's a very valid question when one uses
14 this very sensitive staining method.

15 The response to your second question was why do we
16 see single cells or chains of streptococci or whatever else
17 is in there. As you just indicated, there is quite a
18 significant amount of mutans soluble or insoluble in the
19 plaque matrix. When you saw these photos, two things I'd
20 like to share with the committee members. It's a very
21 elegant method and can really only be seen on a whole screen
22 live and not computer printed overheads. One does lose a
23 little bit of the integrity. Certainly, if I had a Hubble
24 spacecraft imaging system available for you today, you would
25 see every single dot and the surface on every single dot of

1 the bacteria.

2 But in answer to your question, in all
3 seriousness, at the magnification we did, it is possible to
4 scrutinize and even see things like corn cobs with single
5 Strep attached to the filaments. With the hundreds of
6 mutans, it does sometime sort of so-called the effect is to
7 smooth it over. This is the reason we went into analysis
8 using pixel-by-pixel as opposed to a more older technology,
9 I would like to say, in the last several years. People look
10 at areas, rather than pixel-by-pixel.

11 We feel that we have now used this method to the
12 most precision that can technology can afford today.

13 DR. BOWEN: Does a pixel represent one organism or
14 more than one organism?

15 DR. PAN: A pixel represents less than one
16 organism. For instance, there may be as much as 55,000
17 pixels. There are not, in that tiny image, 55,000
18 microorganisms.

19 DR. BOWEN: Thank you.

20 DR. GENCO: Further comments? Questions?

21 DR. SAVITT: Mike, if we go back three or four or
22 five or six meetings, when you discussed Listerine broken
23 down into various ingredients, unfortunately I can no longer
24 remember the data in detail but perhaps you can answer it
25 for me. What was the effect of the salicylate on plaque and

1 gingivitis alone as opposed to Listerine in combination?

2 DR. BARNETT: Gene, if you'll recall, those
3 studies were not based on clinical measures of plaque and
4 gingivitis but rather were in vitro studies, looking at the
5 effects of the formulation minus each one of the four oils
6 successively on the total antimicrobial activity. And it
7 was done, I believe, using a kill kinetics assay.

8 When each of the individual ingredients was
9 removed, the remaining three had significantly less
10 effectiveness than did the total Listerine formulation. So
11 for example, when the methyl salicylate was removed, it had
12 less antibacterial effect than it would have -- and
13 significantly less so -- than if it were in the formulation.

14 DR. SAVITT: Another question, can you discuss
15 with me for a minute how you feel about the relevancy of a
16 systemic anti-inflammatory versus a topical anti-
17 inflammatory might have on gingivitis? You've discussed, in
18 the literature submitted, that the systemic anti-
19 inflammatories didn't seem to have much of an effect on
20 gingivitis. But I'm wondering if you could comment on the
21 difference that might be seen with a topical versus a
22 systemic?

23 DR. BARNETT: I think there are two aspects to
24 that. The first is that because the agent actually has to
25 get into the tissues where the inflammatory process is going

1 on, I think there is a reasonable assumption that at these
2 therapeutic doses of these rather potent non-steroidal anti-
3 inflammatory drugs would be more likely to have an effect on
4 tissues if they were given systemically.

5 And the fact that this, in fact, is the case is
6 evidenced by those situations in which both the amount of
7 alveolar bone resorption and the clinical parameters of
8 gingivitis were looked at in the same study. There were
9 instances where the non-steroidals had an effect on the bone
10 resorption -- that is, in decreasing the amount of bone
11 resorption -- but yet did not result in any kind of
12 resolution of gingivitis.

13 So the thought was, number one, that if you look
14 at these studies -- and they were not all systemic by the
15 way, but the majority. If you look at these studies, if
16 something is going to have an effect on the inflammatory
17 process it's more likely to have an effect given
18 systemically because number one, these things were given at
19 their usual therapeutic doses. Number two, it's more likely
20 that an effective level of the agent would get to the
21 tissues where the inflammatory process is going on. And I
22 think that was the rationale.

23 And so that, coupled with the difference in dose
24 levels that one would have in terms of exposures -- that is
25 to say, something like methyl salicylate, which was very low

1 on a topical basis, versus some of these which are quite
2 high. I think the reasoning was if these potent non-
3 steroidal at their therapeutic levels don't have an effect
4 on gingivitis or have an inconsistent effect, it's extremely
5 unlikely to conclude that methyl salicylate which some would
6 question whether, in fact, it's an anti-inflammatory at all.
7 But even if it were, at that level, would it be able to get
8 in the tissues and exert an effect?

9 And I think that was the reason for the contrast.

10 DR. GENCO: I'd like to address the issue that you
11 brought up last, Michael, and that is that this claim, anti-
12 microbicidal claim, antibacterial claim against plaque and
13 oral organisms, is a claim that's only used in conjunction
14 with the anti-plaque, anti-gingivitis claim. I'd like to
15 get some feeling from the panel if that link is clear? That
16 is, in the studies that you've presented it's clear, at
17 least to me, that this agent will clear bacteria. It's also
18 clear that this agent will reduce plaque.

19 Is it clear that it reduces plaque only because it
20 kills bacteria or does it have some other mechanism,
21 dissolving plaque, solubilizing plaque, reducing adherence,
22 reducing metabolism, et cetera? So I really ask the
23 question and bring this point to the panel and ask you, what
24 is the evidence for the link?

25 I think we have a challenge here, in terms of

1 advising the FDA, because if this is an antimicrobial claim
2 that's not linked then maybe this is the wrong panel to
3 bring that claim to. There might be an anti-infectives
4 panel that would deal with that.

5 So really the essence is the link. This is
6 essentially your last point.

7 DR. BARNETT: Yes, I'll comment about that. I
8 don't think there's any question about the link between
9 plaque reduction and gingivitis reduction. That's a given.
10 Certainly that was demonstrated in all eight of the six
11 month studies that you all reviewed.

12 So I think then that one can reasonably conclude
13 that the reduction in gingivitis was a result of the plaque
14 reduction. So the question then is what is the mechanism
15 for the plaque reduction?

16 In considering the various things that Listerine
17 has been shown to do or not to do, clearly it's been shown
18 to kill bacteria. And I think it's a reasonable conclusion
19 that if you're killing bacteria both in the plaque itself
20 and in sites from which plaque becomes colonized or tooth
21 surface becomes colonized, that is very likely to have a
22 major effect, if not the only effect, in reducing plaque.

23 We've looked at Listerine.
24 For example, I mentioned we've done some studies on
25 artificial biofilms in the laboratory, looking at what

1 happens to these biofilms when they're immersed in
2 Listerine, treated with Listerine. In fact, what we've
3 shown is that there's not a disruption of the biofilm matrix
4 to the extent that the biofilm disappears and disaggregates
5 and comes off the wires. But rather the biofilm is there,
6 but it stops metabolizing. The bugs are killed.

7 So I think that you could exclude, therefore, any
8 significant effect in plaque disruption and matrix
9 disruption and anything of this sort. When you look at the
10 evidence, the vast weight of the evidence suggests that, in
11 fact, the primary mechanism by which this agent, this
12 antiseptic agent, is capable of reducing plaque is through
13 the killing of bacteria in the mouth, both in the plaque and
14 at sites from which plaque becomes colonized. So I think
15 that's the link.

16 DR. GENCO: Any comments or questions? Christine?

17 DR. WU: I need to comment -- I mean I am very
18 happy to see that Warner-Lambert has provided extra data,
19 because I noticed that these two studies were provided like
20 in mid '98 and late '97. We have looked at the previous
21 data and most of the in vitro bactericidal effect studies
22 have done in the past were geared to show the killing of
23 planktonic cells.

24 I'm glad that you have come up with this biofilm
25 model to show that cells that are adhering to the biofilm

1 are being killed. They have showed both in vitro biofilm
2 and also biofilm obtained from human subjects. So to me,
3 I'm pretty convinced about the bactericidal effect of the
4 Listerine mouth rinse.

5 DR. GENCO: Lou?

6 MR. CANCRO: I think there are three very
7 commanding pieces of evidence which say this mechanism is
8 supported. First is really the in vitro work where you are
9 demonstrating a kill, a kill in a certain time, a minimum
10 inhibitory concentration. And there, within the confines of
11 that laboratory setup, the mechanism is clearly kill. It's
12 not washing away bacteria, it's not solubilizing something.
13 It's kill.

14 Secondly, you have a concomitant reduction of both
15 plaque and gingivitis in your long-term trials.

16 And third, in all of your one-time treatment
17 trials, you're demonstrating a viable dye is showing that
18 the bacteria are dead and that the counts are reduced.

19 So when you look at those three independent
20 things, it certainly suggests to me that the mechanism of
21 action has been defined.

22 DR. GENCO: I just want to point out -- and maybe
23 Michael you can correct me or add additional information --
24 the studies we're presented with are four studies of
25 salivary bacteria reduction -- two studies of salivary

1 bacteria reduction, the Baltimore study and the Wales study,
2 with no relationship to gingivitis. The study of the
3 gingival crevicular flora reduction, the Pitts studies,
4 three studies, related to malodor not gingivitis. And then
5 Danny Fine's studies of the pre-procedure rinsing, which is
6 aerosol, has nothing to do with gingivitis, no measurement.

7 We are then presented with the Listerine cidal
8 effect on plaque bacteria in situ, the mutans and Strep
9 studies, again no relationship to gingivitis in those
10 studies, per se. I mean, I'm trying to -- what is the data
11 linking them? The vital standing study is obviously done in
12 situ, but there's no relationship to gingivitis in those
13 subjects.

14 In your gingivitis studies, did you look at
15 killing?

16 DR. BARNETT: Let me comment about that, because I
17 think we need to understand the logistics of answering --
18 there are two different questions that are being asked. The
19 first question is what's the relationship of plaque to
20 gingivitis and how does Listerine affect both plaque as a
21 whole, and gingivitis.

22 As we know, plaque reduction or gingivitis
23 reduction, or gingivitis or plaque inhibition is really more
24 of a cumulative event. It doesn't happen, for example, with
25 a single rinse. So that in order to ask the question what's

1 an agent doing with respect to plaque or gingivitis, I think
2 you have to look at the cumulative effects of the agent over
3 time. It's more of a chronic event rather than an acute
4 event. In fact, that's what happened in all of the six-
5 month studies.

6 So then the question is asked now that you've
7 established that this agent can reduce significantly both
8 plaque and gingivitis, then the question is what is it doing
9 to the plaque? How is it reducing the plaque? The dilemma
10 you get into, of course, is that the kill of bacteria is an
11 acute event. So what you end up doing then is asking the
12 question what's the most likely mechanism? What's the
13 mechanism by which my agent or an agent is reducing, is
14 affecting, the reduction in plaque?

15 The question that was asked last time is how do we
16 know it's killing the bugs? I think when you talk about
17 salivary bacteria, we pointed out where do the bugs and
18 plaque come from? They colonize from saliva. If you're
19 talking about gingival sulcular organisms, obviously this is
20 plaque that's forming in the gingival sulcular area.

21 If you're talking about dorsum of the tongue, I
22 was recently in a review on biofilms that suggested that the
23 dorsum of the tongue is a reservoir for organisms that could
24 subsequently colonize tooth surfaces.

25 So there is some relevance to the studies if

1 you're asking the question is the mechanism by which the
2 agent is reducing plaque one of killing bacteria. Of
3 course, the ones where we looked at the Strep mutans, well
4 Strep mutans can be considered an agent representative of a
5 bacterium in plaque. And certainly the viable stain
6 technique very graphically and visually demonstrated the
7 fact that you're killing large percentage of organisms in
8 plaque.

9 So I think there is a relevance to all of these.
10 They tie together. And granted that if you're asking the
11 question specifically about plaque the ones looking at
12 organisms in plaque are perhaps the most compelling, but
13 certainly I think they're all related.

14 DR. GENCO: So what you've said is that -- and
15 this is not an easy experimental issue. I mean, it's a
16 difficult issue to prove mechanism, obviously. So you've
17 said it wouldn't make much sense to look at killing in the
18 gingivitis experiments, per se, because that's an acute
19 event and what you're seeing over six months is chronic
20 repetitive killing, or whatever is going on.

21 So that you've taken this into other, more acute,
22 experiments, either in vivo or in the test tube to help
23 support the mechanism? And in lieu of not demonstrating
24 major dissolution of plaque removal by disrupting plaque
25 structure, the positive effect of killing, the lack of clear

1 evidence of anti-inflammatory, by process of elimination
2 what else could it be? Is this your argument?

3 DR. BARNETT: I think it's more positive than
4 that. I think you look at it, you see it's killing the
5 bugs. And in the absence of any other explanation, yes. I
6 mean, it's not like you've excluded everything else and say
7 gee, maybe it's this. I think you have a lot of evidence to
8 say yes, it is this.

9 The question, don't forget, is one of primary
10 mechanism. What's the overwhelming mechanism by which it's
11 doing something? I think if you look at the antibacterial
12 data, it is pretty overwhelming. And then look at any other
13 support for alternative mechanisms and it's not there. I
14 think that's reasonable -- it allows for the reasonable
15 scientific conclusion that therefore it's this killing of
16 bacteria that's responsible for the reductions of plaque
17 that we see in our clinical trials.

18 DR. GENCO: Thank you. Further comments,
19 questions? Gene?

20 DR. SAVITT: To some extent this is directed more
21 to the FDA people, but very early on in the first year or
22 two of our deliberations the question of mechanism came up
23 in various aspects of some of the ingredients that we looked
24 at. The general comments from the FDA was that mechanism is
25 almost irrelevant to our deliberations and that it was

1 certainly secondary, if not irrelevant.

2 My concern is that, as Bob has just discussed,
3 it's certainly a difficult thing to try to get a handle on
4 mechanism in any absolute clear-cut manner. My concern is
5 that if mechanism is indeed -- to use a fairly loaded word -
6 - irrelevant to our deliberations, is this something that is
7 appropriate for us to be voting on?

8 DR. BARNETT: There is precedent for mechanism of
9 action indications. I'm not the best person to speak on it,
10 but I think Peter Hud, whom is known to you, is. I'd just
11 like to have him comment about that point.

12 MR. HUD: For the record, my name is Peter Hud. I
13 am an attorney and I am representing Warner-Lambert on this
14 occasion.

15 I think you have raised two separate issues. The
16 first issue is whether mechanism of action must be known in
17 order to determine whether an agent is effective, and the
18 answer to that is no. If it is proved effective then it can
19 be a Category I agent.

20 The second question is whether if a company
21 submits a specific mechanism of action claim, then the panel
22 must determine whether that is supportable, as Michael has
23 pointed out, by the scientific evidence. Absent a request
24 for a specific claim, there's no need to go into mechanism.
25 But because a claim has been requested here, then the panel

1 should deliberate on that and vote on it.

2 Let me also point out that mechanism of action
3 claims are extraordinarily common in the non-prescription
4 drug industry. You frequently will see, for an anti-acne
5 over-the-counter remedy in consumer labeling a cross-section
6 of the skin showing how the drug works. You will see, in an
7 antiperspirant, discussion of how the pores are tightened
8 and therefore you don't sweat as much. In a sunscreen you
9 will see talk about how it blocks the sun rays.

10 These are all mechanism, common mechanism of
11 action claims.

12 MR. SHERMAN: Peter summed it up nicely. Bottom
13 line basically is that if the sponsor is requesting a
14 particular claim, we're asking you do the data support that
15 claim. Simply, is that reasonable?

