FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF

THE DENTAL PLAQUE SUBCOMMITTEE OF

THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

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P R O C E E D I N G S

(8:33 a.m.)

DR. D'AGOSTINO: Because there are no decisions to make, I have been asked to start the meeting.

Again, I'm Ralph D'Agostino from the Nonprescription Drugs Advisory Committee. This is the meeting of the Dental Plaque Subcommittee.

What I would like to do is to have people around table introduce themselves so that the audience can know who they are and where they are, and also the transcriber can make sure that the mikes are working. Lew, why don't you begin.

MR. CANCRO: Lew Cancro, Industry Liaison Representative.

DR. SAVITT: Gene Savitt, periodontist, Boston, Mass.

DR. LISTGARTEN: Max Listgarten, University of Pennsylvania.

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

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

DR. NEAL: Andrea Neal, Executive Secretary to the Nonprescription Drugs Advisory Committee and its Dental Plaque Subcommittee.

DR. SAXE: Stanley Saxe, Professor of Periodontics and Geriatric Dentistry at the University of Kentucky.

DR. BOWEN: Bill Bowen, University of Rochester.

MS. LUMPKINS: Debbie Lumpkins, Division of OTC Drug Products.

MR. SHERMAN: Bob Sherman, CDER Liaison, Division of OTC Drug Products.

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

DR. D'AGOSTINO: I am glad to see the leader here. We just introduced ourselves, but didn't do a single thing beyond that.

DR. GENCO: I'm Bob Genco, from the State University of New York at Buffalo. Good morning.

DR. NEAL: For those of you who aren't aware, before I read the conflict of interest statement, I'd just like to announce that the Dental Plaque Subcommittee has now been transferred from the Center for Devices and Radiologic Health to the Center for Drug Evaluation and Research. That was effective on August 27, which was the day that the charter for the NDAC was renewed.

For our panel members, I have included a copy of the charter in your folders and you might want to read

that just before bedtime.

Now I am going to read the conflict of interest statement.

The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of a conflict.

During the next several years, the subcommittee will review information on ingredients contained in products bearing antiplaque and antiplaque-related claims to determine whether these products are safe and effective and not misbranded for their labeled use.

Since the issues to be discussed by the subcommittee will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products, in accordance with 18 U.S. Code 208(b), waivers have been granted to each member and consultant participating in the subcommittee meeting. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the

participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

Thank you.

DR. GENCO: We'll proceed with the first issue and that is the general combination policy on OTC drug products.

MR. SHERMAN: Excuse me, Bob. I had an announcement before we get started, if that is all right.

DR. GENCO: Sure.

MR. SHERMAN: This is concerning the subcommittee's review of foreign marketing data which will happen tomorrow.

Just as background, FDA's policy has been not to consider foreign marketing experience to determine whether a drug has been marketed to a material extent for a material time. The agency is considering a proposed rule establishing eligibility criteria for defining material extent and material time under which an OTC condition -- and by that we mean an ingredient, a combination of ingredients, indication, dosage form, dosage strength, or

route of administration -- with or without U.S. marketing experience could be considered for inclusion in a monograph system.

In October of 1996, the agency published an advanced notice of proposed rulemaking requesting information and comments regarding these criteria. That proposal is not yet finalized.

It is the agency's intent to take advantage of the subcommittee's expertise to review those data during these meetings. The ingredients, however, would not be classified by the subcommittee.

Data were submitted under the September 19, 1990 call for data with the understanding that they would eventually become publicly available, as is the case with any submission to the OTC rulemaking.

Tomorrow we are simply going to make assignments of those ingredients supported by foreign marketing data and they would not be reviewed until the next meeting at the earliest.

If there is an objection to the public review of data before the eligibility of those data for the monograph system is determined, sponsors may withdraw those data from the review. Sponsors would then be required to petition the agency and show just cause for reopening the administrative record and re-accepting the data.

We do not anticipate any problems with those types of petitions at this time, but we cannot guarantee that they would be accepted. Also the data would probably not be reviewed by the subcommittee. Whether that is a good or a bad thing is a matter of opinion I guess.

If anyone wishes to withdraw a submission before assignments are made tomorrow, you can see me and we can tell you how to do that.

DR. GENCO: Perhaps you could clarify that. You said twice that the data wouldn't be reviewed by the subcommittee, but as individuals are we going to review --

MR. SHERMAN: The data would be reviewed but not voted on.

DR. GENCO: Not voted on, but reviewed.

MR. SHERMAN: Not classified, not put into a category.

DR. GENCO: Thank you.

Does anybody want to get further clarification of that?

(No response.)

DR. GENCO: Thank you.

Now we'll proceed to Warner-Lambert's presentation and I believe it's going to be made by Dr. Barnett. Good morning.

DR. BARNETT: Well, good morning, Mr. Chairman

and members of the Plaque Subcommittee. By way of introduction for the record, my name is Dr. Michael Barnett and I am Senior Director of Dental Affairs in the Worldwide Consumer Healthcare R&D Division of the Warner-Lambert Company.

I am pleased today to have the opportunity to respond to questions raised by this subcommittee at its May 1997 meeting concerning the fixed combination of essential oils in Listerine antiseptic as it relates to the FDA combination drug policy.

Since the last meeting of this subcommittee, we have done a considerable amount of work to respond to questions raised by this subcommittee with regard to the contribution of each of the four essential oils to the activity of the fixed combination, and we will present the results of these additional studies to you today.

As you no doubt recall from previous presentations, the fixed combination we are discussing consists of four essential oils at the following concentrations: thymol, 0.064 percent; menthol, 0.042 percent; eucalyptol, 0.092 percent; and methyl salicylate, 0.060 percent.

In previous presentations to this subcommittee, we have presented unequivocal evidence, consisting principally of eight 6-month clinical trials, that the

fixed combination of essential oils consistently provides statistically significant reductions in plaque and gingivitis.

At the May meeting of this subcommittee, we presented the additional analyses of the 6-month study results which you had requested for all antiplaque/antigingivitis ingredients in order to demonstrate the clinical relevance of data presented.

These additional analyses looked at clinical study results from both a site- and a patient-centered standpoint. They included the percentage of individual sites improving, the percentage of subjects improving as well as the degree of improvement, a comparison of the degree of improvement obtained through the use of the fixed combination with the degree of improvement obtained through the use of other accepted oral hygiene practices, and a computation of odds ratios and confidence intervals for each individual study and pooled across all studies to further establish the clinical relevance of study results.

These additional analyses were conducted for plaque, gingival, and bleeding indices and provided clear confirmation that the fixed combination of essential oils produces a clinically relevant improvement in plaque and gingivitis for a significant proportion of the target population.

Moreover, at the last meeting of this subcommittee, Dr. Saxe reviewed the safety of each of the essential oils and of the complete formulation and concluded that each of the oils is safe for its intended use as is the complete formulation.

Having concluded its discussion of safety and effectiveness for the fixed combination at the last meeting, this subcommittee identified one remaining issue to be resolved prior to a vote; that is, it requested a demonstration that the fixed combination of essential oils conforms to the FDA's general combination policy on OTC drug products.

For those who might not have been present on the second day of the May meeting, we heard at that time a rather extensive discussion by Peter Hutt in which he presented the history of the development of a combination drug policy and an explanation of the general policy and associated guidelines. It is probably not necessary for us to reiterate all this today, so I intend just to present some of the highlights to help focus the subsequent presentation and discussion of data. However, I should point out that Peter is with us this morning and would be pleased to respond to any questions that may arise that he could respond to.

We have -- and I believe in the handout from

the FDA -- provided the complete text of the overall policy and associated guidelines for reference.

The overall policy applicable to the fixed combination of essential oils is the FDA's general combination policy on OTC drug products which states: "An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect; when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population."

The FDA also developed more specific guidelines to guide the application of the more general policy. These are contained in six paragraphs. Of these paragraphs, 3, 5, and 6 are especially relevant to the fixed combination of essential oils which contains active ingredients all having the same mechanism of action.

Paragraph 3 contains the requirement that the combination provides some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance or quality of formulation.

Paragraph 5 recognizes that an ingredient may be appropriate for use only in a specific combination or that data may be available only to support the use of the ingredient in combination.

Paragraphs 5 and 6 then go on to indicate that in such cases only the specific combinations of active ingredients will be listed in the monograph and permitted to be marketed.

It is important to note that FDA has already conducted an extensive review of this fixed combination of the four essential oils when it developed the tentative final monograph for first aid antiseptics. The results of this review were published in the Federal Register issue of July 22, 1991.

FDA concluded that the combination had, in fact, satisfied the conditions of its combination drug policy and therefore that the fixed combination "may appropriately be included in the amended tentative final monograph as Category I for first aid antiseptic use."

FDA specifically cited paragraphs 3, and 5 of the General Guidelines for OTC Drug Combination Products in support of its decision. Additionally, the FDA review referred to the phenol coefficients for each of the four essential oils in the fixed combination. These coefficients are a standard indicator of antimicrobial

effectiveness and showed that each of the four components of the fixed combination has greater antimicrobial activity than does phenol. Thus, each of the four components clearly possesses antimicrobial activity in its own right.

It is noteworthy that the FDA's determination that each of the essential oils contributes to the total efficacy of the complete formulation was based on an in vitro microbiological study which was described to this subcommittee at its last meeting by Dr. Vincent. In this study, the antimicrobial effectiveness of the total formulation, as well as that of the four separate minus-one formulations, were assessed using cultures of Staphylococcus aureus. These minus-one formulations each lacked one of the essential oils in the fixed combination but contained the remaining three essential oils.

In order to enhance the sensitivity of this assay for the purpose of demonstrating the contribution of each essential oil, all the test formulations were diluted with sterile distilled water to 40 percent of their original concentration. Following a 1-minute exposure, aliquots were diluted, plated in triplicate, and colonies were counted after 24 hours' aerobic incubation at 37 degrees Centigrade.

The levels of bacteria surviving after treatment are presented on this slide.

When data from this study were presented at the last meeting, the question arose as to whether the reductions produced by each of the minus-one formulations were statistically significantly different from that produced by the complete formulation which contained the fixed combination of all four essential oils.

Unfortunately, the information was not at hand at that time of our presentation. We reviewed the report which had been previously submitted to FDA and determined that in fact all the minus-one formulations were statistically significantly different from the total formulation.

These data presented on this slide clearly demonstrate that all four oils are necessary to achieve the activity of the complete formulation, and therefore each of the four oils contributes to the antiseptic efficacy of the total formulation.

In summary then, the precedent set for the fixed combination of Listerine ingredients by FDA in the first aid antiseptic monograph was to establish the effectiveness of the total formulation through both in vivo and in vitro studies and to make the determination that each of the four active ingredients contributes to the activity of the total formulation on the basis of an in vitro antimicrobial study.

It is interesting to note that this precedent was somewhat reflected in this subcommittee's discussion at the May meeting, during the course of which one member suggested that a combination with "obvious clinical efficacy and obvious overwhelming in vitro information" would produce a higher comfort level than one with borderline in vitro studies. And later another member agreed that an in vitro minus-one study, using representative plaque microorganisms, could constitute "overwhelming, or incontrovertible, or very persuasive data."

As a result of this discussion, we have conducted additional studies using the minus-one study design. We have included in the new studies five oral microorganisms selected because they are representative of Gram-positive and Gram-negative bacteria, as well as a number of bacterial morphotypes, and additionally, because they have been implicated in supragingival plaque or gingivitis and were common isolates from supragingival plaque in our long-term plaque/gingivitis clinical trials. These bacteria are: Prevotella intermedia, Fusobacterium nucleatum, Actinomyces viscosus, Streptococcus sanguis, and Veillonella parvula.

The results of these additional studies using oral microorganisms are presented on this and the

subsequent four slides. As you will see, these study results are consistent with those of the previous study using Staph. aureus and clearly demonstrate that all four essential oils are required for the effectiveness of the fixed combination.

This slide presents the data for Prevotella intermedia, a Gram-negative anaerobic rod. Note that the formulation containing the complete fixed combination, that is, Listerine, had only 1.2 times 10 to the power of 2 surviving bacteria. This represents an approximately 100 to 1,000 times greater bacterial kill than was produced by any of the four minus-one formulations.

For example, the most next effective formulation, which contained thymol, menthol, and methyl salicylate, had 6.3 times 10 to the power of 4 surviving bacteria. Each of the minus-one formulations was statistically significantly different from Listerine at a high level of significance, that is, with a p value of equal to or less than 0.001.

These findings indicate that the removal of any of the four essential oils will significantly reduce the effectiveness of the original complete fixed combination and therefore clearly indicate that each of the four oils makes a meaningful contribution to the activity of the fixed combination.

The results for Fusobacterium nucleatum are presented on this slide. This organism is a Gram-negative anaerobic fusiform bacillus. Note that here again the p values for the comparisons of the minus-one formulations to Listerine are all equal to or less than 0.001, indicating that each of the minus-one formulations was statistically significantly less effective than the complete formulation.

The results with Streptococcus sanguis, a Gram-positive facultative anaerobic coccus, are presented here. In the case of this organism as well, all the minus-one formulations were statistically significantly different from the total formulation at a p value of less than 0.001.

This slide presents the results obtained with Veillonella parvula, a Gram-negative anaerobic coccus. In the case of this organism, while the complete formulation produced a statistically significant reduction compared to only one of the minus-one formulations, it nevertheless produced numerically greater reductions than did the remaining three minus-one formulations. These reductions were numerically similar to those seen in the case of Actinomyces viscosus which were statistically significant, and we will present those Actinomyces results next.

We believe that the Veillonella data are consistent with those obtained with the other organisms insofar as the failure to achieve statistical significance

in the case of Veillonella is likely a result of the greater variability typically experienced in working with this microorganism.

The Actinomyces viscosus results presented on this slide follow the same pattern seen with the previous organisms. This organism is a Gram-positive microaerophilic filament. The complete formulation produced reductions compared to the minus-one formulations which were all statistically significantly different, again supporting the need for all four oils.

We believe that the extensive body of data showing that the fixed combination has significant antimicrobial activity against a wide variety of oral microorganisms in combination with the body of data presented today demonstrating almost uniformly statistically significant differences in bactericidal activity between minus-one formulations and the fixed combination, constitute the "overwhelming in vitro information" alluded to at the May meeting of this subcommittee.

When these antimicrobial data are considered in conjunction with the extensive body of clinical data clearly demonstrating the safety and effectiveness of the fixed combination, the totality of the data is consistent with the precedent established by FDA in placing the fixed

combination of essential oils in Category I in an earlier tentative final monograph.

It is important to emphasize that in presenting the totality of our clinical and laboratory data, we are maintaining the position consistent with paragraphs 5 and 6 of the combination policy guidelines that the four essential oils at the stated levels should be placed in Category I not as single ingredients, but rather in the specific combination and concentrations used in all our clinical and laboratory studies.

The rationale for using these oils in combination was in fact expressed quite well by Dr. Wu at the May meeting of this subcommittee when she pointed out that these oils need to be combined insofar as, when used individually, they may not be as highly bactericidal as they would be in combination.

In summary then, we have today presented the results of additional studies conducted in response to questions raised by the subcommittee at its last meeting. On the basis of data generated by these studies, as well as data previously reviewed by this subcommittee and FDA, we believe that the fixed combination of four essential oils has been unequivocally shown to conform to the requirements of the FDA's General Combination Policy on OTC Drug Products.

Each of the active ingredients has been clearly shown to contribute to the activity of the complete fixed combination. Combining the ingredients does not result in a decrease of safety or effectiveness of any of the individual ingredients, and the fixed combination has been shown to be safe and to provide significant clinical effectiveness for a significant proportion of the target population.

And perhaps most importantly, it has already been determined by FDA itself, in developing a previous tentative final monograph, that this fixed combination of essential oils satisfies both its general guidelines and the specific guidelines relevant to this combination.

I would like to thank the subcommittee for its attention, and I or my colleagues would be pleased to answer any questions you might have.

DR. GENCO: Thank you very much, Dr. Barnett.

Are there any questions from the panel? Max and then Christine.

DR. LISTGARTEN: Could you clarify one more time how the minus-one solutions were formulated? In other words, how did you adjust the remaining three concentrations?

DR. BARNETT: The concentrations, the remaining three, Max, were the same concentrations as found in the

fixed combination.

DR. LISTGARTEN: So, you still had exactly the same percentages of each one.

MR. CANCRO: Correct.

DR. LISTGARTEN: Okay.

DR. GENCO: Christine?

DR. WU: In the data you presented on the tables regarding bacteria surviving treatment, I do not see any vehicle control. If I look at the booklet you provided us, on page 7, bacteria surviving treatment with Actinomyces viscosus and Strep. sanguis, you look at the vehicle control for Actinomyces viscosus, it is 4.2 times 10 to the 3. It is less than Listerine itself. If you look for the sanguis data, you get also some kind of kill just by the vehicle control.

Do you have any explanation for that?

DR. BARNETT: If you looked at a couple of the typical ones, Christine, it seems to me it was Fusobacterium for a Gram-negative, and was it the Strep. sanguis? These were in fact -- yes, they were all directionally different from the vehicle, with three of the four statistically significantly different from the vehicle, so that these combinations of three did in fact have considerable antimicrobial activity compared to the vehicle control.

That wasn't true of every one of them, and I think we need to recognize that these are done under dilution as well.

But this is the Fusobacterium, and in this case, again three of the four were statistically different from the vehicle and all four were clearly directionally different from the vehicle.

DR. WU: I'm looking at the data with AV and Strep. sanguis.

DR. BARNETT: Yes. I think what you are looking at is essentially reflective of the fact that different organisms have different susceptibilities to these oils. You have to recognize that if they were all used undiluted, they would kill everything.

DR. GENCO: Finished? Further questions, comments? Bill?

DR. BOWEN: I notice that you did have a vehicle control. Can you tell us, Mike, how many microorganisms were in each culture to begin with and the age of the culture, when the tests were carried out?

DR. BARNETT: Yes, I can't. But I'm going to have to ask Pauline Pan, our microbiologist, who did these to answer that. Pauline?

DR. BOWEN: The number of microorganisms in the culture to begin with and the age of the culture when the

tests were carried out.

DR. PAN: The cultures that Mike alluded to were grown under standard conditions well accepted by the industry. These were all log cultures.

The exact number, in order to perform these in as standard a way as possible, the transmission of all these cultures were adjusted to 1 percent transmission. We did this for a purpose. For the majority of these -- I believe four out of five -- I will check my notes -- a log culture, overnight culture, of these organisms is very close to 1 percent transmission. So, we had minimal adjustment to get them all to the same OD, recognizing that 1 percent may represent not the exact same CFU for each strain, but nonetheless we felt that we had some standardization and meaning to this model.

DR. GENCO: Dr. Bowen?

DR. BOWEN: I think also in the interest of completeness, it would be wise to include the strain numbers that you used.

I have one other comment. I don't think I would be too concerned about, for the want of a better term, the relative lack of effect on Veillonella. I would regard, from a caries point of view, Veillonella among the good guys because it does metabolize lactate out of the plaque.

DR. BARNETT: Bill, if you want, we can provide the strains now or after. I have them here.

DR. BOWEN: Afterwards.

DR. BARNETT: We have that information.

DR. GENCO: Further comments, questions from the panel? Fred?

DR. HYMAN: Whenever I see data that I view as surrogate markers, I tend to have questions. I guess my question here is would the data that has been presented now, although supportive of antimicrobial -- how do you relate that to the antiplaque/antigingivitis claim?

DR. BARNETT: Yes. Fred, first of all, I think it's critical to keep this in perspective and that is that the antiplaque/antigingivitis effectiveness of the complete formulation has been I think unquestionably demonstrated.

So, then the question is how best to demonstrate the contribution of each of the four oils.

If we go back to what is now considered a classical study, which is a study published by Harold Lowe -- or as Stan says Harold Lowe. He does it much better than I with the umlaut -- who published the experimental gingivitis model, there was a clear correlation between the formation of plaque and the development of gingivitis. The mechanism by which this combination works in situ is basically through bacterial kill. So, we believe that an

in vitro model which has the requisite sensitivity to demonstrate the contribution, whose endpoint is bacterial kills, has a relationship to what's going on in the mouth.

DR. GENCO: A follow-up. Is there any evidence of anti-inflammatory effects of any of these oils?

DR. BARNETT: Not to my knowledge, Bob. In all cases, the gingivitis reductions were accompanied by significant plaque reductions of considerable magnitude. I am not aware of any evidence, particularly at the levels and the exposures found with use of this combination, that there would be an anti-inflammatory effect.

DR. GENCO: I'd like to ask a couple of questions. In paragraph 5 of the FDA General Combination Policy, we are asked to talk about what range of concentration -- for example, how do you know that the fixed combination you talk about is absolutely necessary? Could you double or halve the concentration of any one of the oils and get the same effect? Do you have any information on the range of effective doses in the combination for each of the reactants?

DR. BARNETT: Well, don't forget that this combination was developed some time ago, and it was based on a number of considerations, only one of which was effectiveness. I think I pointed out last time that the active ingredients also contribute to the flavor and

thereby there is this patient or subject acceptance aspect to it as well.

So, I guess the answer is it's an established combination. It's developed on the basis of both effectiveness and patient acceptability. Therefore, I think the obligation is just to show that the levels as present in the combination contribute.

DR. GENCO: What is the opinion with the FDA with respect to that? In other words, if it gets in the monograph and somebody else could make a combination, are they justified? Is it safe? Is it reasonable to make a combination with different concentrations?

DR. KATZ: It would basically depend upon how one determined what the combination should be. If one takes it as a general broad category, then not necessarily, but if one is saying specifically that it's effective at this combination with the particular ingredients, then that's the way it would need to be made.

DR. GENCO: And that's all the data we have.

DR. KATZ: That would basically be it. That's right.

DR. BARNETT: That in fact, Bob, was the precedent in the previous monograph where it was accepted, the fixed combinations.

DR. GENCO: So, based on the present data, the

fixed combination, if it is approved to be in the monograph as Category I, is all that can be said.

DR. BARNETT: That's correct.

DR. GENCO: It can't be said that other combinations of concentrations of the same four would be as effective.

DR. KATZ: That's correct.

DR. BARNETT: Yes.

DR. GENCO: Second question then. Michael, could you give us the reasoning that all four are necessary? In other words, can you have a combination of two or three and be as effective? You have done the minus-one, but what about combinations of minus-two, minus-three?

DR. BARNETT: I think we've demonstrated that, Bob, because you take any single one out, you lose a significant amount of effectiveness.

DR. GENCO: But do you lose effectiveness? In other words, what if you removed two?