16 DR. GENCO: I'll bring up then this other issue.
17 Michael, I'm bringing this up to get information to help us
18 make this decision.

19 Let me pose the possibility that an agent disrupts
20 plaque, not by killing but disrupts it. That's one extreme.
21 Another agent reduces plaque only by killing. And then a
22 third agent does both to varying degrees. What is the
23 evidence that your agent isn't that third agent, that it
24 does both? That it both kills bacteria, therefore reducing
25 plaque and gingivitis, and disrupts plaque and therefore

1 reducing plaque and gingivitis?

2 DR. BARNETT: If you go back to the data, the
3 study that comes to mind, Bob, is one of the three studies
4 that was done looking at the effect on gingival sulcular and
5 dorsum tongue plaque. What they did in those studies was
6 specifically ask the question how do we know that the
7 reduction is from killing of microorganisms?

8 It seemed to me that in that study they actually
9 quantitated the number of bugs in both the control and the
10 Listerine groups, and found that there was no change in
11 either. So there's a change in viable bugs, in numbers of
12 viable bugs, but not in total bugs which seems to suggest
13 then that you weren't having mechanical or physical removing
14 of the bacteria but rather the reduction that you were
15 seeing was truly as a result of killing.

16 DR. BOWEN: I think we often get a little restrict
17 on what we mean by antibacterial and the effects of killing.
18 If one regards plaque as a biofilm which, of course, is
19 exactly what it is. One has to think of it as a unit. And
20 if you do indeed disrupt the matrix that, in fact, is
21 antibacterial by any reasonable definition.

22 Furthermore, if you block the colonization of the
23 tooth surface at a gingival margin by the agent, that is
24 antibacterial. You're preventing, for want of a better
25 term, primary infection of the site of interest.

1 So if you look at some antibacterial agents,
2 they're classified as antibacterial, some of them are
3 extremely potent inhibitors of glucosyl transferases, which
4 is almost certainly responsible for the bulk of the matrix
5 of plaque. I might add those enzymes are probably the only
6 proven virulence factors of any microorganism in the mouth.

7 So we've really got to broaden our concept of what
8 we mean by antibacterial. It doesn't simply mean killing or
9 bacteria static. It's much, much broader than that.

10 DR. GENCO: I think we're dealing with a request
11 for a bactericidal claim, however. If the claim was
12 antibacterial, I think that would be a very different
13 situation. And maybe that may be something that you might
14 want to take under advisement. Fred?

15 DR. HYMAN: Bob, I was looking at the proposed
16 claim again, in terms of what you were saying. I think
17 we're mixing a little bit mechanism of action with
18 indication or claim. Although it's possible that there may
19 be other factors acting that would explain a mechanism of
20 action here, I think that what actually is being proposed --
21 aids helps in the control of plaque bacteria that
22 contributes to the development of gingivitis -- in terms of
23 that, in demonstrating that, we may not need to know the
24 entire mechanism, as long as this is truthful -- is
25 supported. So that's my comment.

1 DR. GENCO: That would be this more broad
2 antibacterial, control of bacteria involved in plaque and
3 gingivitis formation. Further comments? Questions?

4 [No response.]

5 DR. GENCO: Thank you very much, Michael.

6 And other discussion from either the audience or
7 the panel? And then I would entertain a motion. Stan?

8 DR. SAXE: I don't know if this is a motion or
9 not, but referring to the cover letter on the data that was
10 submitted, the cover letter from Warner-Lambert from Mr.
11 Kirpitch dated October the 13th, when it said these data
12 support the label indication for helping to control, inhibit
13 or kill bacteria. And I, while there may be other
14 mechanisms that are said they're not there or they're simply
15 not known, the statement killing plaque bacteria as a
16 mechanism, I'm not completely comfortable with at this
17 moment. That may be quite true, but I'd still have to study
18 the data.

19 But the idea of control and inhibit, controlling
20 plaque bacteria, inhibiting plaque bacteria, as you stated
21 Bob, I'm very comfortable with that.

22 DR. GENCO: Would you make that a motion then?
23 Aids or helps in the control -- I have their statement,
24 which is the kill statement. Maybe you could phrase it
25 then, as you would like to make a motion, Stan?

1 DR. SAXE: I would make a motion, I would support
2 that the label indication be helping to control and inhibit
3 plaque bacteria that contribute to the development of
4 gingivitis.

5 DR. GENCO: Helps to control or inhibit plaque
6 bacteria?

7 DR. SAXE: Helps to control and inhibit.

8 DR. GENCO: That contribute to the development of
9 gingivitis or the development of plaque and gingivitis?

10 DR. SAXE: The development of gingivitis. Bob,
11 here's the letter of August 21 with the quotes. So the
12 motion would be that "this product aids or helps in the
13 control (inhibition) of plaque bacteria that contribute to
14 the development of gingivitis (or gingivitis, an early form
15 of gum disease).

16 DR. GENCO: Is everybody clear on that? Bill?

17 DR. BOWEN: I have a problem with that because we
18 clearly have evidence that it control because we have a
19 reduction in plaque with no data, you might say, on inhibit,
20 and we have a lot of data on kill. I support what is being
21 requested because I think that's what the data supports.
22 And it doesn't preclude future mechanisms of action or
23 discovering future mechanisms of action.

24 DR. GENCO: So you would argue for aids or helps
25 to control (inhibit)?

1 DR. BOWEN: Inhibit and kill plaque bacteria.

2 DR. GENCO: And kill? Both?

3 DR. BOWEN: Yes, what is requested. I think the
4 data supports it. Taken individually it may not be perfect,
5 but taken collectively I think it is convincing.

6 DR. GENCO: So the claim could be made aids or
7 helps to kill plaque bacteria that contribute to the
8 development of gingivitis? That's a possible variant of
9 that claim then.

10 DR. BOWEN: Control or kill plaque bacteria that
11 contribute in the development of gingivitis.

12 DR. GENCO: So the wording would be aids (helps)
13 to control (or inhibit or kill)?

14 DR. BOWEN: Yes.

15 DR. GENCO: Plaque bacteria that contributes to
16 the development of gingivitis or gingivitis, an early form
17 of periodontal disease? Do you agree with Bill's wording?

18 DR. SAXE: Yes. So I would change my original to
19 agree with Bill then, so that the statement aids or helps in
20 the control would infer that there's inhibition and killing.
21 So killing is one of the mechanisms aiding in the control.

22 DR. GENCO: So what would the wording be?

23 DR. SAXE: The wording would be "aids (helps) in
24 the control (inhibition, killing) of plaque bacteria that
25 contribute to the development of gingivitis (or gingivitis,

1 an early form of gum disease)."

2 DR. GENCO: Bill, does that satisfy you?

3 DR. BOWEN: That's fine by me.

4 DR. GENCO: Any other comments? Bob?

5 MR. SHERMAN: I just want to make a distinction.

6 In the October 13th, '98 submission by Warner-Lambert, the
7 wording is helping to control, inhibit, or kill plaque
8 bacteria. The question I want to ask is do they want all of
9 those words in one sentence or, as is stated in their letter
10 of August 21st, control or inhibit or kill? In other words,
11 are inhibit or kill optional words that could be substituted
12 for control? Or do they want all of those words in the
13 sentence? It's worded slightly differently.

14 DR. GENCO: Mike, do you want to comment on that?

15 DR. BARNETT: Yes. Basically, I think what we had
16 requested was the indication as it was proposed at the last
17 meeting, meaning that these other words are alternative
18 words rather than that they would all be included in the
19 claim.

20 DR. GENCO: So the implication there is that the
21 statement could be used aids in the killing of plaque
22 bacteria that contribute to the development of gingivitis?

23 Stan, it's your motion. Why don't you read it and
24 let's make sure we're clear on it.

25 DR. SAXE: What I think the motion is that the

1 statement simply isn't kills plaque bacteria as the
2 mechanism, but it aids or helps in -- and the choice of
3 words -- in control, inhibition or killing -- any one of
4 those words could be used. But the important thing, it
5 helps or aids in the killing, that the statement not simply
6 be the bland statement kills plaque bacteria, that's the
7 absolute mechanism that we know.

8 DR. GENCO: Bill?

9 DR. BOWEN: [Indicating.]

10 DR. GENCO: Any further discussion on this motion?

11 [No response.]

12 DR. GENCO: Let's proceed with the vote. Let's
13 start with the right.

14 MR. CANCRO: Yes.

15 DR. BOWEN: Yes.

16 DR. WU: Yes.

17 DR. SAVITT: No.

18 DR. GENCO: Yes.

19 DR. SAXE: Yes.

20 DR. GENCO: Okay, let's take a 10-minute break.

21 We're about 15 minutes behind, so let's start here at five
22 minutes to 10:00. Thank you.

23 [Recess.]

24 DR. GENCO: Next we'll have a presentation on
25 antiplaque effect of stannous fluoride by Dr. Mark Leusch by

1 Procter and Gamble. Dr. Leusch?

2 DR. LEUSCH: Thank you, Dr. Genco, members of the
3 committee, for the opportunity to speak with you here today.

4 For the record, I am Dr. Mark Leusch, a senior
5 scientist in the oral care product development with the
6 Procter and Gamble Company. I'm here to discuss the
7 antiplaque activity of stannous fluoride in relation to its
8 contributions towards its antigingivitis benefit, and the
9 implications of this antiplaque activity to product
10 labeling.

11 I'd like to begin today by reviewing the current
12 status of the stannous fluoride ingredient. If you will
13 recall, we have provided the panel with long-term clinical
14 data supporting antigingivitis activity. This
15 antigingivitis benefit is realized in the absence of
16 clinically measurable plaque mass reductions, which is one
17 possible mechanism providing the clinical GI benefit.

18 We've also provided plaque glycolysis and regrowth
19 data which demonstrates the ability of stannous fluoride to
20 effect both plaque metabolism and plaque regrowth. These
21 plaque effects are maintained after long-term exposure to
22 stannous fluoride.

23 As a result, the panel has agreed that this
24 antiplaque activity is, in large part, the mechanism by
25 which stannous fluoride manifests its antigingivitis

1 benefit. Further, the panel has accepted the mechanism
2 based plaque glycolysis and regrowth method as an
3 appropriate profile test for generic equivalent stannous
4 fluoride formulations.

5 Finally, based on our clinical data, the panel has
6 recommended stannous fluoride as Category I for gingivitis.

7 Our objective today is twofold. First, we will
8 provide the panel with additional data supporting possible
9 antiplaque label claims which we believe more accurately
10 represent stannous fluoride's antigingivitis efficacy for
11 both consumers and professionals.

12 Second, based on this data, we are requesting that
13 the committee ensure that the panel report does not exclude
14 the possibility of standard plaque claims similar to those
15 allowed for CPC and essential oils should long-term plaque
16 and gingivitis data become available. To this latter
17 objective, we're not asking the panel to revisit methodology
18 needed to demonstrate these effects, but rather to leave
19 open and acknowledge the possibility that such claims could
20 be attainable through the monograph process.

21 There are four key points which provide the basis
22 of support for restrictive plaque label claims for stannous
23 fluoride. First, the panel has concluded that the clinical
24 evidence is sufficient for stannous fluoride to be
25 recommended as Category I for gingivitis.

1 Second, plaque glycolysis and regrowth data
2 clearly demonstrates inhibition of both plaque glycolysis
3 and plaque regrowth by stannous fluoride supporting an
4 antiplaque mechanism for gingivitis efficacy. This
5 inhibition of plaque metabolism and plaque regrowth is
6 maintained following long-term use of stannous fluoride.

7 Third, the panel has accepted the plaque
8 glycolysis and regrowth assay as an appropriate profile test
9 for generic equivalent stannous fluoride formulations.

10 Finally, the results of several short-term
11 clinical trials, which we will share with you today, support
12 the ability of stannous fluoride to reduce plaque mass. We
13 would like the panel to consider this evidence as supportive
14 of both restricted plaque claims and acknowledge the
15 possibility that longer term plaque mass effects are
16 possible should improvements in the formulation be made to
17 demonstrate a long-term plaque benefit.

18 We've conducted several short-term plaque regrowth
19 studies which used either conventional plaque rating
20 techniques or plaque imaging methods. The studies range
21 from 24 hours to two weeks in length.

22 In the first study plaque regrowth was assessed
23 using the Turesky modification of the Quigley-Hine plaque
24 index following three times exposure to either stannous
25 fluoride or sodium fluoride slurry rinses over a 30-hour

1 period. Virtually no plaque regrowth, that is no increase
2 in plaque mass, was observed in the stannous fluoride
3 treated group when compared to the regrowth observed in the
4 sodium fluoride treated group. Thus, we conclude that
5 stannous fluoride does, in fact, inhibit short-term plaque
6 regrowth.

7 Similar plaque mass effects have been demonstrated
8 using plaque imaging. Digital plaque image analysis has
9 greater objectivity over conventional grading techniques,
10 and has been found to correlate with conventional grading
11 methods such as the Turesky Plaque Index.

12 In this study, plaque regrowth on the facial tooth
13 surfaces was assessed following three exposure to either a
14 stannous fluoride or sodium fluoride dentifrice slurry rinse
15 within a 24-hour period. A 37 percent reduction in plaque
16 regrowth relative to baseline was observed for the stannous
17 fluoride treatment. In contrast, the sodium fluoride
18 treatment did not inhibit plaque regrowth during this
19 period.

20 This result is consistent with those obtained in
21 the stannous fluoride study--in the previous stannous
22 fluoride study which used conventional grading techniques.

23 We have also conducted a four-day non-brushing
24 study to assess plaque regrowth effects on both the Turesky
25 Plaque Index and the Sillness and Loe Plaque Index. The

1 results from this crossover design study are depicted in
2 this slide, and show final plaque scores for both the
3 Turesky and Sillness and Loe Plaque Index, as well as the
4 percent reduction by stannous fluoride relative to the
5 sodium fluoride control.

6 These results clearly show that stannous fluoride
7 treatment significantly inhibits plaque regrowth, 18 percent
8 by the Turesky method and 23 percent via the Sillness and
9 Loe method, when compared to a sodium fluoride control.

10 A second digital plaque imaging study was
11 conducted using a repeated measures design intended to
12 control for variability in subject hygiene and dietary
13 habits. Over a two-week period, subjects exposed plaque on
14 their facial tooth surfaces to dentifrice slurries twice
15 daily as part of their brushing routine. During this
16 period, six independent images of 12-hour facial tooth
17 plaque were taken.

18 Stannous fluoride dentifrice treatment
19 significantly reduced plaque regrowth by 16 percent when
20 compared to the sodium fluoride control. This inhibition of
21 plaque regrowth was comparable to the 12 percent reduction by
22 a triclosan containing dentifrice. I would like to just
23 point out that both of these values are P less than 0.05.
24 It was an omission in the slide.

25 These short-term clinical studies confirm that the

1 inhibition of plaque regrowth by stannous fluoride is
2 manifested in demonstrable reductions in plaque mass as
3 measured by several different plaque grading techniques. We
4 believe this antiplaque activity is relevant to both
5 consumers and professionals, and warrants accurate
6 description as part of the stannous fluoride products
7 labeling.

8 However, truthfulness and accuracy in labeling
9 requires that we address the paradox that despite obvious
10 short-term plaque regrowth effects, why are significant
11 plaque mass reductions not observed following long-term use
12 of stannous fluoride? Published research suggests that
13 inability to measure long-term plaque mass reductions is an
14 artifact caused by increased deposition of a non-pathogenic,
15 pellicle-like mass onto the tooth surface as a result of
16 stannous fluoride use.