DR. BARNETT: I don't understand. In the sense the question that is being asked is, how do you know that each one contributes? I think that the studies where you actually take one out in order and show that any one removed will significantly reduce the effectiveness --

DR. GENCO: Significantly reduce. I think that is the issue there. Is it really -- yes, there is a

statistically significant difference removing one, but does it make any difference clinically? Maybe you can remove two and still have the same clinical effect.

I guess I'm getting to the other issue here, the necessity for all four.

DR. BARNETT: Well, if the clinical effectiveness is based on the effectiveness of the complete formulation and you start removing things and you know that it's significantly less effective antimicrobially, I think you would anticipate that the clinical effectiveness would be thereby reduced as well.

DR. GENCO: Max?

DR. LISTGARTEN: I think perhaps we're off base in pursuing this line of thinking because the four ingredients contribute to the taste and a number of other things. One could argue that if one had 100 percent thymol, it would probably work better than all four put together. I don't think that's the intent of the regulation. I think we have to show that in that particular combination each one contributes something. It seems to me that this has been demonstrated. By starting to play with the formula, you are essentially getting away from the combination that is currently being marketed.

DR. GENCO: I understand that, but I just don't understand if this goes in the monograph, then that

particular concentration is all that's being discussed and somebody can't come along and put two together --

DR. BARNETT: That's exactly the point, Bob.

DR. KATZ: That's exactly correct.

DR. GENCO: Okay.

DR. KATZ: If they want to go ahead and make something with a combination of two of those, they would have to go back and either study it or come back in some way and petition for the monograph.

DR. GENCO: Okay, I just wanted to make sure of that.

DR. D'AGOSTINO: I think that in other arenas where you're dealing with different drugs, there is concern that why would you load up a formulation with three or four drugs of the same category. I sense that there's something quite different here, though, with these essential oils, that it's not the same thing that you're giving a double dose, a triple dose, a quadruple drug dose by loading up more and more of the same category.

So, I guess I'm not overwhelmed by the surrogate aspect of it. You drop something down. Is it going to change the clinical effectiveness? I don't know. Unless you do a clinical trial, you're not going to know that.

But I think that there's something sensible

about the minus-one, and I don't know where you'll go with the minus-two and single ingredients. You'll probably still get some kill and what have you that will relate clinically, but is the combination sensible, acceptable, and do you see something different as you move one is probably a reasonable way of looking at this.

But I do understand what Bob is saying, though, that if these were four active drugs, why are we putting four in the same formulation.

DR. GENCO: Further comments, questions? Bill?

DR. BOWEN: Well, they're not all four equally active. You can see from the data here that some microorganisms are more sensitive to one than they are to others.

I think also a point that we've perhaps forgotten, that in the combination policy, the formulation can be altered to make the product more acceptable, which is also one of the conditions that's in there and which Mike also alluded to.

DR. GENCO: Okay. Further comments, discussions of this presentation?

DR. WU: Just a comment. I wish that we could have gotten these data earlier, not today, so we have some time to read.

DR. GENCO: Yes, Lew?

MR. CANCRO: Yes, Bob. I wanted to really ask a question of Linda, if that would be appropriate.

DR. GENCO: Sure.

MR. CANCRO: It's my understanding that this system which we are describing as a combination, should it be proposed as effective, will go into the monograph as a single entity. It will not go in as a combination of two pharmacological agents from the same class, but rather as a defined system. Is that the correct interpretation of this? In other words, this is a single entity and that's the way it's going to go into the monograph should it be accepted as Category I.

DR. KATZ: It would go in as a combination but as a specific fixed combination, so that in other words, it would not be a broad categorization in that you can mix and match. It would go in as a fixed combination as it's defined.

MR. CANCRO: And henceforth, whenever it's used, that's the ratio in which it must be use and that's the conditions under which it has shown clinical effectiveness.

DR. KATZ: That would be correct.

MR. CANCRO: So, the relevance to this is that the history of this has always been in that ratio. That's why it's being reviewed here today and should anybody want

to change that ratio or leave materials out, that's a new issue. Either by amendment or a new drug or whatever, that becomes a very different issue than the one we're looking at today.

DR. KATZ: That's correct except that you have to remember that in determining whether or not that combination should be allowed, that is part of your panel discussion that the panel needs to come to grips with. Is this combination effective and safe given the combination policy, and is this something that you want to have present in the format that currently exists?

If in fact one decides that, given the current formulation, that there are questions and that this might not be an optimal combination, then that determination also needs to be made. But if one determines that it is safe and effective in that combination, then it would go in as a fixed combination.

MR. CANCRO: And that's really the basis upon which this panel will vote, the clinical effectiveness of that fixed ratio. Is that correct?

DR. KATZ: That's correct, unless of course the panel decides to vote otherwise, but that's basically it.

DR. GENCO: You brought up another issue and that is optimal. How do we know this is optimal? Maybe Mike has some information.

DR. BARNETT: Bob, this is the product that has been marketed for eons, and the clinical studies I think have shown very clearly that it has a considerable effectiveness against both plaque and gingivitis, perhaps more so than most other products. So, I think it's effective.

DR. GENCO: Maybe you could expand on the concept of optimal? Unless you've shown it. Maybe you could get double the effect if you alter the concentrations a bit.

DR. BARNETT: Well, let's get back again to some of the points that were made in terms of acceptability, all these other issues. Here's a product that while not everybody may be overjoyed with the taste, most people accept the taste and are willing to use it, and it's an effective product.

One can begin to tinker with things, but if it tastes such that nobody will use it, then it becomes an unacceptable product irrespective of how better it may or may not be with respect to plaque and gingivitis.

So, I think in terms of what makes a good product, an effective product, in a consumer arena, it has to be both effective and acceptable. And I think that's the product we have. It has been the product that has been marketed and that's the product for which data has been

submitted and is under review.

DR. GENCO: Let me put that question another way. Is there a requirement that this be the optimal formulation for us to approve it?

DR. KATZ: No. What the requirement basically is, is that the product itself is safe, it's effective, it's acceptable for the target population.

Now, if there are concerns that there may be something about the combination itself may not be safe or that there may be something that you're concerned about with the combination, then when I said optimal, I meant optimal in that sense, that if you have concerns about the ingredients or its safety in the combination that's being proposed, then it may not be an optimal combination as opposed to that someone has to go back and prove that a different ratio might be better than what the ratio currently exists.

DR. GENCO: Okay, thank you for explaining that.

Max?

DR. LISTGARTEN: Yes. I just wanted to bounce off my interpretation of this, and that is that assuming that this is effective and safe, nothing prevents someone from going out there and coming up with a different proportion of ingredients that's safer and more effective

and more acceptable, except that since the numbers will be changed, they will have to repeat the clinical trials. But the product as it currently exists may in fact meet the requirements for safety and effectiveness. It may not necessarily be the optimal combination in terms of either safety, effectiveness, or patient acceptance.

DR. SAVITT: Mike, a brief question and something that a lot of people have asked and we haven't quite gotten an answer yet. Have you tried other combinations that aren't awful tasting, just for the record just so we know one way or the other? It has been asked several times, and if you haven't, you haven't but we're all curious.

DR. BARNETT: Yes. No. This is the product that has been marketed for, lo, these many years. In fact, if one were to now start with different combinations, you no longer meet the material time and extent requirements. So, it would be folly to do this. This is the combination that we studied, that's been on the market, and that's been up for discussion here at this panel.

DR. GENCO: Bill?

DR. BOWEN: I want to pursue from the almost ad nauseam this fixed combination. How fixed is fixed? Is there any variation allowed at all, or it has to be these exact numbers?

DR. KATZ: As far as I know, it has to be these exact numbers. Fixed is fixed.

DR. BOWEN: Thank you.

DR. GENCO: Stanley, did you have a question?

DR. SAXE: Just a comment. I think what we're talking about is the fact that when we're referring to the FDA's general combination policy, that paragraph that's under 21 CFR 330.10 -- and in there it says, when each active ingredient makes a contribution to the claimed effect -- it seems as if perhaps this policy came about when there were individual agents which were tested and found to be effective and then people came together and took two or three of these known effective agents and then put them together. And one comes up with this general combination policy. Each one has to be effective. Each one has to contribute, et cetera, et cetera.

Here, in looking at this product, Listerine, it's, if I may say with due respect to Dr. Barnett and Warner-Lambert, kind of a folk remedy in a sense. It has been around for a century or more and it has evolved. What we have done is taken this product which has been a combination and looked at it as a combination with its particular four essential oils, and now we're trying to apply the general combination policy. Instead of individual agents which have been shown to be safe and

effective and putting them together, for which I believe this combination policy probably was devised, we're looking at a product which has been together for a century and now we're trying to look at the individual components. And it's difficult to do in that way, and that's why I think this is a kind of a unique situation looking at this one particular product.

We're asking to break down, in order to look at each one of the essential oils independently and do clinical trials would be -- I don't know if it would be really in all of our best interests.

So, I say that this is a unique situation with this combination policy.

DR. GENCO: Further comments, discussion?

(No response.)

DR. GENCO: I think, Dr. Barnett, you allowed us to also have some discussion of the combination policy, as well as your product. So, thank you very much.

DR. BARNETT: Thanks, Bob.

DR. GENCO: Next we'll have a presentation from the Nonprescription Drug Manufacturers Association. It looks like Dr. Soller will make that presentation.

DR. SOLLER: Thank you, Mr. Chairman, members of the committee. My name is Dr. Bill Soller. I'm Senior Vice President and Director of Science and Technology for

the Nonprescription Drug Manufacturers Association, a 116-year old trade organization representing the manufacturers and distributors of nonprescription medicines. By sales, our members represent over 95 percent of the OTC marketplace.

I'm here on behalf of the NDMA and CTFA Joint Oral Care Task Group, and as you know, the Cosmetic, Toiletry, and Fragrance Association is the 300-member national trade organization for personal care products and represents the vast majority of those products.

We have presented before you on a number of occasions, and today we have two areas of discussion that we'd like to engage in. One are comments on the combination policy, and secondly comments on key aspects of labeling that we'd like to get into.

The blue folder that you have in front of you is our submission to the panel and just looking at the index, we have brief position statements that we'd like to enter into the docket on the combination policy and on labeling found in sections 1 and 3. In the overheads themselves that I'll be running through sequentially will be section 2 and section 4. Dr. Genco, if possible, I think we have enough time to stop at the end of 2 just to ask for clarifying questions on the combination and then proceed directly thereafter on the labeling, if that's all

right.

As we go on, I'm happy also to take clarifying questions that you might have.

So, if we start at section 2 on the combination policy, we'd like to cover several areas. First, review very briefly -- I know Mike has gone into this just a moment ago -- the combination policy itself in 330.10, an overview of the types of combinations in the OTC review, some examples in the review itself, and then our recommendations for this particular category within the OTC review.

So, an OTC drug may combine two or more safe and effective active ingredients that may be generally recognized as safe and effective with three provisos: that each active makes a contribution to the claimed effect; when combining, the actives do not decrease the safety and effectiveness of any of the individual actives; and when combining, that it provides rational concurrent therapy. And there is an attendant guideline that was referenced in the preceding presentation that includes a number of different types of categories and we'll get into some of them in the discussion.

This is a longstanding, established OTC policy. It's supported by the companion guidelines that were given to you prior to this meeting. It's supported by previous

OTC advisory panels, and it's supported by the inclusion of many different types of combinations in virtually all of the OTC rulemakings attendant to the OTC review.

Here are some examples, cough/cold, internal allergies, sunburn, topical ophthalmics, just to pick a few. Looking at in the cough/cold area, ingredients from four different pharmacologic categories can be combined into a four-way cough/cold product like Comtrex, for example.

Internal analgesics. Two internal analgesics, aspirin, acetaminophen, plus an analgesic adjuvant like caffeine, Excedrin, Category I combination.

Sunburn category for the prevention of sunburn. Three sunscreens or a sunscreen and skin protectant.

And perhaps the topical ophthalmic has the greatest variety. It includes different pharmacologic categories, as in the case of an astringent and a vasoconstrictor, or including ingredients from the same category, demulsants or emollients, and then variety of combinations therein, just to give you an example of some of the things that you see in the OTC review.

So, there's precedent for many types of combinations in the OTC review per FDA's longstanding policy, again, that the actives contribute to the claimed effect, that by combining, we don't reduce the activity of

the actives, and the combination provides rational concurrent therapy.

So, looking at our recommendations -- and I will focus on the top three in a little bit more detail, but will also mention D and E -- we would recommend antiplaque/antigingivitis agents be recommended for combination with anticaries agents, antiplaque/antigingivitis agents with tooth desensitizing agents, and in the three-way combination of antiplaque, antiplaque, plus anticaries agents and tooth desensitizing agents. And then combinations of antiplaque, antigingivitis, active ingredients may also be found to be appropriate and provide rational concurrent therapy.

Looking at the first, this is our rationale basically, and we provide some of the published studies that support this construct and thinking, that caries and gingivitis are distinct pathological entities. They affect different structures within the oral cavity. Caries and gingivitis can be treated with different active ingredients, and consumers are vulnerable to caries and gingivitis through a large portion of their lifetimes.

So, we would conclude that concomitant self-care prevention and treatment of caries and gingivitis represents rational OTC therapy.

The second general area of combinations relates

to the antiplaque, antigingivitis, plus tooth desensitizing agents. Depending upon which studies you look at, the prevalence of dentinal hypersensitivity ranges from 8 to 30 percent. Even at the low range, that's a considerable number of consumers, most frequently in adults 20 to 30 years of age, usually the facial surfaces, the canines and premolars. Stimuli like toothbrushing, digital probing, hot/cold, acids, and sweets causes extreme pain in this particular pain syndrome, clinically not always associated with tissue damage, but authors in the published literature do state that this is, when seen, a potential for damage. Up to 68 percent of hypersensitive teeth have been reported to have significant gingival recession. Usually this is a chronic condition with acute episodes.

So, by way of rationale, considering the Category I labeling for OTC tooth desensitizing agents is a four-week duration of use in order to allow the individual to have enough time to get in to see a health professional, a dentist, the proposed combination would allow continued antigingivitis/antiplaque treatment during episodes of dentinal hypersensitivity.

The third area is the antiplaque, antigingivitis, plus anticaries, plus tooth desensitizing agents as what we think is a rational combination. The rationale is very similar to what I've just presented for

the other two, and that is the proposed combination allows continued antigingivitis, antiplaque, and anticaries treatment during episodes of dentinal hypersensitivity.

Now, it may also be appropriate to combine antiplaque/antigingivitis agents. We think that such combinations should be reviewed for safety and effectiveness by the subcommittee and/or FDA, should be determined to be GRAS/GRAE, generally recognized as safe and effective by FDA, and be listed in the monographs.

Before closing, I had one additional area of combinations. It says, other rational combinations. By that we mean with support of the OTC combination policy by the panel. We think that provides the appropriate support for the addition of future combinations through monograph amendment.

So, by way of summary, we would recommend that the Plaque Subcommittee support FDA's policy on combination OTC products, as many other panels have done, and we provide these recommendations that I've just gone through as what we think are appropriate combinations that provide rational concurrent therapy.

What I'd like to do is just stop at this point and entertain any questions that you might have before going on. Dr. Genco?

DR. GENCO: Yes. Thank you very much, Dr.

Soller.

Are you recommending that we consider reviewing tooth desensitizing agents? I know the anticaries agents have been reviewed and they're in a monograph. What about the tooth desensitizing agents?

DR. SOLLER: Those have been reviewed as well. I'm not recommending that you review them per se, allow that to be another panel, another rulemaking, and consider that, as with other OTC rulemakings, that there can be combinations across monographs.

DR. GENCO: So, what you're suggesting is that somehow we address the issue of labeling, let's say, of a Category I antiplaque/antigingivitis agent, that we've discussed and recommended to the FDA be Category I, that it can be combined with an approved, with the proper terminology, anticaries agent or an approved tooth desensitizing agent, or both.

DR. SOLLER: That's correct.

DR. GENCO: So, that's the area where we would address it in the labeling.

DR. SOLLER: That's correct.

DR. GENCO: Thank you.

Yes.

DR. LISTGARTEN: How do we know that these three active agents, one which is active against

gingivitis, antiplaque, the other one which is active against caries, the third one which is active against hypersensitive teeth, that by combining them we are not detracting from the effectiveness of any one of these?

DR. SOLLER: That is a question that might well be addressed in other areas of the agenda that you have.

The experience that companies have I think is what ought to be brought to bear. As there would be a consideration of a particular combination, at least as we have understood this through discussions in our task group, they don't appear to be interacting with the antiplaque/antigingivitis agents. So, that combination of an anticaries agent, for example, with CPC does not apparently affect the activity.

DR. LISTGARTEN: Offhand I don't see any problems with the ones you suggest, but it occurred to me that if one wanted to make an antitartar claim and also provide fluoride to prevent caries, that we could run into a potential problem with one leaching the fluoride out while the other one is trying to put the fluoride in. So, I don't know if Bill has any reservations about that.

DR. GENCO: Bill?

DR. BOWEN: Well, conceptually how could one oppose this? But I do have serious problems with how they're going to reviewed.

Several years ago when chlorhexidine first appeared, a clinical study was started, for example, in Denmark with chlorhexidine included in the toothpaste, and after the study had gone on for about 18 months, it had been found that the formulation had inactivated the chlorhexidine. So, I get a little concerned when things like that happen.

Max has also raised the point about tartar control and caries. One can make the hypothetical argument at least that zinc, for example, which is now in a large number of antiplaque products, one of it's postulated mechanisms of action is that it inhibits urease, and one can make the case that urease helps to prevent caries. You can also hypothesize, as Max has suggested, that zinc can prevent remineralization, and similarly with some of the pyrophosphate products.

So, I think that one cannot blindly assume that because caries and periodontal disease, as you correctly point out, are separate pathogenic processes, that agents that prevent one or the other are necessarily compatible with each other. I think it's a huge problem we're going to have to face.

DR. SOLLER: Well, I think it's important to separate these issues as we are presenting to the panel today for your consideration that you grapple with the

concept of a rational concurrent therapy separate from what might be testing of the formulations. So, what we are presenting is hopefully getting your recognition that combinations such as these do represent rational concurrent therapies when, per the combination policy, that you do have combinations that are appropriate and can be used safely and effectively by the consumer.

DR. GENCO: I'd like to proceed to do just that. Tomorrow morning we're going to discuss final formulation testing, and maybe with this insight we can proceed to discuss beyond the Procter & Gamble report how a final formulation for each one of these may be evaluated.

DR. SOLLER: I think that's fair.

What we were trying to do, as I say, in this particular presentation was raise your awareness as to the types of combinations that might occur across monographs.

DR. GENCO: Lew.

MR. CANCRO: Yes, I think that's quite correct, Bob, that that discussion you're going to have. But the point that I wanted to make was that independent of the number of pharmacological classes that you combine, the responsibility will always be to show that for each of the ingredients from each of the classes that that ingredient meets the monograph condition by whatever is defined. And you've yet to define that for this group of agents. It has

been defined for fluoride, of course, and for the desensitizing.

So, in combining an antiplaque or antiplaque/antigingivitis agent with any of the other two previously defined pharmacological classes and ingredients, then you have assurance that those two aren't impaired, at least by their monograph conditions.

DR. GENCO: Thank you.

Proceed.

DR. SOLLER: Thank you.

I'd like to get into the second portion of our discussion, and that has to do with OTC labeling and some points that we think might be worth considering at this point, this juncture in your discussions of this category.

The particular areas that we will touch on -- I've just hesitated. I've found the right side of the pointer here -- include the statement of identity, the indications, and the warnings.

Now, I think that just looking back at the panel meetings that this group has had, that there has been enough discussion, enough dialogue back and forth and learnings on both of our parts such that we think we've come up with some worthwhile things to consider relative to these elements of labeling. It's extremely important that these be given attention at some point because your

scientific decisions ultimately have to be translated into labeling for safe and effective use of these products by the consumer, and the things that I'll be getting into relate back in part to the combination policy issues that we were talking about earlier, but they also relate obviously to the single-ingredient products that you'll be looking at.

So, I'll start with statement of identity, talking about the regulatory requirement for all OTC products under the OTC review, the examples in the oral care category that exists, and then our recommendations.

Under section 201.61, statement of identity for single-ingredient products -- and I will touch on combination products in a moment, but for single-ingredient products, it's the established name of the drug, if it might be established in the act or otherwise in an official compendium, followed by the general pharmacologic category of the drug or the principal intended action or actions of the drug.

For example -- and I won't read through all of these, but for your reference, 355.50 is for the anticaries in the final monograph for the anticaries products, and 356.62 -- and let's concentrate on that one because it's shorter and it shows the point -- is the labeling of the tooth desensitizer drug products.

Now, this is exactly out of the monograph, and in terms of your panel report, the statement of identity, since it appears in all of the other panels in this format, I would anticipate would also take this type of format.

Here we have for the tooth desensitizing, the labeling of the product contains the established name, if any, and identifies the product as, insert, toothpaste/tooth gel, the formulation, for sensitive or hypersensitive teeth. If you look through the different monographs, that particular statement for a sensitive or hypersensitive teeth, if you were to look for a parallel construct in other monographs, might appear with different words before or after the formulation. So, there's no really set rule for that.

So, what we would recommend for this category is first to consider that the single ingredients that you look at can be divided into two general categories, those that have been shown to have antigingivitis activity and those that have been shown to have both antiplaque and antigingivitis activity and separating those out and considering them as single ingredients, insert the established name of the drug, antigingivitis, insert dentifrice or toothpaste, dental rinse, et cetera.

The same would be true for that second category of those products that have antiplaque/antigingivitis.

So, the example here shown at the bottom, if we would take the chemical name, the established name of the drug here, would be that name, antigingivitis toothpaste or antiplaque/antigingivitis mouthrinse or whatever formulation would be marketed meeting the monograph specifications.

For combination products, the OTC drug that is a mixture and has no established name, the general pharmacologic actions of the mixture or its principal intended actions represents the statement of identity. So, in this particular case, it would be, following the same construct that we looked at for the single-ingredient products, antigingivitis and then insert the particular formulation, same antiplaque/antigingivitis in the formulation. So, you would have these examples for combinations, anticavity/antigingivitis mouthrinse or anticavity/antigingivitis toothpaste or whatever the particular formulation would be relative to the combination.

I'd like to turn now to indications. Our recommended strategy for the statement of identity in terms of splitting these into two categories for the therapeutic ingredients, i.e., antigingivitis and antiplaque/antigingivitis, we think should be followed when considering the indications as well.