17 Tinanoff and coworkers have reported that stannous
18 fluoride treatment causes deposition of a substantially
19 thickened pellicle mass on enamel chips in vivo when
20 compared to chips treated with sodium chloride. These
21 results are supported by the in vivo results of Zameck, et
22 al., in which twice as much pellicle material was recovered
23 from stannous fluoride treated versus untreated buckled
24 tooth surfaces.

25 We have also demonstrated increased salivary

1 protein pellicle deposition in association with Crest Gum
2 Care treatment in vivo--in vitro, excuse me. This slide
3 summarizes a series of experiments in which salivary protein
4 pellicle formation on glass beads was evaluated over a
5 three-day period. Saliva was treated with azide to inhibit
6 bacterial growth.

7 On average, nearly twice as much pellicle protein
8 is deposited on the glass beads treated with stannous
9 fluoride when compared to sodium fluoride treated beads. We
10 believe that this thick, non-pathogenic protein mass formed
11 as the result of stannous fluoride use could allow for the
12 retention of chromagenic materials, such as disclosing dyes,
13 and thus confound conventional plaque scoring methods and
14 mask overall reduction of plaque mass in long-term clinical
15 studies.

16 Over shorter exposure periods, this pellicle
17 artifact is anticipated to be less prevalent, and likely
18 accounts for the ability to discern significant stannous
19 fluoride reductions in plaque mass by conventional plaque
20 grading techniques.

21 In summary, we have provided the panel with data
22 indicating that stannous fluoride is an effective inhibitor
23 of plaque metabolism and plaque regrowth. This antiplaque
24 activity translates into short-term clinical reductions in
25 plaque mass, which further strengthens the relationship

1 between antiplaque activity and antigingivitis benefits for
2 stannous fluoride.

3 Thus, we believe that the antiplaque activity of
4 stannous fluoride warrants accurate, albeit restricted,
5 description in stannous fluoride products labeling as a
6 benefit to both consumers and professionals.

7 We have also offered you a mechanism as to why
8 short-term regrowth effects are not manifested into long-
9 term clinical reductions of plaque mass. In consequence, we
10 believe that it may be possible to improve the cleaning
11 potential of stannous fluoride formulations to remove this
12 pellicle material, enabling measurement of clinical
13 reductions in plaque mass without compromising gingivitis
14 efficacy.

15 With the data we have presented today, we first
16 would like to recommend that the panel report reflect the
17 possibility that a manufacturer could formulate a stannous
18 fluoride dentifrice which might minimize the pellicle
19 artifacts and enable plaque mass reductions to be clinically
20 measured in long-term studies.

21 We also recommend that the following restricted
22 label statements pertaining to stannous fluoride's
23 antiplaque activity be considered for the current
24 recommended as Category I dentifrice formula. These
25 include:

1 Helps to prevent, control, or fight plaque
2 activity, plaque acids, plaque toxins associated with
3 gingivitis.

4 Second, helps to prevent the production of plaque
5 acids, including those associated with gingivitis.

6 Third, helps to protect from or against plaque
7 acids associated with gingivitis.

8 Fourth, helps to inhibit plaque activity
9 associated with gingivitis.

10 Or, finally, helps interfere with deleterious
11 effects of plaque associated with gingivitis.

12 In closing, we request that the panel consider the
13 following two questions during their deliberations today:

14 First, should the panel report leave open and
15 acknowledge the possibility of measurable plaque mass
16 effects for stannous fluoride in long-term clinical trials?

17 Second, based on the data we have reviewed with
18 you today, are the proposed restricted plaque claims
19 acceptable statements to describe the relationship between
20 antiplaque and antigingivitis benefits for stannous
21 fluoride?

22 This concludes my formal remarks, and we thank the
23 committee for their time and consideration. My colleagues
24 and I are available to address any questions that you may
25 have. Thank you.

1 DR. GENCO: Thank you, Dr. Leusch. Did you
2 present that last six-month study? Do we have--the six-
3 month study which shows three and six-month plaque
4 production with stannous fluoride? Is that a new study or--

5 DR. LEUSCH: That was in the--

6 DR. GENCO: You submitted that before?

7 DR. LEUSCH: No, we had not submitted that study
8 before. That was supplemental information that we were
9 going to provide, should the question arise if there was
10 precedent for such activity in a stannous fluoride
11 dentifrice. I apologize. It wasn't in the original
12 presentation.

13 DR. GENCO: I mean, you've made the argument that
14 increased pellicle would account for the lack of showing an
15 effect at six months--

16 DR. LEUSCH: That's correct.

17 DR. GENCO: --and yet this tabulation shows an
18 effect at six months.

19 DR. LEUSCH: That's correct. It was an example of
20 a stannous fluoride formulation which is--has apparently
21 been formulated such that it improves either cleaning or the
22 removal of the pellicle material, thus allowing one to see a
23 plaque effect in a six-month trial.

24 DR. GENCO: So this is a new formulation, not used
25 in the previous studies we have seen?

1 DR. LEUSCH: That's correct. It's not a Procter
2 and Gamble formula. It was from the published research.

3 DR. GENCO: Oh, I see.

4 DR. LEUSCH: I refer to that data in the written
5 submission.

6 DR. GENCO: Okay. Thank you.

7 Any comments or questions of Dr. Leusch? Bill?

8 DR. BOWEN: Could I ask a question of the staff?
9 Is there anything to preclude any company from submitting
10 data sometime in the future to show that there are
11 antiplaque claims? Is the monograph it? That's the end of
12 the--

13 MR. SHERMAN: No. One can always submit
14 additional data. There could be a petition. The monograph,
15 this monograph is also quite a ways off. We are still at a
16 very early stage in this review, and even at the final stage
17 of the monograph, one could always petition with additional
18 data.

19 DR. BOWEN: I have a couple of questions. As I
20 understand it, you've done four clinical studies covering 24
21 hours, 30 hours, 4 days and 2 weeks.

22 DR. LEUSCH: That's correct.

23 DR. BOWEN: At what stage were you dealing with
24 pellicle and at what stage were you dealing with plaque?

25 DR. LEUSCH: We believe that there's a

1 relationship which exists between the formation of tooth
2 staining as a result of stannous fluoride use, which begins
3 to occur at roughly two to three months in a clinical trial,
4 and that's approximately the same time we begin to see the
5 ability to measure plaque via conventional grading
6 techniques fall off. So approximately two to three months.

7 DR. BOWEN: Would you agree that it's possible
8 that the mechanism of action of stannous fluoride is the one
9 you've offered now on pellicle, that in fact you're getting
10 a deposition of, for the want of a better term, pellicular
11 proteins on the surface of the gingiva which is protecting
12 the gingiva from whatever toxins are in plaque, without ever
13 getting any reduction in plaque? There is in fact a quasi-
14 astringent effect.

15 DR. LEUSCH: We are not--we don't completely
16 understand the mechanism of stannous fluoride on plaque. We
17 do know that stannous fluoride activity does affect plaque
18 via the effects on plaque glycolysis and plaque regrowth,
19 and this, we believe this plaque mechanism is what's
20 responsible for the GI benefit.

21 There's reasonable scientific evidence to explain
22 the fact that the development of this pellicle is non-
23 pathogenic in nature, because if the pellicle were
24 pathogenic in nature, then we wouldn't necessarily see a
25 gingivitis benefit from stannous fluoride.

1 DR. GENCO: To follow up on that, this last page
2 is--I think could be--we'd have to really go into that
3 study. Let's assume that what you showed us before is the
4 reality, that with your dentifrice there's no reduction or
5 no statistically significant reduction in plaque at six
6 months, but there is a reduction in gingivitis.

7 DR. LEUSCH: That's correct.

8 DR. GENCO: And you're proposing the pellicle as
9 the reason. In our inadequate measure of what we call
10 plaque, it includes pellicle. So have you looked at the
11 six-month plaque with your dentifrice to see if indeed the
12 counts of bugs to mass, total mass, are different? In other
13 words, if there was more pellicle, you'd have fewer bugs per
14 milligram. Is that the case?

15 DR. LEUSCH: I think, as perhaps Dr. Fine pointed
16 out earlier this morning, that to try to quantitate bacteria
17 and measure plaque mass is a difficult thing to do because
18 of the fragility of the plaque. We have measured bacterial
19 counts but we've never tried to correlate those counts with
20 respect to a plaque mass for fear of losing the sample.

21 DR. GENCO: But indeed if you had--if there was a
22 major contribution of a protein, you could use maybe DNA or
23 you could use bacterial counts, Gram stain or what have you
24 of, you know, a dispersed plaque; weigh it first, and then
25 look at numbers of bodies of bacteria. I don't think it's

1 impossible to do that. So--but the fact is, you don't have
2 that information to support your contention that it is a
3 thickening due to pellicle which then is inappropriately
4 measured as plaque.

5 DR. LEUSCH: We don't have any direct data, but
6 there's been a fair amount of work done by Dr. Tinanoff
7 where they've looked at bacterial counts in association with
8 pellicle material. They've seen, with stannous fluoride
9 treatment, they've seen reductions in bacterial numbers as
10 the development of this pellicle-like material gets on the
11 tooth.

12 DR. GENCO: We have the dilemma, the challenge, of
13 responding to your request for an antiplaque claim without
14 an antiplaque--with evidence, without evidence of it. And I
15 think that I'd like to present to the panel as our issue, as
16 our challenge. Yes?

17 DR. BOWEN: I'd like to clarify. I supported your
18 claim the last time, and I still do, that using the plaque
19 glycolysis assay as a profile test is acceptable. That was
20 simply to show that the stannous ion was in fact active in
21 the mouth. When I voted in support of that, it was not in
22 any way to be interpreted that that was a mechanism, a
23 proposed mechanism of action; simply a valid profile test of
24 the activity of the stannous ion.

25 DR. LEUSCH: Okay. We've used the plaque

1 glycolysis and regrowth method as a tool to identify
2 clinically effective formulations, and have shown that in
3 long-term clinical trials. We believe that stannous
4 fluoride activity, antimicrobial activity, does have a
5 benefit, a plaque effect, as measured by both the glycolysis
6 portion of PGRM and the regrowth portion, and that these
7 combined effects do in fact provide the gingivitis benefit
8 based on the mechanism of action of the stannous fluoride.

9 DR. GENCO: So you're not asking for an antiplaque
10 claim. You're asking for a restricted antiplaque claim as
11 listed on your recommendations sheet.

12 DR. LEUSCH: That's correct.

13 DR. GENCO: I wonder if I could ask the panel to
14 look at those recommendations and, if appropriate, make a
15 motion, or let's discuss those recommendations. In other
16 words, these are not straight out plaque claims. They are
17 restricted, quote/unquote, antiplaque claims.

18 DR. BOWEN: While I might agree that the plaque
19 acids, the organic acids in plaque might have something to
20 do with gingivitis, I am not aware of any evidence that
21 supports that. Also, I don't know that there's any evidence
22 that stannous fluoride inhibits the production of,
23 quote/unquote, toxins in plaque. So if you can enlighten me
24 on those two topics?

25 DR. LEUSCH: Perhaps my colleague, Dr. Don White,

1 could address that question.

2 DR. WHITE: Don White, P&G. Could you repeat the
3 question, Bill, again?

4 DR. BOWEN: Yes. I think I might agree with you
5 that the organic acids in plaque might have something to do
6 with gingivitis, but I don't know of any direct evidence
7 that they do. And, furthermore, I don't know of any
8 evidence that stannous fluoride reduces the toxins in plaque
9 per se.

10 DR. WHITE: Yes. Well, you'd have to know exactly
11 what the toxins would be, and of course there's a lot of
12 properties of the plaque that can contribute to its
13 pathogenicity.

14 I think the point is, is that we don't know two
15 things. We don't know the mechanism of action completely of
16 stannous fluoride, and we don't completely know what the
17 cause of the long-term plaque evaluations are, this so-
18 called artifact with the pellicle, but we do have a pretty
19 good idea from precedent that that might be a factor.

20 And what we--so what we know is that stannous
21 fluoride is a fairly potent antimicrobial, and that in
22 short-term assays you can see a plaque mass effect, and in
23 short and long-term clinical studies you can see a metabolic
24 effect, and that's well established. Secondly, it's the
25 only mechanism which we know of, which there's direct

1 support related to its clinical action in preventing
2 gingivitis.

3 And so it seems reasonable to us that labeling
4 should be able to reflect some aspect of its metabolic
5 activity. Now we can argue about the specific words. If
6 "plaque acids" is a term that's too specific because there
7 isn't enough data to support specific use of acids, then one
8 could revert to talking about plaque activity which is
9 associated with gingivitis, or possibly plaque toxins if
10 you're willing to leave open that possibility.

11 So you may want to craft some of your own language
12 into what we have there, into what would be acceptable. But
13 one important point I would like to make, though.

14 It seems to us--we just had a discussion a while
15 back about, you know, how much does killing or metabolic
16 effects or whatever have to do with antiplaque activity
17 related to gingivitis--it seems to us that effects on plaque
18 metabolism that end up providing statistically significant
19 long-term reductions in gingivitis are just as relevant to
20 consumers and professionals as 10 or 15 percent reductions
21 in plaque mass.

22 We don't understand mechanistically why plaque
23 mass measurements in a six-month trial would be preferred to
24 some other measurement of antiplaque activity, although we
25 do completely agree that it should be accurately--the

1 activity should be accurately described in labeling. So if
2 words are necessary to differentiate it from the more
3 generic plaque claim, then so be it, which is why we asked
4 for the restricted plaque labeling.

5 DR. GENCO: It may be our problem is that the data
6 suggest there's a temporal sequence between increase in
7 plaque mass and gingivitis, and decrease in plaque mass and
8 reduction of gingivitis. But we don't have data comparing
9 increase in metabolism of plaque, factor X or Y, with
10 gingivitis, and decrease in that factor with gingivitis. So
11 that's the problem.

12 DR. WHITE: A specific factor.

13 DR. GENCO: Right.

14 DR. WHITE: All you have is a generic--

15 DR. GENCO: I think this is what Dr.--

16 DR. WHITE: --a generic activity.

17 DR. GENCO: This is, I think, what Dr. Bowen is
18 referring to.

19 DR. WHITE: The point, yes.

20 DR. GENCO: What is it? What is that metabolic
21 activity? It's reasonable, but what is it?

22 DR. WHITE: Yes, and it's not certain exactly what
23 it is, or what combination, probably, of things it is.

24 DR. GENCO: Right.

25 Further comments? Questions?

1 [No response.]

2 DR. GENCO: Okay. Well, thank you very much, Dr.
3 Leusch.

4 DR. LEUSCH: Thank you.

5 DR. GENCO: Panel, what is your interest now in
6 responding to these recommendations? Anybody want to make a
7 motion, or what is your view? Concern that the gingivitis
8 claim would be--what could be allowed or recommended to the
9 FDA for this product, and any other claims?

10 DR. BOWEN: Do we have to consider all of these en
11 masse, or individual ones?

12 DR. GENCO: I think that if there is--

13 MR. SHERMAN: You can consider any, all, or any
14 other reasonable ones that you can come up with.

15 DR. BOWEN: Well, I personally have problems with
16 the top four. I certainly could entertain consideration of
17 the lower one, "Helps interfere with deleterious effects of
18 plaque associated with gingivitis."