I have a brief comment here to just be sure that we're on the same ground, recognizing the difference between the statement of identity and the indications.

The statement of identity is required to appear on the principal display panel. Indications may appear there, but they most often appear in the information panel. Indications are synonymous with uses, and an easy way to think about that would be aspirin analgesic tablets that would represent the statement of identity, but under indications or uses, it would be for the temporary relief of minor aches and pains associated with the common cold, headache, and a list of other particular conditions. So, that distinction between statement of identity and indications.

Again, I will show you now for the antigingivitis products and then we'll get into the antiplaque/antigingivitis products. But for those that have been reviewed as GRAS/GRAE Category I antigingivitis active agents, we would recommend a basic monograph indication for the control, reduction, treatment, and prevention of gingivitis or gum disease. And then additional optional indications so that the ingredient has that basic monograph claim and then that would appear on the product and then these other claims may also appear such as controls with these verbs, gingival bleeding,

controls red swollen gums, controls bleeding gums.

For that category of agents that have both antiplaque/antigingivitis activity Category I GRAS/GRAE in the monograph, again the same basic monograph indication based on the antigingivitis activity, the same optional claims based on the antigingivitis activity, and then we would recommend the following two optional claims for antiplaque activity in these agents with antiplaque/antigingivitis activity, controls plaque that leads to gingivitis or gum disease, controls plaque bacteria that lead to gingivitis or gum disease.

I'd like to touch on OTC warnings. Over the discussions that you had and as you consider these particular products -- and this has been true of every panel -- the question comes up, what kinds of limitations of use might be applied in the context of warnings. I know that this discussion has not been presented to you, but as you get into, I think, this phase of your work and you start thinking about what that panel report, which represents the advanced notice of proposed rulemaking, looks like, I think it's important to remember where FDA has been for the last 25 years in the construct of warnings and the hurdles that need to be overcome or the criteria that need to be met before a warning statement actually appears on a product.

We have a detailed paper in section 4. I'd recommend the reading of it, but what I'd like to do is just to run through sort of the bare bones outline of what this longstanding FDA policy is on OTC warnings.

The legal requirement is to disclose material facts, and that is interpreted through a number of rulemakings. Here are a couple of examples, four examples. But over and over again in the monographs, that represents essential information, that is what goes on the OTC label.

Now, the question is in the context of the warning, what is essential? FDA has defined a three-step process, if you will, or three criteria that ensures the validity, the interpretation and the practical application of the underlying data to the OTC use conditions.

Those three steps or those three criteria is embodied in this statement that OTC warnings should be those that are scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer. Scientifically documented, the validity; clinically significant, the interpretation; and then important to the safe and effective use of the consumer, the practical application.

Just a word on that. Scientifically documented is adequate design, collection, and analysis of data in a reliable and scientifically acceptable manner. I think

perhaps the particular example that is best known, at least within the industry and perhaps the FDA, is the Reye's syndrome example when the state surveys were issued in 1980. It wasn't until the raw data were reviewed some 18-plus months later that FDA determined that in fact the proposed association was not adequately scientifically documented and at least one more study through the Public Health Service needed to be done prior to a warning going on it.

So, that first hurdle of scientific documentation -- and this has been replayed in a number of other categories and for other ingredients -- is a very important hurdle, perhaps one of the ones that has been the points of contentions, the stumbling blocks, certainly the kinds of discussions before you even get to thinking about whether that particular statement will represent clinical significance.

On clinical significance, not just statistical significance, an interesting example is the cellulose bulk laxatives that will interfere with the time to peak digoxin levels. However, while that is statistically significant, that does not affect how well diged the particular patient is, and they are quite well maintained, even if they take that bulk laxative at different times. As a result of that, even though a statistically significant, quote,

clinical finding found in a clinical study had been demonstrated, it did not have clinical significance in terms of managing the patients. So, no warning on the cellulose based bulk laxatives.

Then finally, important for the safe and effective use by the consumer, not based on a contrived clinical situation that's not applicable to actual use conditions or even a clinical condition that isn't. Some products may have professional labeling and there may be attendant warnings applied to that particular condition of use of the product that might be for much longer durations of use than for the OTC self-care condition, and the labeling there would not have a practical application to the self-care situation for the OTC-labeled product.

So, by way of overall summary, just returning to the first portion of our talk, the recommended combinations of antiplaque/antigingivitis agents with anticaries agents, with the tooth desensitizing and the three-way combination, the possibility of combining antiplaque/antigingivitis agents and the criteria that we set forth in our comments we think are important things for the panel to discuss in the context of the general therapeutic categories, separating that out from a separate discussion of final formulation testing, as Dr. Genco has pointed out.

The statement of identity, here shown by an example for a combination product, might be antiplaque/antigingivitis toothpaste.

And the indications. The basic condition for the control of gingivitis as a basic monograph condition.

And then the following optional claims for controlling gingival bleeding, red, swollen gums, bleeding gums, controls plaque that leads to gingivitis, controls plaque bacteria that lead to gingivitis, all part of an example for an antiplaque/antigingivitis agent that would get your recommendation for a Category I GRAS/GRAE status.

Then finally, as you think about the labeling for these ingredients, we would hope that you'd keep in mind this three-step process that FDA has for the warnings, that they be scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer.

Thank you.

DR. GENCO: Thank you, Dr. Soller, for a very interesting and useful presentation.

Any comments or questions from the panel? Yes, Max?

DR. LISTGARTEN: How do you deal with -- I am sure it can be done in the labeling, but how do you deal with the situation where a product might be effective in

reducing gingivitis but not sufficient to cure the problem and might give a patient a false sense of security? Now, you had bleeding gums. Now, all of a sudden, they do not bleed nearly as much, but the patient may be in the process of developing periodontitis. The patient may be under the impression that the label that says controls gingivitis or reduces gingivitis is indicative that this is a product that will take care of his condition.

DR. SOLLER: So that you have a -- if I understand what you're saying --

DR. LISTGARTEN: I'm concerned about the false sense of security.

DR. SOLLER: Yes. No, I understand.

I suppose the same thing could be said about an anticaries agent, that an individual thinks they're preventing cavities and they may be preventing some cavities but not all cavities.

If I take your question right, are you suggesting that that be either subclinical, in which case there would be a question I guess as to whether that really was progressing. But you're actually saying that there is a frank clinical condition that the individual doesn't know is going on. Yes.

Well, I think some of the ADA labeling does help that in terms of recommending regular checkups, and I

think that that kind of labeling is important. I think tied to what will be a better format and content for the information panel, which is a pending rule at this time, will also help to make that particular label more consumer friendly, more likely to be read, more likely to be followed.

DR. GENCO: That provides a nice segue to the next presentation after the break. I don't mean to stop the discussion, but I'm sure that Dr. Whall will address that.

Any further comments or questions of Dr. Soller?

(No response.)

DR. GENCO: If not, we're right on schedule, so I'd like to announce that we're going to take a break and we'll start at 10:15 with discussion from the American Dental Association. Thank you.

(Recess.)

DR. GENCO: I think we should get started if you could take your seats please.

We'll have a presentation by a representative of the American Dental Association, Dr. Whall.

DR. WHALL: Thank you, Dr. Genco.

Today I'd like to outline the American Dental Association's policy on the acceptance of fixed combination

drug products in the ADA Acceptance Program. I provided the subcommittee with a copy of the slides I'll be using.

On behalf of the ADA, my goal is to once again provide the subcommittee and the FDA with the benefit of over 10 years of the ADA's Seal Program experience in the evaluation of the safety and effectiveness of drug products that reduce plaque and gingivitis.

The Council developed its first set of guidelines for the acceptance of chemotherapeutic products for the control of supragingival plaque and gingivitis back in 1986, which I've provided the subcommittee on previous occasions.

The Council has also recently updated these guidelines to widen the scope of the types of products it will accept. Basically the old guidelines only evaluated products whose mechanism of action was strictly antimicrobial. The new guidelines also include products that reduce gingivitis by some other means. And I'll provide the subcommittee with a copy of these later today. I'm waiting for them to come through on the fax.

Under the bylaws of the ADA, the Council on Scientific Affairs, which I'll subsequently call the Council, studies, evaluates, and disseminates information with regard to the safety, efficacy, promotional claims, and proper use of dental therapeutic agents, their

adjuncts, and dental cosmetic agents used by the public and the profession. The mechanism used by the Council to do this for therapeutic agents is the Acceptance or Seal Program.

The Acceptance Program in turn operates in accordance with its provisions for acceptance, copies of which I've also provided to the subcommittee. The provisions go over such areas as products considered for acceptance, general provisions for acceptance, evidence for safety and effectiveness, labeling, package, insert, and advertising and other promotional materials, and fixed combination drug products.

I'd now like to briefly go over those sections of the provisions that directly relate to the acceptance of fixed combination drug products. If you're looking at that in the provisions right now, I've sort of picked several areas from the provisions, so you won't really be able to follow by looking at the provisions.

Eligible products in general include all dental drugs and chemicals which are employed in the diagnosis, treatment, or prevention of disease. And as I said, all of these are eligible for the program.

Required evidence of safety and efficacy includes substantial objective data from clinical and laboratory studies on the final product, not just on the

active ingredients. I think this addresses one of the issues that came up a few minutes ago about what happens if you have two agents that are effective, you add them together, and somehow you decrease the effectiveness of one of the other agents.

I guess that's a fundamental difference, as I've said before in how the FDA and the ADA work, in that we evaluate products, the final formulations. We don't evaluate ingredients. And that takes care of that issue because we want to see the clinicals that are performed on the final product that's going to be marketed, and it takes that into consideration.

Other evidence is all proprietary studies for the final product. A manufacturer may submit three or four studies to support the effectiveness of their product. We want to see what other studies they have on that final product that may not demonstrate effectiveness. It does not necessarily mean that we wouldn't accept the product if these other studies did not show a significant benefit because the Council looks at all the studies, how they're designed, how they're done, and makes a judgment overall based on all the data.

And finally, a list of the other published studies using the final product. There may be other investigators who have done research that the company might

not have provided to us, and the Council would like to know all that data. Again, these are all on the final product that we're looking at.

Besides reviewing the clinical studies submitted for acceptance, the Council also conducts post-marketing surveillance of accepted products. One mechanism it does this is upon the renewal of the acceptance which occurs every three years, when the Council may require evidence demonstrating continued acceptable clinical performance, and such evidence could include the request for new clinicals to be performed if some information has come up that would indicate that was needed, reports on adverse reactions which should be given to us as they occur anyway, but this three-year period of re-acceptance that we have gives us a formalized way to check and make sure this is being done. And maybe some of the previous clinical studies need some follow-up. So, maybe the Council liked the study as far as it went, it was enough for acceptance, but we wanted the company to go a little bit farther, maybe continue on a little bit longer.

Now, what is the policy on a fixed combination drug product?

Products are eligible, number one, when there is adequate evidence of effectiveness in the practice of dentistry. Again, this would be demonstrated through the

clinicals.

Number two, when each of the components makes a contribution to the claimed effect or effects.

Number three, when the dose of each component is safe and effective for a significant patient population.

Also, combination drugs having components added to enhance safety or efficacy of the principal active component or to minimize the potential for abuse are also eligible to be included in this combination product.

The Council actually wants to see data to support each of the active agents. So, if you have an active for caries and you have an active agent for gingivitis and you have an active agent for hypersensitivity, the Council requires studies that show effectiveness of each of those three indications using the final product.

On the label we simply require that each of the therapeutically active ingredients be listed and their concentrations given, very similar to the FDA.

And finally, some examples of products that have received the seal that have combination ingredients are fluoride plus potassium nitrate for caries and hypersensitivity. We have several products accepted in that category. That means they've done both the studies for caries and the studies for hypersensitivity with that

product.

Fluoride plus pyrophosphates. Now, while we don't consider calculus to be a therapeutic end benefit, we do require clinical studies demonstrating an anticalculus effect. So, we have these products that have both of these ingredients and have done both of those kinds of studies.

Another example is fluoride plus triclosan and Gantrez for caries and gingivitis. That was a recently accepted Colgate product.

So, all of these are the combination products.

Thank you. That concludes my presentation.

I did want to make one comment, though. There was a question that I think Dr. Listgarten raised about how do you prevent consumers from being misled for gingivitis products so that they don't think that it's going to cure their periodontitis. This is a concern the Council has had over the years, not just for this area but for other areas. The way we have dealt with that is a couple of different ways.

One is we always require a statement with an accepted over-the-counter product. The statement for gingivitis products clearly states that the effectiveness of the this product for periodontitis has not been determined. The guidelines we developed are strictly to look at gingivitis. Now, we are developing other

guidelines for periodontitis, but for the purposes of what we're talking about here, it's just gingivitis. So, we do have that disclaimer right on the box saying we don't know what this product does for periodontitis.

I think the other part of it is just education, and the ADA continually tries to educate consumers on the differences between periodontitis and gingivitis so that they won't be misled like that.

I think the third part is in our statement we also say to use this product in conjunction with regular professional care, so you're always going to your dentist and the dentist can then do the diagnosis if it's anything other than gingivitis.

So, I just wanted to make a comment about that. Thank you.

Are there any questions?

DR. GENCO: Yes. Thank you very much, Cliff.

Ralph?

DR. D'AGOSTINO: To go back to the discussion about the retarding type effect of the combination on the particular ingredients, in the combination, say, that has a caries agent in it, you're interested in is the caries agent still effective, but are you interested in is it as effective as it was when it was all alone?

DR. WHALL: The ADA Seal of Acceptance simply

means that the product is effective for what it says it is. We have never really gotten into the issue of ranking products in terms of effectiveness. But that is a question that we do ask. If the effectiveness of the caries part of the product was markedly decreased, the Council would have concerns. I don't have numbers to give you what that would be, but yes, they do take that into consideration.

DR. GENCO: Max?

DR. LISTGARTEN: I notice one of your product combinations was one I was concerned about, namely fluoride for caries combined with pyrophosphates for antitartar effect. Do you actually require clinical trials to show that both caries and tartar are reduced?

DR. WHALL: Yes, we do. Any kind of a product that comes to us initially has to do their clinical tests for both of those indications. If you have me-too products that come along, then we have other laboratory tests that they can do to show that they're similar to that initial product that was clinically tested. But yes, both caries and calculus clinicals.

DR. GENCO: What about products from the same category, mixtures, combinations from the same category? Would you require in vitro or clinical trials to show that each one contributes?

DR. WHALL: Are we talking about the essential

oil type question?

(Laughter.)

DR. GENCO: As an example.

(Laughter.)

DR. WHALL: That was a question the Council did ask. When they initially looked at the product, they said, well, should we require each of these ingredients to have to demonstrate a clinical effectiveness by themselves and in various combinations and that the four ingredients together act better than any of the individual ingredients?

And they came to the conclusion that this was a fixed combination active. They looked at it that way, that this particular active that was used in all the clinical studies had demonstrated effectiveness, and their conclusion was it did not require that the individual ingredients had to be looked at. But it's also interesting that Dr. Barnett did show that the in vitro studies showed that each one had some effect at least on bacterial kill.

DR. GENCO: Further comments, questions? Bill?

DR. BOWEN: Can I push you a little more on the reduction in the effectiveness of fluoride? You said you can't give us a number, but as you well know, probably 95 plus of all the toothpastes used in the United States today contains fluoride. If you get a reduction, say, by adding an anticalculus agent of, say, even one-tenth of one

surface, from a public health point of view, you're looking at a pretty effective reduction. So, I was just wondering what number would trigger alarm in the ADA?

DR. WHALL: I'm still not going to be able to give you a number. This is an issue the Council looked at very, very carefully. They're aware that the pyrophosphates inhibit remineralization, and that's directly competing with what you want the fluoride to do.

We do believe and the studies we've seen do tend to show that the pyrophosphate products are slightly less effective than just the plain fluoride products. The Council and the consultants that they sent these submissions out -- in their judgment it was not significant enough to cause concern, and I guess that can be open to debate.

DR. GENCO: Further comments, questions?

I note Dr. Katz is going to make the next presentation, but could we address this issue of has the FDA in the labeling also recommended regular professional care, use of product with regular professional care? Is there a precedent for that?

DR. KATZ: It doesn't really state that specifically in the labeling itself. There are some warnings and there are some advisory recommendations when to go back to seek professional assistance, but wording

like that, not specifically.

DR. GENCO: So, could you expand on it? We are all familiar with it, but what are the words used?

DR. WHALL: The statement reads something like X product has been shown to be an effective decay preventive dentifrice when used in a conscientiously applied program. I didn't know I was going to be quizzed on this.

(Laughter.)

DR. WHALL: Of oral hygiene and regular professional care. Then if it also has an anticalculus ingredient, it would say, this product has been shown to effectively decrease calculus formation. A third sentence would say -- what's interesting, in that case for the calculus ingredients it would say that this product has not been shown to have any effect on gingival health because the tartar ingredients haven't been linked to gingivitis at all, at least in the studies we've seen.

For the product that has an antigingivitis effect, the statement will add something like the effect of this product on periodontitis has not been determined, something along those lines.

DR. GENCO: You know we are all professors in our days jobs, so quizzing students and each other is what we do.

Well, thank you very much. That was very useful.

It looks like that would be very unusual for the FDA to accept or to consider.

DR. KATZ: To a point. It would again depend upon how the product is labeled. In some cases there's more of this product or the efficacy or effectiveness in a particular area has not been shown. That may exist, but as to specific catchall like what you're saying, that doesn't right now, although that's not to say that it would not and could not.

DR. WHALL: I could get you the exact statements if you like and provide them to the committee.

DR. GENCO: No. I think the point is made. Max, maybe we can discuss this later.

Further comments or questions? Yes, Fred?

DR. HYMAN: The one comment that I wanted to make was in terms of the ADA's statements. Particularly the one that comes to my mind is the statement about periodontitis effect with the ones that get the gingivitis claims. When we write the OTC labels, we tend to gear more towards the consumer. Personally I feel that although a dentist would clearly understand that, I have often wondered if the average consumer really knows the difference between gingivitis and periodontitis. I sort of

doubt it. So, just a comment.

DR. WHALL: Well, that's well taken. I guess it was debated whether to put advanced gum disease or periodontitis. Periodontitis was chosen but it could have gone either way. But I understand what you're talking about.

DR. GENCO: Further comments, questions?

DR. SAVITT: Also I believe that in the ADA labeling, they refer to gingivitis as a mild form of gum disease as opposed to just gum disease which I think is pertinent considering Dr. Soller's presentation where he referred to gingivitis as gum disease, and it goes along with what Dr. Hyman noted.

DR. GENCO: Thank you.

Max?

DR. LISTGARTEN: I do believe I've seen labels to the effect that if these signs and symptoms persist for longer than whatever, go see your doctor or dentist, and I think we can probably squeeze one of those in.

DR. GENCO: Further comments?

(No response.)

DR. GENCO: Thank you very much, Cliff.

DR. WHALL: Thank you.

DR. GENCO: Now we'll have a presentation on this issue of combination policy from Linda Katz, who's the

Deputy Director of the Division of OTC Drug Products. Dr. Katz?

DR. KATZ: I'm actually making my remarks from here since I don't have any overheads or slides. Basically since most of what I'll say has been said earlier today and at the time of the last meeting, my comments are going to be fairly brief.

At this point, suffice it to say that the OTC combination policy, as we've both seen and we've heard, is addressed in 21 CFR 330.10(a)(4). OTC drugs may combine two or more safe and effective active ingredients that are recognized as being safe and effective when each makes a contribution to the claimed effect or effects, and when combining these ingredients, there is no decrease in safety or effectiveness of any of the individual ingredients, and in addition that there is rationale that's provided for this therapy for the target population to which it's intended to be used.

In 1978 the OTC guidelines were published in the Federal Register in an attempt to help to define some of the situations in which this policy could be applied, so that this was really an attempt to go through and to clarify where there might be some confusion with the policy as stated.

At this time I would basically like to bring

you back more to the task at hand for today and over the next two days, which is really to address the ingredients that have been presented to this committee to decide which of these ingredients might be safe and effective for a combination or combinations. In trying to assess these ingredients, one can look at it in two terms, in terms of a broad combination policy as is seen with the cough/cold combination policy in which there are, for example, two categories or three or four, depending upon what the product is, of categories of drugs or ingredients, one which would be, let's say, for example, an antihistamine which would contain a list of Category I active ingredients that could be combined with an antihistamine from also Category I, so that the decongestant and the antihistamines might be combined and interchanged. That would be what we would mean or imply by your broad type of a combination policy.

We heard the other example which is that of a fixed combination or a more specific combination. One example would be that of phenol and camphor in a mineral oil in which the formulation is fixed, it's specific, and this combination is in the topical analgesic, also first aid antiseptic rulemaking. This is an allowable fixed combination.

So, at this point in time there are options for

both, both broad generalization in which different ingredients can be applied as Category I, from one category to the other can be combined, or specific formulations can be mixed together and that would be fixed. That would be something that this panel can determine and give us advice on.

Further, when looking at these formulations for both broad and fixed combinations, once you consider the data that has been presented to this panel on the formulations that may or may not have been evaluated, the target populations that have been reached or attempted to be reached, remembering that the effectiveness and safety should not be altered when any of these active ingredients are combined.

In addition, if there's some concern with some of these combinations or certain of the active ingredients that can be seen that the committee feels they should not be in a Category I combination, we are looking for recommendations that this panel might be able to give us as to what additional information they would require or need or studies that might be needed or recommended to be able to have such a combination be included as a Category I combination.

With that, I will refer you back to the questions. There are seven of them which we look forward

to the guidance of this panel on making these determinations for the combinations.

DR. GENCO: Comments or questions of Dr. Katz? Yes, Bill?

DR. BOWEN: All of the examples that have been given by both Dr. Soller and Dr. Katz refer to, for the want of a better term, a single condition, for example, a cough and a cold, signs and symptoms of a single condition, similarly with an internal analgesic and similarly with a sunburn. When we come to caries, periodontal disease, and hypersensitivity, we have three quite distinct conditions, each with its own etiology and pathogenesis.

The question I have is, is there any precedent for using a combination of drugs to treat three distinct or even two distinct pathological entities?

MS. LUMPKINS: Normally what we've done with the combination products is to address symptoms so that when you look into cough/cold, you're treating an array of symptoms. So, that would be the closest thing that we have by way of precedent. In other words, we're treating a cough with a sore throat and that kind of a setup.

DR. GENCO: Further comments, questions of Dr. Katz? Yes, Dr. Soller?

DR. SOLLER: Bill Soller, NDMA.

I also gave the example of a sunscreen plus a

skin protectant. So, that would be two different categories, the windburn plus the sunburn protection. Separate categories I think is what you were asking, Dr. Bowen.