19 DR. GENCO: Do you feel strongly enough about that
20 to put it in a motion?

21 DR. BOWEN: No, but I think it's--I'll put on the
22 table for a discussion.

23 DR. GENCO: Okay. Let's discuss it.

24 MR. CANCRO: I'd like to ask Bill a question.

25 DR. GENCO: Yes. Go ahead.

1 MR. CANCRO: Bill, could "deleterious" have a
2 substitute word such as "harmful"? Would that be
3 appropriate?

4 DR. BOWEN: Yes, I could buy that.

5 DR. GENCO: Anybody else have an opinion on that?
6 Comfortable with allowing that recommendation? Are you
7 concerned about you not knowing what those harmful effects
8 are? Bill?

9 DR. BOWEN: As a scientist, obviously I'm very
10 concerned, so I'm here in a double position. I think it's
11 clear it is overcoming the harmful effects of plaque,
12 because otherwise it's difficult to imagine how this action
13 --how this product could reduce the gingivitis. And I
14 reviewed the data, and as I recall, the studies showed
15 clearly that it reduced gingivitis, but in five of the six
16 studies, as I remember, there was no plaque production. So
17 it's reasonable to assume that it is interfering with the
18 harmful effects--is that what you said, Lou?

19 MR. CANCRO: Yes.

20 DR. BOWEN: Of plaque. I don't think anyone has
21 seriously suggested it as having a systemic effect in
22 reducing inflammation per se. At least I haven't heard it
23 suggested, and I don't think the track record of stannous
24 fluoride is consistent with that interpretation.

25 DR. GENCO: I'll ask the panel another question:

1 Is this consistent with our previous recommendation of not
2 allowing a plaque claim per se?

3 DR. BOWEN: We do have gingivitis in this claim.
4 That's why I feel comfortable with it. If it was plaque
5 alone, I certainly wouldn't agree with you, no.

6 DR. GENCO: Feel strongly enough to make a motion?

7 DR. BOWEN: Well, again, to get the dime moving,
8 I'll propose we accept Claim No. 5, is it?

9 DR. GENCO: With the substitute, "harmful" for
10 "deleterious."

11 DR. BOWEN: Yes.

12 DR. GENCO: So the motion is: "Helps interfere
13 with harmful effects of plaque associated with gingivitis."
14 Is there a second? Gene?

15 DR. SAVITT: Second.

16 DR. GENCO: Thank you. Okay, any discussion of
17 that? Yes?

18 DR. SAXE: Yes. I mean--

19 DR. GENCO: I'm looking for some discussion here.

20 DR. SAXE: --the same thing as Bill's, just echo
21 what he said. It's sort of an inference that since the
22 gingivitis effect was shown, that the stannous fluoride as
23 an active agent must have had in some fashion an effect on
24 plaque's ability to be the etiologic agent.

25 But, you know, again I wonder, if indeed the

1 pellicle is taking up the disclosing solution as was
2 suggested, and therefore confounding the clinical plaque
3 assessment, if, difficult as it is, some measure could be
4 made of the number of organisms present at the time, at six
5 months when the plaque is assessed.

6 So I don't know what I'm saying. It's a difficult
7 question, and I guess by inference, since the lack of
8 absolute evidence, the inference is that indeed there is
9 some interference with plaque's ability to initiate the
10 gingivitis.

11 DR. GENCO: Gene?

12 DR. SAVITT: I just want to follow up on what Stan
13 just said. The presentation we just had would suggest that
14 indeed there may be a plaque reduction and that's what is
15 causing the--which is not measurable for whatever reason--
16 which is what's causing the reduction in gingivitis, and yet
17 the way this claim is worded, it's not suggesting a
18 reduction in plaque, which may be what's going on but we
19 just don't know.

20 I mean, it's--were in a situation where we're
21 presented with a lot of maybes and could be's and perhaps's,
22 and offered this statement which is rather broad and based
23 upon a lot of "Well, it seems like" and could be's. And I'm
24 somewhat uncomfortable with it, yet at the same time I see a
25 certain level of value with it.

1 DR. GENCO: Christine?

2 DR. WU: I'd like to ask Bill, what is your
3 objection about No. 4?

4 DR. BOWEN: My objection to No. 4 is that it
5 implies a direct effect on the plaque activity, and we don't
6 have any evidence that it affects plaque activity per se.
7 So there is quite a distinction between 4 and 5. No. 5
8 could be simply that there's a layer of pellicle laid down
9 on the gingiva that protects the gingiva from the
10 deleterious effects of plaque. The statement before that
11 implies it is having an effect on the plaque per se, and
12 that's why I have a problem with that.

13 DR. GENCO: So in supporting this statement, Bill,
14 you feel that there isn't any evidence for any other
15 potential effect, so that it could only be reducing the
16 harmful effects of plaque, however it does that?

17 DR. BOWEN: However it does that.

18 DR. GENCO: Reducing bacterial mass, increasing
19 innocuous pellicle, reducing some activity, metabolic, what
20 have you. And it's not some anti-inflammatory or other non-
21 antibacterial effect.

22 DR. BOWEN: The two pieces of evidence that we
23 have are that it affects glycolysis in plaque, and as far as
24 I know, and you know better than I do, that there is no
25 evidence that plaque glycolysis is associated with

1 periodontal disease. It might be, but I don't know of any
2 evidence that it is.

3 And the other is the plaque regrowth, and most of
4 those are such a short term that I'm not sure of the
5 relevance they are to periodontal disease or gingivitis. I
6 do accept that stannous fluoride has an effect on
7 gingivitis. I do believe it's mediated through plaque. So
8 it's not an unreasonable assumption to say that it does,
9 that stannous fluoride does interfere with the deleterious
10 or harmful effects of plaque, without necessarily having any
11 effect on plaque per se.

12 DR. GENCO: Okay. I see. Are we ready to vote?
13 Any further discussion? This time let's start on the left,
14 left of center.

15 DR. SAXE: May I hear the motion repeated, please?

16 DR. GENCO: Yes, The motion is, "Helps interfere
17 with harmful effects of plaque"--

18 MR. SHERMAN: Excuse me. Just a point of
19 clarification. Dr. Bowen's review stated that stannous
20 fluoride is approve for gingivitis only, so that we're still
21 saying that that is the case--

22 DR. GENCO: Yes.

23 MR. SHERMAN: --we're still saying we can't use
24 the "Helps," aids, "Helps control, reduce or prevent plaque
25 that leads to gingivitis" claim. We're simply stating that

1 this additional claim can be used. Okay? Is that correct?

2 DR. BOWEN: Just that one, and only that one.

3 DR. GENCO: There's no antiplaque claim.

4 DR. BOWEN: No antiplaque claim.

5 DR. GENCO: It is, as the company put it, a
6 modified antiplaque claim, restricted.

7 MR. SHERMAN: Well, right. This, one could
8 consider this an antiplaque claim. But just to clarify,
9 it's gingivitis only, with this particular claim allowed for
10 that ingredient.

11 DR. GENCO: Okay, so as I understand it, the
12 motion is, "Helps interfere with harmful effects of plaque
13 associated with gingivitis."

14 DR. HYMAN: Yes.

15 DR. SAXE: Yes.

16 DR. SAVITT: Yes.

17 DR. WU: Yes.

18 DR. BOWEN: Yes.

19 DR. GENCO: Okay. Thank you very much.

20 Now we have another discrete topic for after
21 lunch, professional labeling, and then a review of
22 recommendations. We're a little early, but I think this
23 would be a good time to break for lunch, and then we'll come
24 back at 1 o'clock. 1 o'clock, after lunch. Thank you very
25 much.

1 [Whereupon, at 11:42 a.m., the subcommittee
2 recessed, to reconvene at 1:00 p.m., the same day.]

1 AFTERNOON SESSION

2 [1:07 p.m.]

3 DR. GENCO: Welcome back. We'll now discuss the
4 Warner-Lambert professional labeling request, and Michael
5 Barnett will make the presentation. Michael?

6 DR. BARNETT: Thanks, Bob. I often wish that the
7 cloning experiment would work, so I don't have to give all
8 of these but my clone could have given some.

9 One of the things that we learned, especially
10 coming from an academic background, is some of the arcane
11 rules of food and drug regulation, and one of the things
12 that we have been told is that labeling in the context of
13 today's discussion isn't necessarily the same labeling that
14 we're used to be talking about on packaging. And so once
15 again I'd like to call on Peter Hud just to give a very
16 short explication of the definition and differences between
17 this and a label, per se. Peter?

18 MR. HUD: Thank you. There is a difference
19 between "the label" and "the labeling" under food and drug
20 law. And mindful of the fact that a picture is worth a
21 thousand words, I'd like to illustrate it in the following
22 way.

23 I have in my hand the Listerine package with the
24 label, and what is on the front and back is, under the law,
25 known as "the label" and it is defined as the material that

1 is on the immediate container of the product.

2 Now you're all used to seeing in your professional
3 life, labeling, which are pamphlets like this, package
4 inserts, reprints of any kind of document that is frequently
5 distributed to the profession or, indeed, the consumers. It
6 can be both consumer labeling and professional labeling.

7 FDA recognized, going way back to the 1940's, that
8 there were some things for OTC drugs like Listerine that
9 should be said only to the professional body of audience and
10 not to consumers. The first and still one of the best
11 examples of that was antacid products. FDA recognized that
12 antacids might well be, even though they were over-the-
13 counter, recommended by the medical profession for ulcer and
14 related ailments.

15 At the same time--that was before the more modern
16 ulcer remedies became available as prescription items--but
17 at the same time FDA recognized that no consumer could self-
18 diagnose or self-treat ulcers; that consumers were not
19 capable of, obviously, of differential diagnosis. And so
20 FDA came up with the rule that you could put an ulcer claim
21 in professional labeling, pamphlets and other things going
22 to physicians, but could never use the word "ulcer" in
23 consumer labels or labeling.

24 This was carried through in the over-the-counter
25 drug review. I conducted a little survey of the Code of

1 Federal Regulations last night. Almost half of the final
2 monographs that currently exist have provisions for
3 professional labeling, and each one explicitly states that
4 the information can be provided only to the health
5 professions and not to consumers.

6 There are basically two types of that labeling.
7 One type of professional labeling tells a doctor how to use
8 the product in professional practice. The other type tells
9 the doctor new indications, like the ulcer indication for an
10 antacid, that are appropriate but that can't be told to
11 consumers.

12 There is also a third category, and some of you
13 may recall from the anticaries monograph, where FDA has
14 authorized different package sizes for professional packages
15 of a drug that can't go to consumers. You'll remember that
16 in the anticaries monograph FDA was concerned about the
17 toxicity of fluoride products and limited consumer package
18 sizes. There's an explicit exception for professional
19 package sizes.

20 But I want to emphasize that's not what we're
21 talking about today, so we can take the package size off the
22 table for today. What Michael is going to be talking about
23 is professional labeling in the true sense, that is,
24 information that is given to the dentist but that is not
25 going to be on the package label or in any consumer

1 labeling.

2 MR. HUD: Thank you, Peter.

3 For the record, again, my name is Michael Barnett,
4 and I am the Director of Dental Affairs in the Consumer
5 Health Care Research and Development Division of the Warner-
6 Lambert Company. We appreciate the opportunity to address
7 you this afternoon on the subject of professional labeling
8 for Listerine antiseptic.

9 In its original submission to this subcommittee
10 dated June 17th, 1991, Warner-Lambert requested approval of
11 the professional labeling indication "for the reduction of
12 viable aerosolized bacteria during dental procedures," and
13 included in that submission clinical study data in support
14 of this indication.

15 The purpose of today's presentation is to
16 reiterate our request for approval of this indication and to
17 provide a brief overview of the body of clinical studies
18 which demonstrate the effectiveness of pre-procedural
19 rinsing with Listerine antiseptic mouth rinse in reducing
20 the level of recoverable viable bacteria in dental aerosols.

21 Some of the data I'm going to be reviewing today
22 were not available at the time of the original submission.
23 All of the clinical studies have been published in peer
24 review journals, and a copy of each publication and its
25 respective Warner-Lambert research report have been

1 previously forwarded to this committee in August of this
2 year in a submission.

3 The studies utilize two different protocol
4 designs. In the first, qualifying adult subject who
5 refrained from all oral hygiene procedures for a 24-hour
6 period received a 10-minute baseline ultrasonic scaling of
7 one-half of the mouth, during which time the aerosol was
8 sampled under standardized conditions. Subjects were then
9 randomly assigned either a Listerine antiseptic or a
10 negative control mouth rinse, and rinsed under supervision
11 with 20 milliliters for 30 seconds, following which the
12 following half mouth was scaled ultrasonically and the
13 aerosol was sampled.

14 Following a seven-day washout period, these
15 procedures were repeated with the alternate rinse. For each
16 aerosol sample, bacterial counts were determined, colony
17 counts were transformed, and treatment differences were
18 assessed using analysis of variants.

19 It should be noted that prior to initiating the
20 study, the appropriateness of the sampling method was
21 demonstrated by experiments which showed that neither the
22 act of sampling per se nor the presence of residual rinse in
23 the aerosol significantly affected the viability of bacteria
24 collected. The results were replicated in duplicate studies
25 using this model.

1 In the two studies, pre-procedural rinsing with
2 Listerine mouth rinses produced respective reductions in
3 viable bacteria in the sampled aerosols of 94.1 percent and
4 92.1 percent, compared to baseline levels. These reductions
5 were statistically significantly greater than those produced
6 by rinsing with the negative control.

7 The second pair of studies was designed to test
8 the effectiveness of pre-procedural rinsing using a protocol
9 design which simulated conditions of an actual dental visit.
10 In these studies, 18 subjects who had refrained from all
11 oral hygiene procedures for 24 hours received a 5-minute
12 baseline ultrasonic scaling of a randomly assigned maxillary
13 quadrant, during which aerosol sampling was conducted as in
14 the first set of studies.

15 After completion of the ultrasonic scaling,
16 subjects rinsed for 30 seconds with 20 milliliters of either
17 Listerine or a negative control rinse, randomly assigned.
18 They then received a periodontal probing of all teeth except
19 for those in the maxillary quadrant not ultrasonically
20 scaled at baseline, followed by a hand scaling of all
21 mandibular teeth. These procedures were performed over a
22 40-minute period immediately following rinsing. The
23 remaining maxillary quadrant was then ultrasonically scaled
24 for 5 minutes and the aerosol collected. These procedures
25 were repeated with the alternate rinse one week later. The

1 aerosolized bacteria collected were cultured and enumerated.

2 Duplicate studies using this design produced
3 consistent results with respective 93.6 percent and 91.3
4 percent reductions in viable bacteria from baseline 40
5 minutes after rinsing. These reductions were statistically
6 significantly greater than those produced by the negative
7 control rinse.

8 Use of an effective antiseptic mouth rinse prior
9 to aerosol-generating dental procedures has become a
10 recognized component of an overall in-office infection
11 control regimen. The clinical data presented today clearly
12 demonstrate the effectiveness of pre-procedural rinsing with
13 Listerine antiseptic in significantly reducing the level of
14 viable bacteria in dental aerosols under conditions
15 simulating actual clinical practice.

16 We therefore believe that these data fully support
17 the indication for the reduction of viable aerosolized
18 bacteria during dental procedures, and request that this
19 indication be approved for professional labeling.

20 I or one of my colleagues again would be pleased
21 to answer your questions.

22 DR. GENCO: Thank you, Michael.

23 Comments? Questions? Stan?

24 DR. SAXE: I have a question. I see where the 18
25 and 18 subjects were used and then it was repeated again

1 with kind of similar results. And I ask this question very
2 respectfully and not in a flip manner. But, granted the--as
3 was measured by Dr. Fine--the number of organisms in the
4 aerosol is reduced, but my question is well, that's nice,
5 but so what?

6 What does this have an effect on patient care?
7 Are patients adversely affected if there is a lot of
8 bacteria in the aerosol? Is there evidence of that, that
9 when you decrease the number of bacteria by the rinse, that
10 while the number of viable bacteria as counted are reduced,
11 does this have an effect on the welfare of the patient or of
12 the office staff?

13 DR. BARNETT: No, I don't consider that a flippant
14 question at all, Stanley. I think it's a very key question.
15 And the answer is that one doesn't know, and let me
16 backtrack by saying that we have had these data and claims
17 reviewed, for example, by the American Dental Association,
18 and what we have put in all our advertising, professional
19 labeling, if you will, is a disclaimer that the effect on
20 disease transmission has not been determined.

21 So the question is, what's the significance of
22 this? Well, I think these studies came about as a result of
23 the efforts that really started say in the early to mid '80s
24 when there was such an increased emphasis on infection
25 control procedures in the dental office. And one of the

1 questions was, what can you do to decrease the bugs, the
2 risks, whatever? And these studies were done to show that
3 in fact you can significantly decrease the numbers of viable
4 bacteria flying around in the course of doing aerosol-
5 generating procedures.

6 In itself, is it going to make a big difference in
7 terms of disease transmission? Possibly not, although one
8 couldn't do those studies. I mean, they would be forever
9 studies with large numbers. But I think the key is that in
10 the context of an overall infection control regimen in an
11 office, I think the general consensus would be that it's
12 better for everybody to have fewer live bugs flying around
13 than more live bugs.

14 And I think it's in that context of making some
15 contribution to the overall regimens that this claim is
16 being put forward. And I might add, just parenthetically,
17 that the use of pre-procedural rinses for this purpose has
18 in fact been advocated by infection control people.

19 For example, there was a paper in the 1991 volume
20 of the Journal of the American Dental Association by Tony
21 Molinari in which the use of pre-procedural rinsing was a
22 recommendation. There was also a recommendation in the
23 American Association of Dental Schools guidelines for clinic
24 infection control procedures in dental schools. So it is a
25 procedure that's recognized as making some contribution,

1 some beneficial contribution, to infection control in
2 today's environment.

3 DR. GENCO: Further comments? Questions? Gene?

4 DR. SAVITT: Mike, is there--has anyone done
5 something simple like seeing whether or not there is a
6 reduction in bacteria on various surfaces radiating from the
7 mouth with or without a rinse before sonication, some sort
8 of a wipe test?

9 DR. BARNETT: Gene, you know, without being
10 flippant, I can't answer if anybody has done it. I know we
11 haven't done it.

12 DR. GENCO: Bill?

13 DR. BOWEN: I have two questions, Mike. Is any
14 information available on the specific organisms that are
15 reduced, or is it just a broad reduction in the populations?
16 And the second thing, by my calculations, if you take a 10-
17 minute sampling you're looking at 5.5 cubic feet of air, and
18 to start with you have fewer than a thousand bacteria in
19 that 5.5 cubic feet of air, and as a result of the
20 procedures it's reduced to probably 500 or 600 or less. Is
21 it worth the effort?

22 DR. BARNETT: Let me ask Dr. Fine to address those
23 questions, if he will.

24 DR. FINE: Well, firstly, this was a very brief
25 collection period, so that the period of collection was only

1 limited, a snapshot in time, and in a very limited area.
2 And so I think from that point of view your point is valid,
3 but you know, this is only--this does not reflect the total
4 number of organisms that could be emitted at this--certainly
5 in the control group.

6 DR. GENCO: Do you want to comment to the
7 specificity?

8 DR. FINE: There was no effort to specifically
9 identify the organisms in these studies.

10 DR. GENCO: Thank you. Further comments?
11 Questions?

12 [No response.]

13 DR. GENCO: Is there anybody who would like to
14 make a motion?

15 The argument is that this would be part of
16 infection control procedure in an office, and with no claim
17 for any benefit being shown. And as Dr. Barnett said, the
18 actual request then would be for the claim with a
19 disclaimer. Am I correct?

20 Let me just--what you are proposing, then, is a
21 claim that would read "For reduction of viable aerosol
22 bacteria for dental procedures. The effect of this
23 reduction on transmission of organisms is not determined."

24 DR. BARNETT: Yes, that's just about it. "For the
25 reduction of viable aerosolized bacteria during dental

1 procedures."

2 DR. GENCO: During dental procedures?

3 DR. BARNETT: Yes, yes, and that disclaimer,
4 "effect on disease transmission not determined."

5 DR. GENCO: Anybody want to--predisposed to make
6 that recommendation to the FDA?

7 [No response.]

8 DR. GENCO: Well, I can't make it myself. This
9 has to be a consensus recommendation from the panel.

10 DR. SAVITT: Perhaps I can make a motion and then
11 we can vote appropriately.

12 DR. GENCO: Fine.

13 DR. SAVITT: So that the motion would be to
14 include as professional labeling that Listerine is indicated
15 "for the reduction of viable aerosol bacteria during dental
16 procedures."

17 DR. GENCO: With the disclaimer? Do you want to
18 add that, too? "The effect on oral transmission has not
19 been determined."

20 DR. SAVITT: Very good. "The effect of oral
21 transmission has not been"--

22 DR. GENCO: Excuse me. "The effect on disease
23 transmission has not been determined." Sorry.

24 Second? Bill?

25 DR. BOWEN: I don't want to second it. I just

1 want to ask staff a question, or maybe somebody else.

2 In terms of labeling, what's the position of the
3 FDA, either now or historically, concerning labeling that
4 does not involve any proven or unproven clinical benefit?

5 DR. KATZ: Historically, the agency does not like
6 to have labeling without--where it doesn't really--you can
7 say a thing is without clinical benefit. However, one needs
8 to be careful how it is phrased and what section of the
9 label it would go in.

10 And probably the easiest way to look at it is from
11 a prescription label. In a prescription label there will be
12 some trials that are described, and sometimes you'll see the
13 little caveat, "The clinical relevance of this is unknown."

14 However, one must remember that whenever one puts
15 anything into a label, it's something that can be used for
16 advertising claims, depending upon where in the label it is.
17 And in some cases it has even been held that if it's in the
18 descriptive portion, it could still be there, with the
19 disclaimer though having to go on the advertisement.

20 So that, again, this is what's been done on the
21 prescription side. Professional labeling is actually closer
22 to being akin with--professional labeling is closer to being
23 akin with prescription labeling, because this is not
24 labeling that would readily be available to a consumer but
25 it would be available to a practitioner, so that the

1 labeling itself would look more similar to that of a
2 prescription label, and it can have disclaimers; whereas on
3 an OTC type of a label, you don't want anything with a
4 disclaimer because the consumer really won't understand it.

5 However, there have been exceptions and there have
6 been labels which sort of indicate, as with the case for
7 children, where this product is not indicated in children
8 under the age of whatever because it hasn't been studied.
9 You might see that kind of a disclaimer on an OTC product.

10 But usually the preference is not to have
11 something in a label where you either don't know what it
12 means or you're not sure what it means, unless there is some
13 very good reason to do it.

14 DR. GENCO: Thank you.

15 Yes, Peter?

16 MR. HUD: Could I just say I agree with what Linda
17 said, but I again would like to draw the distinction between
18 the label and the labeling. Linda, sometimes you used the
19 word "label" and I think you meant "labeling."

20 This, what we're talking about here is only
21 labeling, not the label. Nothing that we're talking about
22 here would go to a consumer. It would only go to the
23 dentist and other dental professionals, so that it is
24 exactly, as Linda pointed out, comparable to the physician
25 package insert that you're all familiar with for

1 prescription drugs.

2 And that, as she also pointed out, frequently will
3 have additional explanatory information that is not
4 definitive. And clearly, as Michael has said, this is not
5 definitive, and therefore we fully support the disclaimer as
6 well as the useful information.

7 DR. GENCO: Linda?

8 DR. KATZ: There's only one additional thing that
9 I'd like to make mention of for professional labeling in an
10 OTC product which is somewhat different than the labeling
11 for an Rx product. In the prescription labeling, the
12 package insert itself is easily locatable. In most cases
13 you can find it in a PDR, you can find it someplace quickly
14 for reference.

15 For the professional labeling for the OTC
16 products, it's not as readily available, and that's been
17 somewhat of a problem in some cases in the past where it is
18 accepted, it has been approved as professional labeling, but
19 it's not--in some cases it may be in the PDR, but oftentimes
20 it's not. And that sometimes can create a problem, too, if
21 there's important information that you want to get known to
22 people beyond the time when it's initially being detailed.

23 DR. GENCO: Thank you. Linda, I'd like to pick up
24 on your comment. If it's important, if it's important to do
25 this, the professional label should be included, could be

1 included.

2 I'd like to ask and bring up the whole point of
3 control of aerosolization. There are other techniques for
4 controlling aerosolization, for example, aspirator tips on
5 ultrasonic. There may be other agents.

6 I wonder if Warner-Lambert has some relative
7 benefit? In other words, the reduction that you've showed,
8 what does it--how does it compare with reduction by using an
9 aspirator tip specifically designed for an ultrasonic, for
10 example? Just to give us some perspective as to how
11 important is it to allow this claim at this point, in the
12 absence of relative data on other agents or other modes to
13 reduce aerosolization.

14 DR. BARNETT: I mean, there's no data I have to
15 answer that, Bob, except to say, I mean, that even in--I
16 mean, I have been--let's just say I've been out of the
17 clinic for a while, and you're still there using these
18 things, so the technology may have changed.

19 But from my day, I seem to recall that even with
20 the high-speed aspirators, there was still an aerosol that
21 made it out of the patient's mouth into the ambient
22 atmosphere of the operatory. So from that point of view I
23 guess unless you had an aspirator that was able to capture
24 every bit of the aerosol being produced, I think there would
25 still be obviously a benefit, insofar as you would be

1 reducing the bugs. But as far as actual numbers, I don't
2 have any for you.

3 DR. GENCO: Thank you. There are on the market
4 some aspirators for ultrasonic tips that specifically are
5 aimed at reducing aerosolization. I guess the question I
6 was asking, what is the relative effect of those versus a
7 product that you're proposing, and what would be the impact
8 on the dentist to follow your proposal versus using
9 something else? I think that's the--and what is the
10 importance? I mean, if it's a modest effect, would we--

11 DR. BARNETT: I don't know the answer to that, but
12 I mean, clearly they're not mutually exclusive and, you
13 know, there wouldn't be any harm obviously to reducing bugs
14 over and above that which may escape any of these aspirated
15 devices. But in terms of quantitation, obviously we don't
16 have those numbers for you.

17 DR. GENCO: Thank you.

18 Bill?

19 DR. BOWEN: I have a lot of ambivalence about this
20 topic. Conceptually one might argue that it's a good idea
21 to reduce the number of microorganisms in an aerosol, but to
22 solve what problem? And we haven't got a problem.

23 And I think the labeling makes, despite the
24 disclaimer, an implied benefit, and I could envision a
25 situation where it might in fact cause some harm, and

1 particularly in the absence of data. We don't know the
2 effect of the agent on specific populations. I'll just pick
3 two for example.

4 Let's suppose that as a result of this, that the
5 aerosol now contains a preponderance of strep mutants and
6 Candida? One could then make the case that as a result of
7 this enhanced population, that people are more at risk as a
8 result of using the aerosol than they were before, assuming
9 there was any risk to begin with.

10 So in the absence of specific effects, I feel very
11 uncomfortable about voting in favor of this claim.

12 DR. GENCO: Further comments?

13 [No response.]

14 DR. GENCO: Are we ready for the vote? Well,
15 let's start on the right this time.

16 DR. BOWEN: No.

17 DR. GENCO: Christine?

18 DR. WU: No.

19 DR. SAVITT: No.

20 DR. GENCO: No.

21 DR. SAXE: No.

22 DR. GENCO: Okay. Thank you.

23 Shall we proceed now and ask Bob Sherman if he
24 would review the recommendations and conclusions for the
25 draft subcommittee report?

1 MR. SHERMAN: Thank you. Good afternoon. I'm Bob
2 Sherman, with the Division of OTC Drug Products.

3 To help us in developing the subcommittee report
4 that will be on public display shortly after this meeting,
5 we'd like to present an overview of some of the major issues
6 that were discussed, to be sure that the report--that the
7 agency accurately reflects the recommendations and the
8 conclusions of the subcommittee. And this will include
9 recommended ingredients, labeling, testing, and various
10 other issues that we may need clarified or would like some
11 further discussion on. Okay?

12 All right. First of all, very quickly, Category
13 I, antiplaque, antigingivitis ingredients, cetylpyridinium
14 chloride, Category I for gingivitis and plaque. Stannous
15 fluoride, Category I for gingivitis. The fixed combination
16 of essential oils, thymol, menthol, eucalyptol, methyl
17 salicylate, Category I for gingivitis and plaque. Okay?

18 All right. The statement of identity for Category
19 I ingredients for stannous fluoride would be antigingivitis
20 and then the dosage form. For cetylpyridinium chloride and
21 the fixed combination of essential oils it would be
22 antigingivitis, antiplaque, again with the dosage form.

23 Okay. For combination drug products, and this is
24 combination products across classes as opposed to or as
25 distinguished from combination ingredients, these are

1 permitted combination drug products. One would be an
2 antigingivitis, antiplaque agent plus an anticaries agent.
3 Another would be an antigingivitis, antiplaque agent plus a
4 tooth desensitizer. A third would be the combination of all
5 three of those: an antigingivitis, antiplaque agent, plus
6 an anticaries agent, plus a tooth desensitizer.

7 The statement of identity for these combination
8 products would be, one, one could be anticaries,
9 antigingivitis, antiplaque, with the dosage form. A second,
10 antigingivitis, antiplaque, insert dosage form, for
11 sensitive teeth. And then anticaries, antigingivitis,
12 antiplaque, insert dosage form, for sensitive teeth; you
13 need a big label for that one.

14 Okay. Category I indications for antigingivitis
15 ingredients. That would be stannous fluoride. And we had
16 "aids or helps in the control"--or you could substitute
17 "reduction" or "prevention" for "control"--of gingivitis, or
18 substituting "gingivitis, an early form of gum disease." An
19 optional indication would be "aids or helps in the control"
20 --reduction, prevention--"of bleeding gums" or "red bleeding
21 gums."

22 Category I indications for antigingivitis,
23 antiplaque ingredients, which would be CPC and the fixed
24 combination of essential oils, would be "aids in the
25 control"--reduction, prevention--"of plaque that leads to

1 gingivitis" or "gingivitis, an early form of gum disease."
2 Again with the optional "aids in the control"--reduction,
3 prevention--"of plaque that leads to bleeding gums" or "red
4 bleeding gums."

5 Okay? Then we have the indication that was agreed
6 to this morning and penciled in, which says, "aids or helps
7 in the control, inhibition, killing of plaque bacteria that
8 contribute to the development of gingivitis" or "gingivitis,
9 an early form of gum disease." And this would be for the
10 fixed combination of essential oils only.

11 We also have the additional indication for
12 stannous fluoride which reads "helps interfere with harmful
13 effects of plaque associated with gingivitis." Is that
14 correct?

15 Okay. The warnings we discussed at the last
16 meeting, these would be for all antigingivitis, antiplaque
17 drug products. It reads, "Keep out of the reach of children
18 under 6 years of age. If you accidentally swallow more than
19 used for brushing or rinsing, consult a poison control
20 center or seek professional assistance immediately. If
21 gingivitis, bleeding or red gums persist for more than 2
22 weeks, see your dentist."