DR. BOWEN: No. Separate pathological entities.

DR. SOLLER: Well, they have different etiologies, sunburn and windburn.

DR. BOWEN: Yes, but you could argue they both end up with inflammation of the skin, whereas in caries and periodontal disease, you've got something quite distinct.

DR. GENCO: Yes.

DR. OKARMA: Thank you, Mr. Chairman. Paul Okarma, Colgate-Palmolive Company.

The agency has previously reviewed data submitted by Block Drug Company and has previously determined that a hypersensitivity agent, namely 5 percent potassium nitrate, is a rational combination with an anticaries agent. So, there is an example of two distinct things that can be combined.

Thank you.

DR. GENCO: Further comments, questions?

(No response.)

DR. GENCO: Now, we've been challenged to look at the questions regarding combinations and come up with

some discussion and guidance. If you all have that set of questions, I'd like you to look at those. They're revised. It's the third page of the agenda.

First question, what combination of ingredients would support antiplaque and/or antigingivitis indications?

The idea here is you want some guidance on what theoretically or what we've been presented with as possibilities for combination?

DR. KATZ: Both.

DR. GENCO: Both, okay.

Does anybody want to address that? Max?

DR. LISTGARTEN: I'd like to preface this by saying that many of us around this table are not very experienced pharmacologists so that we may know of individual ingredients that do certain things. We may not be sure what happens when you start to mix them. As was pointed out before, a good example was the attempt at taking chlorhexidine and incorporating this into toothpastes, something which didn't work because chlorhexidine got inactivated.

Having said that, there are some combinations that come to mind like, for example, triclosans which have a slight inflammatory effect as well as a slight antimicrobial effect, and nobody has tried it perhaps because they know better. But chlorhexidine and triclosan

would make a nice combination, but I haven't the foggiest idea if one could actually do this, just to mention one.

DR. GENCO: So, one combination for gingivitis would be antibacterial and anti-inflammatory, a theoretical possibility.

DR. LISTGARTEN: Yes.

DR. BOWEN: I think one could also possibly include an astringent agent.

DR. GENCO: For antigingivitis.

DR. BOWEN: Right.

DR. GENCO: So, in reality what we've been presented with, though, is what? Just antibacterial in the products that we've been asked to review.

DR. LISTGARTEN: Well, I think we also need to go back to the beginning of our deliberations way back when when we decided that an effective product should have both antibacterial and antigingivitis effects, that antibacterial without antigingivitis wasn't good enough. So, we're basically looking at something which, for lack of a better word, would be an antiplaque/antigingivitis agent or an antiplaque/antigingivitis product which could be a combination of two, one which may be more effective in one area than the other.

DR. GENCO: So, theoretically, you could have an antibacterial that affects the bacteria, and what else

would affect gingivitis? Give an example.

DR. LISTGARTEN: Triclosan being one of them.

DR. GENCO: Lew?

MR. CANCRO: Bob, I think the existing combination policy which defines the conditions under which within the same pharmacological class you can combine two ingredients having the same mechanism of action, and additionally the combination policy also covers ingredients intended for the same clinical effect but with different mechanisms of action. So, there does exist definition at least conceptually that the FDA has already provided us. If you go back to the guidelines, they have defined the conditions under which those two events are appropriate.

DR. GENCO: Right. They've asked us what theoretically could affect plaque, what theoretically could affect gingivitis. So far I've heard antibacterial can affect both, anti-inflammatory can affect gingivitis or astringent could affect gingivitis. So, various combinations of those which might be different pharmacological classes are possible for antiplaque/antigingivitis.

Clearly there can be a combination of several antibacterial and several anti-inflammatory within the class.

So, is there any more to this than that in

terms of antiplaque or antigingivitis?

MR. CANCRO: Hypothetically, you may ultimately discover that several specific microbes are implicated in this disease process and hence the combination of a bactericide and another bactericide having different --

DR. GENCO: Spectrum of activity.

MR. CANCRO: So, from that perspective, that's a possibility.

DR. GENCO: So, antibacterial with different spectra with respect to killing of various species, okay.

Another possibility might be a plaque dispersal agent of some sort or an anti-adhesion agent that coats the tooth and prevents adhesion. Two other possibilities.

DR. BOWEN: Wouldn't they come under the category of antibacterial, Bob?

DR. GENCO: They may not kill bacteria but they prevent plaque formation. So, if we're talking about theoretical, we are really going back to basics here.

MR. CANCRO: Yes, but I think as you get to dispersion and things like that, where are you with respect to pharmacological action? Is that within the realm of what we're looking at here? If you can disperse or something like that, is that still within effectively what we're reviewing?

DR. GENCO: Well, theoretically an agent that

dispersed preformed plaque could prevent both plaque and gingivitis and maybe periodontitis. Theoretically. We're being asked to discuss the specifics of the theoretical possibilities.

Is that what you'd like, that sort of discussion?

DR. KATZ: That, as well as bringing it also back to some of the ingredients that you've seen before because again remembering that we're going to eventually take some kind of a vote on the ingredients, some that still remain, as to which ones we might also want to consider in these combinations specifically.

DR. GENCO: Now, we've dealt also with abrasives, but we've said we're not going to discuss those or classify those because they're not drugs in the sense that they don't have pharmacologic action. Is this what your point is about the dispersal?

MR. CANCRO: Right, right.

DR. GENCO: So, theoretically some abrasive could also have antiplaque effect and antigingivitis effect, obviously do.

Is there any more discussion relative to the theoretical combination of ingredients that would inhibit plaque, inhibit gingivitis, or inhibit both?

DR. LISTGARTEN: My concern is that many of the

things we've looked at seem to be class 3 ingredients as opposed to class 1 ingredients. There really aren't that many class 1 ingredients. So, maybe we should zero in and see what kind of class 1 ingredients we have and if we can combine these in any way. That may be the most practical way to go about this.

So far we have fluoride. That's a class 1 ingredient for caries.

DR. GENCO: Stannous fluoride for gingivitis we've voted on and cetylpyridinium chloride for gingivitis and plaque. So, those are the agents we voted on in class 1.

DR. LISTGARTEN: I don't remember. We don't have too many.

DR. GENCO: We voted on two so far in class 1.

DR. LISTGARTEN: Yes, and what we have to find out is are there any chemical incompatibilities or other incompatibilities in combining some of these very few class 1 products that we have. I'm not sure that I have the expertise to say yes or no.

DR. GENCO: Do you want to address that, Bill?

DR. BOWEN: Well, I don't know much about incompatibilities. I know they certainly do exist and some of the surfactants/antimicrobial agents probably will inactivate chlorhexidine for certainty. And there are

certain other agents in toothpaste that will inactivate probably CPC. So, we're getting into an area that personally I find the waters much too deep for me, other than I'm aware of some of the potential problems. It is clear that in the past that industry also got their fingers burned on some incompatibilities after the event. So, it's an extraordinary difficult area. That, of course, is begging the question.

DR. GENCO: Yes. We'll be discussing limitations on combinations and maybe we can get into incompatibilities there.

Let's focus on what are the possible combinations. Is there anything more than what we've discussed?

For plaque, it's dispersal, antibacterial, anti-adhesion, and then we've said we're not going to discuss abrasion in this panel.

For gingivitis, it's antibacterial, anti-inflammatory, and astringent.

There are some enzymes that have been proposed, anti-protease for example, or protease enzymes. What are those? Those are in the category of antibacterial or dispersal, some products that we've been asked to look at that have proteases in them.

DR. LISTGARTEN: What are they doing?

DR. GENCO: We're talking theoretical now. It could be a protease to disperse plaque. This gets very theoretical. I don't know how much further we want to pursue this, but those are all the possibilities. Okay, fine.

All right, shall we go on? Are there any more comments about the first question? Yes.

DR. WU: I think there's also an enzyme like dextranase or gluconase that are added to some of the foreign products. Would that be considered dispersal?

DR. GENCO: Which could disperse plaque by degrading the matrix.

DR. BOWEN: That's truly academic because they don't work.

(Laughter.)

DR. GENCO: Well, as Max said, we've only got two so far in class 1.

Now, the second question. Specify what other ingredients can be combined with antiplaque ingredients -- and I would extend that to antigingivitis ingredients -- and for which indications. In other words, these are the so-called non-active I would interpret this as. What else can be combined? Okay.

Lew, formulation expert.

MR. CANCRO: I think this question really needs

clarification. Is the FDA asking this panel to look at all of the potential in our ingredients that could be combined with these active systems, or are they really talking about what other active ingredients can be combined with these actives? I would like clarification of the question.

DR. GENCO: That's a good point.

MR. SHERMAN: I think the question isn't really clear. I think for number 2 what we're asking is what other classes of ingredients can be rationally combined with antiplaque ingredients. We're not looking for specific ingredients.

DR. GENCO: Active, like anticaries.

MR. SHERMAN: In other words, anticaries and antiplaque.

DR. GENCO: Yes. I misinterpreted that.

What other active ingredients? Dr. Soller presented that this morning. Any further comment? We've got anticaries, drugs that treat hypersensitivity, antitartar.

DR. LISTGARTEN: Are we going to get into cosmetics?

DR. GENCO: Hopefully not.

MR. CANCRO: I think if you lump in tartar to that, you are getting into cosmetics because you've defined it as a cosmetic effect. I don't think that's appropriate

because then there's no limitation to where you want to go with respect to all the cosmetic properties of many ingredients.

DR. GENCO: Is the issue, though, that if in fact in reality these active ingredients would be combined, should we advise the FDA on their potential adverse effects like the antitartar even though they're cosmetic?

MR. CANCRO: I think if you look at monographs which have already been established -- and you've yet to do this for this one, but there are very specific conditions under which these agents will work, concentration, et cetera, availability, and in the case of fluoride, the profile tests. So, for established Category I ingredients from other classes, from other monographs, those ingredients with any change to a formulation, be it an active ingredient or an inactive ingredient, necessitate that the manufacturer shows that that ingredient still meets the Category I conditions.

So, we can get in a very complicated situation here looking at all of the potential things that can happen, but simplistically speaking, conditions for effectiveness have been established for these ingredients in other monographs. As long as those ingredients are still meeting those conditions, then it's perfectly okay to combine materials and ingredients.

DR. GENCO: All right. So, you've gone on to the third question, stability. I would interpret that as activity also.

Yes.

DR. D'AGOSTINO: Can I ask about the second one? We've heard caries sensitivity and possibility tartar and so forth. I guess I read that to be, given what Lew said, is that once you state something, in fact you have to go through a hurdle to make sure that you've maintained it.

But isn't it also asking, given this panel, are there other indications that you think might be sensible to combine with the antiplaque and antigingivitis indications? Is it only caries sensitivity that we think are reasonable things to put together with the antigingivitis? We're not being asked what tests have to be done, but what do you think is sensible to put together with these.

MR. CANCRO: I think Dr. Soller's point was that the combinations that he proposed reflect an existing need out there. You can have gingivitis. You can have dental caries. You can have hypersensitive teeth and the other two conditions. So, there exists a need out there to treat these things concomitantly, at the same time, and hence it's very rational.

Now, beyond that, that doesn't close the door on perhaps other things, but you'd have to establish that

these other conditions are there and that this new agent would then treat whatever those other conditions are.