23 And then "See your dentist immediately if you have
24 painful or swollen gums, pus in your gums, loose teeth or
25 increased spacing between your teeth. These may be signs of

1 periodontitis, a serious form of gum disease."

2 Now some of these--some of the wording here was
3 slightly different than a summary that was submitted by
4 NDMA. I think we're pretty close, and if anyone wants to
5 comment on these, that's fine.

6 There was an additional warning for both CPC and
7 the fixed combination of essential oils. "Do not administer
8 to children under age 6. Supervise use for children between
9 the ages of 6 and 12."

10 We had an additional labeling statement for
11 stannous fluoride that reads "This product may produce
12 surface staining of the teeth. Adequate tooth brushing may
13 prevent these stains, which are not harmful or permanent and
14 may be removed by a dentist."

15 Under "Directions" there was some discussion. The
16 subcommittee agreed that directions used in the clinical
17 trials would be the basis for recommended directions.
18 Stannous fluoride would need to have the same directions as
19 are in the anticaries monograph.

20 The mouth rinses, I guess I can read this:
21 "Adults and children 12 years of age and older. Vigorously
22 swish 20 milliliters of rinse between your teeth for 30
23 seconds and then spit out. Do not swallow the rinse.
24 Instruct children under 12 years of age in good rinsing
25 habits to minimize swallowing. Supervise children as

1 necessary until capable of using without supervision.
2 Children under 6 years of age, consult a dentist or doctor."
3 And then: "This rinse is not intended to replace brushing
4 or flossing."

5 DR. BOWEN: Do you think that the "consult a
6 dentist or doctor" should be "dentist or physician"?

7 DR. GENCO: You might find some support for that.

8 DR. BOWEN: I had a feeling I might.

9 MR. SHERMAN: Okay. The comment is noted.

10 Okay, what was next? We had considered
11 traditional dosage forms as a dentifrice, a gel, paste,
12 powder, or rinse.

13 And we had some questions about testing that we
14 would like to discuss a bit. Those should be at the back of
15 your slide package, but let me read this. We have--this is
16 from part of the subcommittee report as written:

17 "The following testing should be conducted on the
18 product formulation: a standard formulation with
19 effectiveness documented by clinical trials and a negative
20 control. For a product to be considered effective, it must
21 demonstrate that it is substantially equivalent to the
22 standard formulation and statistically superior to the
23 negative control, as assessed by reasonable statistical
24 analyses."

25 Specifically for cetylpyridinium chloride we had,

1 one, in vitro antimicro--these are types of tests--in vitro
2 antimicrobial activity against organisms associated with
3 gingivitis. Then we had minimal inhibitory concentration
4 assays, time kill studies, chemostat bacterial fermentation
5 growth system studies, plaque biofilm assays such as plaque
6 removal or plaque wire models. In vivo activity should be
7 demonstrated using enumeration of viable bacteria in plaque
8 or stimulated saliva. Availability using a disc retention
9 assay, and biological activity using plaque glycolysis and
10 regrowth model.

11 Okay. I think this is a list of the
12 representative organisms. Representative organisms include
13 but are not limited to Actinomyces viscosus, Fusobacterium
14 nucleatum, porphyomas gingivalis, Prevotella intermedia,
15 Bacteroides forsythus, Candida species, and gram negative
16 enteric rods. Okay.

17 For stannous fluoride paste, gel, powder or rinse,
18 again, in vitro antimicrobial activity against plaque
19 organisms associated with gingivitis, and the same other
20 tests as we listed before, MIC assays, time kill studies,
21 chemostat bacterial fermentation growth system, plaque
22 biofilm assay, and then biological activities in PGRM.

23 For the fixed combination of essential oils we
24 have the in vitro antimicrobial activity using 30-second
25 time kill studies in the presence of exogenous protein using

1 standard laboratory strains and wild type saliva organisms,
2 and in vivo activity through a short-term experimental
3 gingivitis study of at least 2 weeks duration.

4 Okay, and some of the questions that we wanted to
5 ask of the subcommittee, one, are these effectiveness
6 criteria specific enough? For example, in the first
7 statement--can you find that, Stephanie? It's back a few
8 slides. This is the statement about substantial
9 equivalents. Can you elaborate on that, possibly define
10 that? What do we mean by "substantial equivalents"?

11 DR. GENCO: Do you want to go through these one-
12 by-one now?

13 MR. SHERMAN: Okay.

14 DR. GENCO: Or do you want to finish and we--

15 MR. SHERMAN: Well, I can read the list and we can
16 come back to all of them.

17 DR. GENCO: Good.

18 MR. SHERMAN: Okay. Are these effectiveness
19 criteria specific enough?

20 How do you define "substantially equivalent"?

21 Are there particular in vitro tests that would be
22 better than others? What we're asking is, we have a list of
23 tests. Do you want to see all of those tests for each
24 particular ingredient, some of those, one of those?

25 Are there additional organisms that should be

1 included in the list that was discussed at the last meeting?

2 There is a specific time point for time kill
3 studies with the essential oils, but not with the two other
4 ingredients, and we need some information about that.

5 And should the recommended in vitro tests be
6 consistent across the board? In other words, the essential
7 oils, the recommended studies for the essential oils
8 included only a time kill study, whereas the other two
9 ingredients had some other ones.

10 Okay, so going back to this kind of blanket
11 statement, "The following testing should be conducted on the
12 product formulation: a standard formulation with
13 effectiveness documented by clinical trials and a negative
14 control. For a product to be considered effective, it must
15 demonstrate that it is substantially equivalent to the
16 standard formulation and statistically superior to the
17 negative control, as assessed by reasonable statistical
18 analyses." Can you elaborate a little bit on this notion of
19 "substantially equivalent"?

20 DR. GENCO: Stan?

21 DR. SAXE: Well, in the latter half of that
22 sentence, Bob, following where it says "substantially
23 equivalent to the standard formulation and statistically
24 superior," I think that sentence is better served by using
25 the word "clinically superior to the negative control, as

1 assessed by reasonable statistical analyses." The word
2 "statistical" is already in there.

3 MR. SHERMAN: Okay.

4 DR. SAXE: And we know that indeed slight
5 differences in whatever is--maybe assessed, whether it's an
6 index, particularly indices may not be clinically very
7 different, but by having large enough numbers, one could get
8 a statistically significant difference but clinically there
9 is no significance. So what I'm suggesting is that the word
10 "clinically superior" be used instead of the term
11 "statistically superior".

12 MR. SHERMAN: Clinically superior to the negative
13 control?

14 DR. SAXE: Right.

15 MR. SHERMAN: That's what you're talking about?

16 MR. CANCRO: I'd like to discuss that, please.

17 DR. GENCO: Yes, go ahead, Lou. So the suggestion
18 has been made to change from "statistically" to "clinically"
19 superior.

20 MR. CANCRO: Yes, but these are laboratory tests.
21 Are you suggesting that differences you see in a laboratory
22 test should be--

23 DR. GENCO: Excuse me. These are clinical trials.

24 MR. SHERMAN: No, this is testing. We're talking
25 about final formulation testing.

1 DR. GENCO: I'm sorry.

2 MR. SHERMAN: Okay.

3 DR. GENCO: Yes, we're both looking at the wrong
4 sheet here.

5 DR. SAXE: I was referring to clinical trials.

6 MR. CANCRO: Bob?

7 MR. SHERMAN: Yes.

8 MR. CANCRO: I need some clarification on some of
9 these points, if you wouldn't mind. You went through the
10 listing of the combination policy, and I assume, although
11 it's not listed here, that for a product which is showing
12 only antigingivitis activity, and conversely for a product
13 that wants to declare only antiplaque activity, and both of
14 those qualify with appropriate testing, that the same
15 combinations are appropriate. For example, antigingivitis
16 plus anticaries; antigingivitis plus tooth desensitizing;
17 antigingivitis, et cetera, et cetera, et cetera.

18 MR. SHERMAN: Right. Yes.

19 MR. CANCRO: And, similarly, should for some
20 reason a manufacturer want to declare the product only as
21 being antiplaque, and it qualifies by the rules we have set
22 up, it too can be used in combination with these three other
23 category ingredients. Is that correct?

24 MR. SHERMAN: But I think that we've said that a
25 product cannot be only antiplaque, that it must be--

1 MR. CANCRO: Well--

2 MR. SHERMAN: It can't be only antiplaque. It can
3 be only gingivitis but it can't be only plaque. Isn't
4 that--

5 MR. CANCRO: Okay, so that--

6 MR. SHERMAN: So that wouldn't be the case.

7 MR. CANCRO: --that doesn't exist at all, then.
8 Is that correct?

9 MR. SHERMAN: Correct.

10 DR. GENCO: If we could get back to this issue of
11 "substantially equivalent," are you satisfied with that
12 answer?

13 DR. SAXE: Yes.

14 DR. GENCO: Thank you.

15 MR. SHERMAN: So, in other words, do we need to
16 define this term further? Are we talking--you know, how
17 close--

18 DR. GENCO: What else could be "substantially
19 equivalent" other than what's in, let's say, the first or
20 the second sentence? It says the product formulation, "a
21 standard formulation with effectiveness documented by
22 clinical trials," so that's the predecessor, the prototype
23 drug or product. So in that product there's a concentration
24 already set, or a range. We've discussed that for the
25 Category I products.

1 So "substantially equivalent" would mean it would
2 be in that range of dosage, of concentration. Do we need to
3 spell that out, or--I mean, that would probably be the most
4 important element here, that you're not using 10 times more
5 than is in the prototype product.

6 MR. SHERMAN: Okay, but we're talking about the
7 effectiveness of the product.

8 DR. GENCO: Right.

9 MR. SHERMAN: The effectiveness would have to be
10 equivalent to some standard, and what do we mean by that?
11 Exactly the same? Within a certain percentage?

12 DR. GENCO: Does not "statistically superior"
13 answer that?

14 MR. SHERMAN: Well, the "statistically superior"
15 is referring to the negative control--

16 DR. GENCO: Right.

17 MR. SHERMAN: --not the standard formulation.
18 We're saying it must be in some way equal to this standard.

19 DR. GENCO: Okay, so--

20 MR. SHERMAN: And we're using the term
21 "substantially equivalent" and we're trying to define that a
22 little bit better. It's a little bit of a vague term.

23 DR. GENCO: What is the present FDA view of
24 bioequivalence? There's a statistical technique for
25 bioequivalence which is, what, within 80 percent, plus or

1 minus 20 percent? Or is this still an issue?

2 MR. SHERMAN: Can you--

3 DR. KATZ: It basically--it depends, but there is
4 a standard, and we will--I will put that to the biopharm to
5 tell us what they would prefer to use as the standard in
6 this case, because it is somewhat different for generic than
7 it may be for some of the other products, and 80 percent
8 would be correct if it were generic.

9 DR. GENCO: So could we be instructed by that to
10 define "substantially equivalent" brackets within 80 percent
11 of the effectiveness of the standard product? Would that
12 help? What's your feeling?

13 DR. BOWEN: I feel a little uncomfortable with as
14 low as 80 percent. We are looking at final formulation, and
15 it's conceivable that a competitor of the parent product
16 could put in 20 percent less of the active ingredient and be
17 able to sell it as equivalent with something with 20 percent
18 more. I don't think that's what we have in mind.

19 DR. GENCO: As I recall, the 80 percent comes from
20 the variability in those bioassays. That is felt, if it's
21 within 80 percent, it's probably batch-to-batch over time
22 going to be comparable. I think that's the rationale, that
23 that's the error, accounting for error, so that--

24 DR. BOWEN: Well, obviously it would vary
25 enormously depending on the agent, and I was thinking it

1 would have to be defined depending on the agent. I'm not--
2 I'm just using it as an example. Obviously I don't use the
3 specifics. But if you took CPC and you do the in vitro
4 testing that we want and the variation is 5 percent, well,
5 then the formulation should be within 5 percent.

6 DR. GENCO: And you're saying--

7 DR. BOWEN: So I think it should be within the
8 variation of the parent product.

9 DR. GENCO: --statistically significantly
10 comparable to or equivalent to. So that would be another
11 way of saying that. "Substantially equivalent" should be
12 statistically significantly not different from the parent
13 product, in vitro.

14 MR. CANCRO: I suspect here that what really is
15 intended is to establish the power of the test, and that's
16 what we're talking about. We're not talking about a product
17 being 20 percent different from another product and being
18 eligible to meet this monograph condition. We're talking
19 about the power of the test to discriminate between two
20 things which should be the same.

21 DR. GENCO: So that's the statistical argument
22 that--

23 MR. CANCRO: And it's traditionally a power that
24 is set, that you set the test power sufficient so that you
25 have an 80 percent confidence to say that these things

1 aren't really different.

2 DR. GENCO: And Bill is arguing for a 95 percent
3 confidence.

4 MR. CANCRO: Yes, but if you set the power of a
5 test to 95, you're looking at one enormous test in terms of
6 samples. I mean, it's a very different--

7 DR. BOWEN: It depends on the variation of the
8 initial product.

9 DR. GENCO: Linda, in other categories that's been
10 about what has been accepted, hasn't it? The 80 percent
11 beta power has been the thing that has kind of been
12 accepted? I mean, that's a question. I'm sorry.

13 DR. KATZ: Yes, it's really--it's 80 percent of a
14 95 percent--with the 95 percent confidence interval, so that
15 80 percent is what has usually been used.

16 DR. GENCO: Michael?

17 DR. BARNETT: Yes. I'm just wondering if the
18 criteria ought to be dependent upon the actual test that's
19 being used. For example, when we presented our suggested
20 final formulation tests, which were the kill kinetics and
21 the 2-week experimental gingivitis model, we had proposed
22 criteria, which obviously are up for discussion, but at
23 least some criteria which seemed to be reasonable criteria
24 for judging sameness or difference of formulations. And I
25 think in one case it was within a half a log reduction, in

1 the case of the kill kinetics, and in the case of the 2-week
2 experimental gingivitis it was using the "at least as good
3 as" statistical construct. So maybe in terms of discussion
4 it ought to be dependent upon the test rather than some
5 absolute that would try to apply to all tests.

6 DR. GENCO: Yes, I think that's certainly an
7 approach, and that means that the statement as it is, Bob,
8 is adequate, and that it would fall on the FDA to determine
9 if substantial equivalence was shown. These are going to be
10 submitted to the FDA case-by-case. You'd have to look at
11 that data and determine if it was substantially equivalent
12 according to some present day statistical power, which may
13 change. So maybe--I'd like to suggest that that is all you
14 need at this point; that the intent is that there be some
15 flexibility in making that decision, as Dr. Barnett said,
16 based upon case-by-case.

17 MR. SHERMAN: Okay.

18 DR. GENCO: And that it not be proscribed and in
19 doing so may be onerous for certain medications.

20 MR. SHERMAN: Okay.

21 DR. GENCO: Panel, what do you feel about that?

22 DR. BOWEN: I agree that you can't write an all-
23 encompassing statement other than what you have here,
24 because as you point out, each test has different outcomes
25 and different variability.

1 DR. GENCO: Bob, do we want to go on to number
2 three? Are there particular in vitro tests that would be
3 better than others? Does this address the issue of should
4 they all be required, or just a few?

5 MR. SHERMAN: Yes, exactly.

6 DR. GENCO: Okay.

7 MR. SHERMAN: We had a number of--there was a
8 discussion and we basically, as written in the report, have
9 culled this from the transcripts, and we want to be clear if
10 all of these things are required, any one of them may be
11 required, that type of thing.

12 DR. GENCO: Could we go to the--

13 MR. SHERMAN: The CPC?

14 DR. GENCO: --the CPC, yes, final formulation, as
15 an example? So be thinking, panel about the CPC. There's
16 in vitro antimicrobial activity versus a panel of organisms;
17 in vivo activity in the presence of saliva; availability
18 using the DRA, and then the PGRM. Was it our intent to
19 include--to require all of these for the new batch or new
20 preparation or new formulation of CPC? All of these or--

21 MR. SHERMAN: Particularly the in vitro studies.
22 MIC, time kill, plaque biofilm assays. Are those suggested
23 types of tests, any one of which could be done? Do you need
24 all of those? Are there ones that are preferable? That's
25 what we're trying to get at.

1 DR. GENCO: I heard this morning that the plaque
2 biofilm was an important one. Bill, do you want to make
3 some comments?

4 DR. BOWEN: As I recall the discussion, we
5 requested all of these on the CPC. That's my recollection.

6 And if I may switch very briefly to the stannous
7 fluoride, we also recommended the plaque glycolysis for the
8 stannous fluoride also.

9 DR. GENCO: So that your recollection was that for
10 the CPC it would be under A, all four of those, plus B, plus
11 C, plus D?

12 DR. BOWEN: Uh-huh.

13 DR. GENCO: Any further comments on that?

14 And then for the stannous fluoride, again, all
15 under A Plus B.

16 DR. BOWEN: Yes. And under "B" we also had plaque
17 glycolysis.

18 DR. GENCO: Okay.

19 DR. BOWEN: Yes. That is what it is.

20 DR. GENCO: Yes. PGRM is plaque glycolysis and
21 new growth model.

22 DR. BOWEN: I mis-read it, sorry. So, it is
23 there.

24 MR. SHERMAN: It is there.

25 All right. And then for the fixed combination of

1 essential oils we had basically only a time-kill study.
2 Would some of these other tests be appropriate? And these
3 were based on the sponsor's recommendations. Would some of
4 these other tests be appropriate for this ingredient?

5 DR. GENCO: Comments?

6 DR. BARNETT: I think in the case of our
7 suggestions we only included--I guess you are asking the
8 question, Bob, specifically about the in vitro tests or more
9 specific tests?

10 MR. SHERMAN: Right. In other words, should it be
11 consistent across-the-board? Should we say that all
12 ingredients need all of these tests?

13 DR. BARNETT: Right. If you recall, our rationale
14 for selecting these two tests, in particular, one of which
15 is in vivo, the other in vitro, was that we did believe that
16 some assessment of the formulation against a bio-film be
17 done.

18 And, in so far as our assessment actually involves
19 the in vivo experimental gingivitis model we thought this
20 would preclude the need to do it in vitro since essentially
21 you are doing a bio-film determination in vivo. So, my
22 response to that is because the in vivo component of our
23 suggestion I would argue is a bit more rigorous than the
24 others, therefore, it's not necessary to do your in vitro
25 studies to the same extent, other than to demonstrate that

1 you have retained the same spectrum of anti-microbial
2 activity.

3 And in this regard, I would just like to make one
4 other comment. That is we, in fact, had, rather than having
5 a general statement using standard laboratory strains, we,
6 in fact, had made a recommendation of organisms to include.
7 And I think that as a result of a discussion last time the
8 decision was made actually to expand that list to include
9 additional organisms such as the ones you had on the
10 previous list. So, it might not be inappropriate in this
11 case, as well, to list the specific organisms.

12 I would like to make just one other comment.

13 DR. GENCO: Sure.

14 DR. BARNETT: And there was additional discussion
15 last time with respect to formulation testing of essential
16 oil containing products and that is the question if one were
17 to look at an alternate dosage form, such as a dentifrice,
18 what might be required? And I think there was some rather
19 lengthy discussion and the conclusion was that in that case
20 because there was no precedent standard formulation a six-
21 month plaque gingivitis clinical trial would be the
22 appropriate essentially final formulation test for change in
23 dosage form. I just wanted to say that.

24 DR. GENCO: There are three points you are making.

25 The first point is that for a fixed combination

1 the in vivo two-week experimental gingivitis inhibition
2 study is done, therefore, less in vitro testing is needed
3 for the essential oil combination.

4 It is inconsistent with the other two products but
5 it may be appropriate for the fixed oils because of the
6 difficulties in doing MICs, for example. You get
7 volatilization over time.

8 DR. BARNETT: No. I'm not sure whether it's a
9 question of difficulty as opposed to necessity. I mean
10 certainly one can do MICs. That's not the issue. The
11 question, I think, is in terms of what, you know, without
12 making it too onerous, what would be the test that might
13 show substantial equivalence, however we define that,
14 between two formulations?

15 And I think we had thought that this combination
16 would be a very efficient way of doing it and answering the
17 relevant questions.

18 DR. GENCO: Okay. Let me put that to the panel
19 then.

20 What are your feelings? You have a different set
21 of criteria for essential oils as for the other two. Are
22 you comfortable with that?

23 Are you comfortable with the essential oil, in
24 vitro anti-microbial and in vivo two-week?

25 Okay. Now, second point. With respect to the

mwb

1 essential oil in vitro anti-microbial Michael said that they
2 made some recommendations for bacteria. We have this final
3 formulation testing that representative organisms include
4 but are not limited to this whole list. That's essentially
5 the list that would apply to all in vitro testing in my
6 view, as I understand it. So, maybe the language has to be
7 clarified using standard laboratory strains and wild types
8 of strains as indicated in paragraph such and such above,
9 referring to that list of organisms.

10 MR. CANCRO: I think that is a very important
11 point, Bob.

12 DR. GENCO: Okay.

13 MR. CANCRO: That there is some uniformity here.
14 And I don't quite like the expression "not limited to"
15 because I don't know what that means. I mean if you've got
16 several organisms that you want to see a definitive action
17 against and you state them, everybody understands that.

18 DR. GENCO: Somebody could use some others if, for
19 some reason, there is a question that this agent may give
20 rise to a bizarre new bug and we only know 14 percent of the
21 organisms in plaque now anyway, so, I think that leaves now
22 the possibility to the future 20 years to look at some new
23 organisms. That may be onerous.

24 DR. BOWEN: I have a slight problem with this
25 list. While I am reluctant to add to the burdens, I look at

1 the list and I find that there is just one that is possibly
2 associated with the formation of the matrix in dental
3 plaque, namely actinomyces viscosus. So, I would make a
4 recommendation that strep mutans be included also at a
5 minimum.

6 DR. GENCO: Okay. Is there any objection to that?

7 [No response.]

8 DR. GENCO: So, the list would read A.viscosus,
9 fusobacterium nucleatum, porphyomas gingivalis, P.
10 intermedia, B. forsythus, candida species, strep mutans and
11 gram negative anaerobic rods.

12 The third point that you made, Michael, was that
13 for brand new dosage forms, the mouth rinse approved, now
14 somebody wants to put it in a toothpaste, that the full six
15 month clinical trial would be necessary.

16 I recall that, too. Let's get the bugs first
17 here. We are not taking out the bugs, we are adding bugs.

18 After candida species, streptococcus, new tense,
19 and gram negative enteric rods.

20 Okay.

21 MR. SHERMAN: Okay. Could you repeat that?

22 DR. GENCO: After candida species, insert
23 streptococcus mutans.

24 Now, new point, before we forget it. Bob, is
25 there some place in the document that this issue is

1 addressed of new dosage form, for example, something is a
2 mouth rinse and now somebody wants to put CPC in a tooth
3 paste that there be a six-month trial?

4 MR. SHERMAN: Yes, I believe there is.

5 DR. GENCO: Okay. Good. Thank you.

6 MR. SHERMAN: Actually I think it comes just
7 before that general statement that we looked at.

8 DR. GENCO: Okay.

9 MR. CANCRO: I'm sorry. I need some
10 clarification. I would like to go back to CPC final
11 formulation testing. Under A, you identify or I guess the
12 question is, there is a group of four tests under A, minimal
13 inhibitory concentration, time-kill studies, chemostatic
14 bacterial fermentation growth studies, plaque biofilm. What
15 specifically does that mean? Does it mean any one of those
16 or all of those under A? What are we talking about there?

17 Does A say, do any one of those studies? Or, I
18 mean what is that break out mean?

19 MR. SHERMAN: You seemed to say earlier that all
20 of that list would be needed, is that correct?

21 DR. GENCO: Yes.

22 MR. DOYLE: That's not my recollection. Matt
23 Doyle, from Procter & Gamble. I thought we aligned
24 principally around the need to establish chemical
25 availability and biological effectiveness and during our

1 application we recommended what you have as C and D there.

2 We also agreed with the panel and thought it was
3 prudent that an additional in vitro type of test ought to be
4 done but didn't come to closure on what--we were open as to
5 what that should be. At that point in time, it didn't
6 appear to us that that was a battery of tests including
7 chemostatic measurements, time course assays, MICs and on
8 and on and on. That singular additional tests would be
9 sufficient to establish chemical availability and biological
10 effectiveness.

11 And consistent with the data base we shared with
12 you, both on our product and other products, that that kind
13 of an extensive list of testing is not requisite.

14 Similarly for the stannous fluoride list, a
15 similar context there, the chemical availability and
16 biological effectiveness can be established through PGRM in
17 combination with a soluble fluoride measurement and here,
18 again, we thought it prudent that an additional in vitro
19 test could be done as well. But, again, not an established
20 battery of in vitro tests.

21 DR. GENCO: Was the feeling that any one of those
22 would be adequate? We already had the suggestion for our
23 feeling was that it was required to do all but I think you
24 make a good point that this may be onerous.

25 MR. DOYLE: Truthfully, the value added from that

1 is limited at best within the context of the primary and
2 principal assays that we had described.

3 DR. GENCO: I mean traditionally the MICs were
4 done.

5 MR. DOYLE: Absolutely.

6 DR. GENCO: Or time kill if the MIC was difficult.

7 MR. DOYLE: Absolutely. You are going right down
8 the path.

9 DR. GENCO: And that doesn't say anything about
10 its affect on biofilm but that has already been established
11 for these compounds?

12 MR. DOYLE: That's correct.

13 DR. GENCO: So, you just want to know about that
14 formulation?

15 MR. DOYLE: Final formulation testing.

16 DR. GENCO: Does it kill bugs?

17 MR. DOYLE: Right.

18 DR. GENCO: So, what would you say about--from
19 this list but to include MIC and time kill studies as
20 appropriate or something like that?

21 MR. DOYLE: That would be fine. Yes.

22 DR. GENCO: Well, what do you think? The
23 chemostat may be onerous.

24 DR. BOWEN: I think it would be very onerous. I
25 think the MIC, the time kill and the PG and for this we're

1 on CPC now--

2 DR. GENCO: Right.

3 DR. BOWEN: The DRA and the PGRM would suffice.
4 That is four tests, five tests.

5 DR. GENCO: So, you're saying that B, C, and D for
6 sure. And then from A--

7 DR. BOWEN: From A, minimal MIC and a time kill.

8 DR. GENCO: Okay. Any further comments on that?

9 All right. So, how this would boil down for CPC
10 would be under A, to include on that battery of organisms
11 already referenced above, MIC and time kill. Additional
12 tests may be performed including chemostat and plaque
13 biofilm.

14 Those are optional right now.

15 MR. DOYLE: I don't want to become overly
16 prescriptive here, but some rational combination. So, for
17 example, MIC and/or time kill as necessary or biofilm to
18 replace either of those. I mean there are several options
19 here.

20 I understand principally what is trying to be
21 achieved, but I don't know how prescriptive the process
22 needs to be. That's all.

23 MR. CANCRO: It becomes important if a product is
24 going to be placed on the market to match a goal standard
25 that there is a very clear testing sequence that people

1 understand and, you know, whatever that is, it is. If it's
2 MIC and time kill and then B, C, and D, then that's what it
3 is.

4 I'm not sure that's coming across clearly to me.
5 Maybe everybody else understands it, but I don't.

6 DR. GENCO: Okay. So, the suggestion--let me just
7 put this out on the table. For CPC in vitro antimicrobial
8 activity testing versus that panel of organisms to include
9 MIC or time kill, as appropriate, and omit the other two
10 under A.

11 It still allows the company to do that if they
12 want but they don't have to. Plaque biofilm assays can't be
13 carried out on some of these organisms because they don't
14 form plaque on layers. It's impossible to do.

15 So, that's a suggestion. In other words, drop the
16 chemostat, drop the plaque biofilm; require MIC or time kill
17 as appropriate for that entire battery. And that is a
18 substantial amount of testing.

19 And then, of course, B, C, and D.

20 MR. DOYLE: B is redundant with D, quite frankly.
21 You are actually, if you recall how that measurement is
22 made, D is an in vivo measurement. It's actually done in ex
23 vivo measurement.

24 DR. GENCO: I'm sorry. B and D are comparable?

25 MR. DOYLE: I mean if you're doing D, there's no

1 need to do B.

2 DR. GENCO: Okay. In the process of doing the
3 PGRM you get B. So, that would reduce this list to A, C and
4 C, and under A, maximum inhibitory concentration or time
5 kill as appropriate.

6 Does the group feel comfortable with that? In
7 other words, let's go back over that, Bob, so it's clear. A
8 gets revised to in vitro antimicrobial activity versus
9 organisms as referenced above or below to include minimum
10 inhibitory concentration assays or time kill assays as
11 appropriate. And then C becomes B, and D becomes C.

12 MR. CANCRO: That's fine.

13 DR. GENCO: I mean as appropriate. I am thinking
14 if there is some formulation that volatilizes the CPC or
15 makes MICs impossible to do, then the time kill might be the
16 test to do it. It's an alternate to look at, does this
17 product kill bugs.

18 Okay.

19 Now, with respect to final formulation for
20 stannous fluoride. This could be essentially the same, that
21 is to leave out--unless there was reason to include the
22 chemostat or the plaque biofilm--to leave those out. All
23 right.

24 So, A would be in vitro antimicrobial activity
25 against plaque organisms, again, as referenced above, that

1 group of organisms, to include minimum inhibitory
2 concentration assay and/or time kill.

3 Now, can we be instructed, what is the advantage
4 of the time kill or is MIC always going to work for stannous
5 fluoride?

6 Are there conditions under which it wouldn't work
7 and you would need a time kill?

8 Thank you. They're shaking their heads. Three
9 fine gentlemen, scientists from Procter & Gamble. Thank you
10 very much for the record.

11 Okay. So, it would read, to include minimum
12 inhibitory concentration assays or time kill assays as
13 appropriate.

14 Take out chemostat, plaque biofilm and then leave
15 in B.

16 Everybody comfortable with that on the panel?

17 MR. WHITE: Don White, Procter & Gamble.

18 The only problem that I have with specifically
19 stannous fluoride, you know, you can get hydrolysis in
20 solution over time and that can complicate time kill
21 studies. I think what we had originally intended was
22 soluble fluoride, you know, to make sure that the stannous
23 fluoride was in solution. Certainly the PGRM assay and also
24 possibly an in vitro plaque biofilm model or something like
25 that. I don't remember us discussing MICs or time kills,

1 certainly not chemostat bacterial fermentation.

2 So, what was it that you were recommending?

3 DR. GENCO: Okay. The recommendation was under A,
4 in vitro antimicrobial activity, some measure of the ability
5 to kill bacteria. Either MIC or time kill. You think there
6 would be problems with both of those in terms of hydrolysis?

7 MR. WHITE: Well, for some of the organisms there
8 might depending upon what the culture conditions are.

9 DR. GENCO: You mean it is organism dependent?

10 MR. WHITE: Well, yes, for some of the assays it
11 might be quite tricky to do that for stannous fluoride for
12 the reason that you were mentioning earlier. You know, that
13 you were worried about the volatization of some component.
14 In this case it would be because of hydrolysis or something
15 like that.

16 DR. GENCO: I see. The media differs for the
17 organism.

18 MR. WHITE: Yes.

19 DR. GENCO: For some media--

20 MR. WHITE: Precisely. Because what we gave you
21 was a chemical test and then a bio-availability test, we
22 offered up that there could some in vitro test, such as what
23 we would typically do instead is a plaque biofilm assay to
24 Dr. Bowen's point. Because it's a better--it is a biofilm
25 anyway, you can do a treatment within a minute or so and

1 then you can see what the effect on the biofilm over time
2 is.

3 DR. GENCO: All right. Theoretically you want to
4 know that this material kills bugs and if it kills one, it
5 will probably kill others?

6 MR. WHITE: Right.

7 DR. GENCO: So, as appropriate might solve that.
8 In other words, MIC and/or time kill as appropriate.

9 MR. WHITE: And/or, how about and/or plaque
10 biofilm assays because we have more experience with those
11 with stannous fluoride than we do with MICs and time kills.

12 DR. GENCO: What does the panel--in other words,
13 should there be three choices for demonstrating bactericidal
14 activity of stannous fluoride? Three assays? In vitro, of
15 course. Pick the one that works best for that particular
16 organism in that particular media.

17 DR. BOWEN: Given the problems, you said that it
18 is conceivable that you won't be able to do stannous
19 fluoride on several of the organisms under any of the
20 conditions. Some of them won't form biofilms. Some of them
21 will be in such complex media that if you add stannous you
22 end up precipitating--

23 MR. WHITE: Yes, my microbiologist says, yeah.

24 DR. BOWEN: I think what you say, Bob, namely,
25 where appropriate, we would probably have to rely primarily

1 but not exclusively on B.

2 DR. GENCO: Do we include A at all then?

3 DR. BOWEN: Where possible and appropriate.

4 DR. GENCO: Okay. So, that could read, in vitro
5 antimicrobial activity against this panel of organisms
6 including a minimum inhibitory concentration assays or time
7 kill or plaque biofilm as appropriate.

8 So, that gives quite a bit of flexibility. I
9 guess the end result is that you want to know that it kills
10 one or another, hopefully, you can test in one or another
11 assay all of that panel but if you can't, you can't.

12 MR. CANCRO: I think that is satisfactory.

13 DR. GENCO: That deals with the complexity of the
14 reality.

15 MR. CANCRO: Right.

16 DR. GENCO: And then the biological assay.

17 Thank you very much.

18 MR. SHERMAN: Do we need to define the time frame
19 of these time kill studies as was done with the essential
20 oils?

21 DR. GENCO: What was the rationale for the
22 essential oil 30 seconds? Because it mimicked the exposure
23 in vivo? It mimics a rinse time.

24 DR. BARNETT: Yes. There were two rationales.

25 One was, of course, that it mimics the rinse time. The

1 second was that by limiting the time and quantitating the
2 level of kill you would be able to more precisely compare
3 formulations. And that's when that half-log difference
4 became effective.

5 DR. GENCO: So, what is the panel's feeling? Do
6 you want to prescribe 30-second time kill studies for all
7 three of these?

8 DR. BOWEN: That would be ideal.

9 DR. GENCO: Any objection to that?

10 [No response.]

11 DR. GENCO: Okay. Bob, for all three then 30-
12 second time kill.

13 MR. SHERMAN: Okay. Thank you.

14 Then I think we have answered all of these
15 questions. That leaves us with just a couple of various
16 minor clarifications that we can take care of at the table.

17 DR. HYMAN: One thing that I think may need a
18 little clarification and the slide that was just up prior on
19 the final formulation was a little unclear to me about the
20 dosage form for stannous fluoride. When we were looking
21 through some of the transcripts and trying to put everything
22 together, at some points it looked as though just the
23 stannous fluoride paste was really the form that was studied
24 and the compelling evidence was submitted for.

25 But we have paste, gel, powder or rinse in this

1 final formulation testing implying that those are all
2 acceptable formulations for stannous fluoride without a six-
3 month additional study.

4 So, I'm a little unclear. Is anyone else unclear
5 on this?

6 DR. BOWEN: As I wrote the report, my intention at
7 the time, referred solely to the paste. There were problems
8 with a lot of the other agents that I looked at either in
9 combinations or some of the studies were unsatisfactory.
10 And it so transpired that the best data and the one that I
11 relied on were the paste studies submitted by P&G and most
12 of the others, although I reviewed them and commented on
13 them, the vast, vast majority were unsatisfactory.

14 DR. HYMAN: So, any of the powder, rinse or a gel
15 without an abrasive would not fall under the final
16 monograph. That would require an additional six-month
17 clinical trial?

18 DR. BOWEN: That's my opinion, yes.

19 MR. SHERMAN: Thank you.

20 Are you using the term dentifrice to mean the same
21 as the paste?

22 DR. BOWEN: Paste, yes.

23 DR. GENCO: So, the suggestion now is that final
24 formulation testing stannous fluoride dentifrice and the
25 others be eliminated? And that any of the other forms would

1 require the six-month clinical trial?

2 Don or somebody from P&G, did you want to comment
3 to that?

4 MR. WHITE: Don White, Procter & Gamble.

5 Dr. Hyman already made the distinguishing features
6 that we call some toothpaste gel forms but they have
7 abrasives and just so long as a dentifrice is a dentifrice.

8 DR. GENCO: Could cover a gel-like toothpaste with
9 abrasives?

10 MR. WHITE: Yeah, exactly. What we would call a
11 toothpaste.

12 DR. GENCO: Not a gel that you put in a tray.

13 MR. WHITE: Precisely.

14 DR. GENCO: Different formulation.

15 MR. WHITE: Precisely.

16 DR. GENCO: Okay.

17 DR. HYMAN: We needed one clarification also in
18 looking back. This concerned the safety of CPC. There was
19 some discussion about some adverse events that were
20 uncovered in some of the CPC trials. And we needed some
21 assurance that--there was a note that there were actually
22 three deaths involved and some serious adverse events. Yet,
23 there was no conclusion. The statement that we pulled out
24 of the transcripts was, it is not clear to what extent other
25 ingredients in the mouth rinse contributed to these severe

1 adverse events.

2 We wanted to have a conclusion that the CPC was
3 safe, that there was no reason to associate the deaths with
4 that.

5 DR. GENCO: Well, as I read--I reviewed that--as I
6 read the FDA reports of adverse effects there were three
7 deaths. Then there was an updated report that we were just
8 given for this meeting from FDA and also from Procter &
9 Gamble and there were no deaths in those two.

10 So, the feeling was--and I'm bringing this up to
11 see if this is the interpretation--that the deaths were only
12 associated with Cepacol and not with the other formulations.

13 Therefore, it's likely to be something other than
14 Cetylpyridinium Chloride.

15 Am I correct in that interpretation?

16 MR. DOYLE: Based on our decades of testing, we
17 have never encountered anything of the nature you're
18 describing. I'm not sure where that --

19 DR. GENCO: But you would get reports for product,
20 which is not Cepacol?

21 MR. DOYLE: That's right. That's entirely
22 inconsistent with our experience or history.

23 DR. GENCO: The three reports were with Cepacol,
24 am I correct in that?

25 MR. DOYLE: I don't know, I've not reviewed their

1 data.

2 DR. GENCO: It's FDA data. It's the FDA reported
3 three deaths.

4 MR. SHERMAN: We're just looking for some language
5 that explains why this is not a significant --

6 DR. GENCO: Would you like highly unlikely?
7 You're not really concerned about -- I mean we aren't, I
8 don't think.

9 MR. SHERMAN: But when one sees that in the
10 report, it's a flag. We're just trying to -- looking for
11 some language to explain that, in a sense. And that's
12 something we can work on outside of this.

13 DR. GENCO: But while the panel is here, is
14 anybody concerned about that?

15 [No response.]

16 DR. GENCO: So we have to work on the language.
17 Okay, good.

18 DR. HYMAN: I believe Bob Sherman gave out some
19 additional literature about calculus.

20 MR. SHERMAN: Yes, I handed out a definition of
21 calculus and I believe this was discussed early on in the
22 meetings. There seems to be a lengthy definition about
23 calculus and its importance, and yet we need some kind of
24 conclusion as to why we still only consider it a cosmetic
25 type of claim. You know, it appears to be very important,

1 but...

2 DR. GENCO: Is the essential problem that nobody's
3 able to just prevent calculus and not plaque, therefore you
4 can't say that anti-calculus agents don't work because they
5 also prevent plaque. And therefore, because you prevent
6 plaque you prevent gingivitis? Is that the essential
7 conundrum.

8 DR. BOWEN: As I recall the discussion what we
9 were concerned about subgingival calculus which is
10 undoubtedly associated with periodontal disease, as we were
11 primarily concerned with supragingival plaque and there's
12 little association. That doesn't mean there isn't any, but
13 there's little association with calculus and gingivitis.
14 That's why we stayed away from it.

15 DR. GENCO: After reading the statement, do you
16 think there could be some wording that would more strongly
17 put that opinion, this is what you'd like?

18 DR. SAVITT: At that meeting long ago, I remember
19 Max made the point that sterile calculus doesn't seem to
20 have much of an effect. You can put it under the skin and
21 that sort of thing. I think that also entered into the
22 discussion and we were forced into drawing a line somewhere.

23 DR. GENCO: Jerry.

24 MR. McEWEN: I'm Jerry McEwen and I'm with the
25 Cosmetic, Toiletry and Fragrance Association. I think this

1 goes way back and the problem, as I recall, was a way to
2 identify that calculus that might have some relation to the
3 disease state and make certain that we still allowed the
4 cleansing of calculus as a cosmetic claim because the
5 calculus was a visible stain on the teeth, to acknowledge
6 that that can take place and that is a cosmetic claim and
7 not a drug claim. So there was a fairly detailed and long
8 discussion to try to make that distinction so that the panel
9 didn't run afoul of the differences between the definitions
10 of cosmetics and drugs.

11 So that's where some of this problem came in.

12 DR. GENCO: Bob and Fred, your concern is that we
13 go on and on and tell how bad calculus is and then we say
14 well, if you remove it it's only cosmetic. So it's the way
15 it's written and --

16 MR. SHERMAN: Right. There's no conclusion,
17 there's no explanation as to why...

18 MR. CANCRO: I think you touched on the problem to
19 start with. Calcification doesn't need bacteria, you can do
20 it in a test tube. It's strictly a crystallization type of
21 phenomenon, very common with all types of salts, that you
22 can crystallize things and that's what dental calculus is.

23 But the association of bacteria in and around
24 calculus is such that it's difficult to separate the viable
25 entity from the inorganic and hence, in a procedural

1 situation, it's obviously removed because it's in the way to
2 treat the teeth or to treat the gums. But it's strictly an
3 inorganic phenomena. You don't need bacteria to form
4 calculus.

5 Whereas, in the mouth, it's never free of bacteria
6 because they're there all the time and hence you've got
7 viable bacteria, you've got dead bacteria, and you've got
8 the crystallization process continually going on. So I
9 think it's very obvious that you can't prevent the
10 crystallization phenomena and yet you may do nothing to the
11 viable bacteria and hence do nothing to gingivitis.

12 DR. MANDEL: All of these points are well taken
13 but we've wrestled with this for many years and it's very
14 difficult to quantitate this because for one, you have
15 supragingival calculus in fairly specific locations. When
16 you do the scoring, you do the scoring around the lower
17 anterior teeth, for instance, but then you do the gingivitis
18 scoring is a full mouth score.

19 So it's really inappropriate to take what is a
20 limited partial amount of score and try to relate it to a
21 full mouth score. If you actually did it on those teeth
22 that have calculus and you can do that indirectly with a so-
23 called calculus retention index, which then also measures
24 the plaque accumulations on there, then you might find an
25 association with the gingivitis.

1 You could also show an association with gingival
2 recession in the area of the calculus, however the
3 inflammatory process which leads to it is related to the
4 bacteria on the surface of the calculus.

5 So I think to really define it more precisely is
6 very, very difficult. I think, as I was reading the
7 language, although it's lengthy it does fairly reflect the
8 combination of the science and the art at this point. It is
9 not an easy problem to settle out.

10 DR. GENCO: Do you feel that we have handled it
11 reasonably well? That is, we have set an anticalculus
12 effect would not necessarily be an anti-gingivitis effect,
13 therefore anticalculus is a cosmetic claim?

14 DR. MANDEL: At this point, because the
15 anticalculus effect, at least for all practical purposes, is
16 interference with mineralization. It's just a mineral
17 portion of it. That aspect of it, as Lou points out,
18 clearly is not involved, only to a limited extent. The
19 calcified portion, if it has porosity, can retain some
20 antigenic material or toxic material, but that association
21 with disease can be made in the subgingival area. It has
22 never really been made in a supragingival area. Whether
23 it's worth the investment to really go through everything
24 that you would need to do, I don't think people are doing.

25 DR. GENCO: So clarifying this document with

1 supragingival calculus inhibition is not synonymous with
2 antigingivitis effect, therefore it's cosmetic?

3 DR. MANDEL: At this point, I think you don't have
4 an evidential base to go beyond that.

5 DR. GENCO: So somehow this has to reflect that
6 statement. I think this statement is --

7 MR. SHERMAN: Could you repeat that?

8 DR. GENCO: Yes, supragingival calculus inhibition
9 does not necessarily, given our state of knowledge, relate
10 to a reduction of gingivitis. Therefore, we would not
11 consider a supragingival agent that removes it to be an
12 antigingivitis agent necessarily or logically.

13 DR. MANDEL: Or inhibits its growth.

14 DR. GENCO: That's right, inhibits its growth,
15 supragingival calculus growth would not necessarily be an
16 antigingivitis agent. Therefore it wouldn't warrant being a
17 drug claim for an antitartar agent.

18 So you're not recommending that we go back to
19 little strips?

20 DR. MANDEL: No.

21 DR. GENCO: Further comments on the calculus
22 issue? Jerry, are you comfortable with that?

23 MR. McEWEN: Yes.

24 DR. GENCO: You have memory of that that's lost to
25 us. I think you were very active in that discussion, too,

1 appropriately so.

2 MR. SHERMAN: Thank you. That about takes care of
3 business for today. We hope to have a draft copy of the
4 subcommittee report on display in dockets management the
5 first week in November and the next meeting scheduled for
6 December 2nd and 3rd will be spent mostly going over that
7 document in some detail, also depending on whatever public
8 comment we get. Because at that point we need the panel's
9 sign off on the document.

10 DR. GENCO: Thank you, Bob. I'd like to thank the
11 panel members and the guests, especially the consultants
12 brought here. You were very helpful.

13 I'd like to also thank Kathleen for making all
14 these very fine accommodations for us and keeping the
15 temperature reasonably comfortable.

16 A special thanks to Bob Sherman and Fred Hyman. I
17 think you two have gone through that document in some detail
18 to make sure that it represents what our deliberations over
19 these many years have been, and that's not an easy task.
20 Thank you very much.

21 See you in December. Thank you.

22 [Whereupon, at 2:48 p.m., the committee meeting
23 was concluded.]

CERTIFICATE

I, **PAMELA BRIGGLE**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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