So, I think what the manufacturers are proposing are really a series of four or five combinations which appear very rational. They don't want you to close the door on the potential that other things may come up. I can't specifically give you an example of that, Ralph, but in effect they're looking for you to endorse an existing combination policy that the FDA has.

DR. D'AGOSTINO: One way of interpreting Dr. Bowen's comment earlier with the cough/cold type of thing, that these symptoms all come together. Do these symptoms, sensitivity, caries, really all come together that we want to put them all in a single package? I think that's the way I'm reading it. It sounds sensible.

DR. GENCO: Maybe it's more that the delivery system allows one to treat concomitantly caries and periodontal disease or gingivitis, although they're very distinct pathologic processes, but the way you deliver it makes sense to put both in the same toothpaste.

Yes.

DR. SAXE: Yes. I think you just noted, Bob, what the crux of the issue is. Just because they both happen to occur in the mouth, these are two distinct pathological processes dealing with periodontal disease and

caries. We may have to come down on a case-by-case basis because while you have a delivery system, if we had, let's say, a fixed combination of ingredients or even a single ingredient, then we want to put in an anticaries agent and somebody has dry mouth or perhaps we can put in some sort of a saliva stimulant, and then maybe also an anti-anxiety agent because they shouldn't worry about what's going on in their mouth.

(Laughter.)

DR. SAXE: And the possibilities of drug interaction or a lack of effectiveness of any one agent is apparent. I think just because there are a lot of things going on in the mouth, we can't, I think, hope to treat all of them with one magic cocktail or paste or gel.

I think the crux of the issue, again, Bob, is as you stated it, that just because they're common pathological entities, tooth decay and gum disease, they can't easily be lumped together in terms of an effective treatment or effective agent.

DR. GENCO: Bill?

DR. BOWEN: Well, as I said earlier, in principle I think the consumer will probably benefit if appropriate agents can be combined in an equi-effective way. But the problem I have is this. Let's say -- and I'm going to use examples that may or may not be correct.

But let's say you have a combination of fluoride with -- pick anything -- let's say pyrophosphates, and the pyrophosphate is in there to prevent gingivitis. In doing that, it reduces the effectiveness of fluoride by -- we'll say a number -- 50 or 60 percent. Now, the fluoride continues to be effective, but it's very much less effective than it is on its own.

By the current OTC rules, if I understand them correctly, we do not make relative effectiveness. It's either effective or it's not effective, and we're not allowed to make assessments on degrees of effectiveness.

I think under these circumstances, I think I could make a case that a consumer would be ill-served because, yes, on one hand you may prevent calculus; on the other hand, you're reducing the effectiveness of fluoride but it's still technically effective. That's one of my concerns that I'd like to see addressed.

DR. GENCO: So, we recognize that there are some rational combinations, anticaries, antigingivitis, antiplaque, and activity against hypersensitivity, and maybe even salivary stimulation. Certainly those are all possibilities.

So, is there anything else then that we want to discuss?

And there may be some clever company or person

in the future that comes up with yet another agent that could be combined in a toothpaste or mouth rinse that has beneficial effect.

Is there anything else that anybody else would like to say about 2 before we get into limitations and stability, et cetera? Those are separate questions. These are theoretical combinations. Max?

DR. LISTGARTEN: I just want to point out that even though we're dealing with caries and periodontal disease as two different pathologic entities, for those who are uncomfortable with this, you could look at it as saving teeth which is sort of the unifying factor. So, I'm just proposing this as a rationale for combining anticaries and anti-periodontal disease products.

DR. GENCO: Ralph?

DR. D'AGOSTINO: Can I get a point of clarification actually? Because I think Dr. Bowen has mentioned a couple of times the real concern that if you make these combinations, for example, the fluoride may be diminished. I've always read the combination policy, in certainly any trials I've been involved in, as that the combination, as you go indication by indication, has to be at least as effective as the individual ingredient, that you can't be losing the caries effectiveness in the combinations. Have I been misreading that?

DR. KATZ: No. Actually what the combination policy says is that you need to be as effective or better, that you shouldn't be losing.

However, one additional caveat which the OTC combination policy has through the guidelines is a risk/benefit type of an assessment which is not written into or applied on the NDA side for prescription combinations, but it is a part of the guidelines for the 1978 OTC policy.

So, even if you look at it, there may be circumstances in which the agent itself is still effective and when you add in the risk/benefit type of an assessment for that combination, that the product may be acceptable as combination for OTC.

DR. D'AGOSTINO: Thank you. So, in the general sense, though, the general idea is that the ADA may not force that question, but the FDA forces the question of equal effectiveness or a risk/benefit.

DR. GENCO: Any further comments on question 2 then?

(No response.)

DR. GENCO: It looks like we're ready for the next set of questions. 3 and 4 seem to be quite related.

Bob, could you maybe give us a summary of what you want out of 3 and 4 or what the FDA would like out of 3

and 4? Is this safety/efficacy as combinations? Is stability really an issue here, or what would you like us to discuss here? Specific concerns about specific combinations with respect to efficacy, which has already been addressed, the pyrophosphate/fluoride? Do you want to hear from this panel, who has had experience with those things, and others in the audience what kinds of pitfalls are there when you put these combinations together? Okay, good.

Bill, further comments?

One we've identified is the reduction of fluoride in combination with whatever, pyrophosphate.

DR. BOWEN: Calcium.

DR. GENCO: Calcium. So, that's one.

I heard earlier today inhibition of chlorhexidine, an antiplaque/antigingivitis agent, by formulation. These are all obvious and well-known, but these are very easily inactivated.

DR. BOWEN: There's also a concern coming out of Scandinavia, for example, the inclusion of SLS in toothpaste reduces the uptake of fluoride by the tooth surface, and I think this may need a little additional attention.

DR. GENCO: Further concerns, caveats with respect to combinations that are unique to these dental

combinations? Christine?

DR. WU: We've done some studies and we've found that in some instances chlorhexidine, when combined with a high level of essential oils, in some cases there's an antagonistic effect, and so does CPC.

DR. GENCO: CPC plus chlorhexidine?

DR. WU: No, with some of the essential oils.

DR. GENCO: Oh, CPC with essential oils or chlorhexidine with essential oils inhibits -- there's mutual inhibition?

DR. WU: Right, antagonistic effect.

DR. GENCO: Lew?

MR. CANCRO: There's no doubt that there's a great potential for chemical interaction with chlorhexidine, but the agency cleared chlorhexidine as a particular product. It wasn't cleared as an ingredient. The people who are marketing that are marketing under a prescription either through an approved NDA or an abbreviated NDA, and hence it reflects for those formulas what is compatible with chlorhexidine.

I think when we say, well, if you combine SLS with chlorhexidine, you lose effectiveness, or phosphates, you lose effectiveness, that's fine, but it's not a good example to look at when that was cleared on a product basis as opposed to an individual ingredient basis.

DR. GENCO: Well, is it true, though, that antiplaque/antigingivitis agents, these small organic molecules, are easily inactivated by formulation?

MR. CANCRO: Well, I'd prefer to stick with the fluoride because you've yet to decide for this category how you want to handle the potential for --

DR. GENCO: Well, we had a long discussion of cetylpyridinium chloride. You remember the Merrill Dow studies versus the P&G.

MR. CANCRO: Right, right.

DR. GENCO: It appeared to the panel that there was inactivation.

So, is this not a problem? It's not just chlorhexidine. Is it a potential problem with other antiplaque/antigingivitis agents? I think that's the issue.

MR. CANCRO: Well, you referred to cetylpyridinium chloride. The manufacturer has indicated that there are certain conditions in the formula which make it active and hence you must assume there are conditions which make it inactive.

DR. GENCO: Yes, that's the point. It's a problem. It's a potential problem. They're asking us, what are the pitfalls? What are the potential problems? It's not something that you can ignore.

MR. CANCRO: Well, I think the potential problems become clear when you go back to these systems which you declared as Category I and defined a scope under which they meet Category I conditions. That obviously is concentration. That's clearly one example of where a decision has to be made.

Regarding the potential for chemical interaction, certainly what came out of the fluoride review was that, A, it had to be available through a shelf-life. It had to show a certain amount of fluoride. B, it had to meet certain testing requirements. So, in the end the activity of the fluoride is pretty well defined through many generations of formula changes which have now gone on since 1972.

But that's just an example of how one monograph treated this problem. That's the thing you've got to come to grips with rather than I think look at the potential for interaction because you haven't scoped that out yet for this category.

DR. GENCO: Just thinking about the future of what we're going to be doing, do you think we're going to be in the same sort of discussion with the antiplaque/antigingivitis agents?

MR. CANCRO: I believe you will be discussing this, and hence it will be easier to come back to this

question when you know the limitations that you're saying for these ingredients.

DR. GENCO: Well, we're just outlining general possible limitations. One is formulation effect on antiplaque agents. Another is formulation effects on fluoride, which is well-known, well-described, and the profile is in place to prevent that. We're being asked by the FDA to talk about these theoretical possibilities and not just theoretical, but real things that have to be dealt with. Some of them may be obvious, but some may not be.

MR. CANCRO: I think with any chemical entity there is always -- always -- some potential for an interaction which would not make that ingredient available. But again, that's jumping ahead of your review. If you want to talk on a hypothetical basis, then the bottom line is, yes, there is potential for interaction.

DR. GENCO: Okay. Do we need to discuss this any further, 3 and 4, the limitations?

(No response.)

DR. GENCO: Okay, good.

Number 5, target populations, special considerations for target populations. Let's take them one at a time. Antiplaque/antigingivitis. Specific age range. Should they be used in children, not used in children, pregnant women, older individuals, any target populations

they should not be used in or any populations they should be recommended highly for use? General population? Max?

DR. LISTGARTEN: Well, I recall that SLS caused an increased number of ulcerations in patients who were susceptible to aphthous ulcers, and that should be clearly stated someplace, that if there is SLS in a product --

DR. GENCO: That's in the realm of a warning more than a target population.

DR. LISTGARTEN: Well, it's a target population that's at greater risk of developing a problem. I don't know if that is included here, but that's something to keep in mind.

DR. GENCO: Are these antiplaque/antigingivitis agents meant for the general population or not? That's really what they're asking here. Is there any indication that they're not?

DR. BOWEN: What's the need for them in children under the age of 6, for example?

DR. GENCO: Okay, good point. Certainly if you don't have teeth, maybe --

(Laughter.)

DR. GENCO: -- you don't need a toothpaste. Obvious.

But now you've said the primary dentition may not benefit from an antiplaque/antigingivitis agent. Let's

discuss that. Yes, Gene?

DR. SAVITT: Well, while the rate of gingivitis in those under 6 is relatively small, there are still kids with gingivitis. I don't specifically see the limitation.

DR. GENCO: Max?

DR. LISTGARTEN: Maybe we should make it 3 instead of 6.

DR. BOWEN: Well, at what age is the swallowing reflex controlled? At 3, 4?

DR. GENCO: So, you're concerned about swallowing and adverse effects of swallowing versus targeting for the beneficial effect.

DR. BOWEN: Well, that's one aspect of it.

DR. GENCO: So, it's a risk/benefit consideration.

DR. BOWEN: Right.

DR. LISTGARTEN: Maybe one could apply just enough toothpaste so that if they swallow it, it makes no difference.

DR. BOWEN: With fluoride, there's another day's discussion, as you well know.

DR. GENCO: Lew, do you have some comments?

MR. CANCRO: If the agent itself, the ingredient, has no safety problems, then that's a factor in terms of the issue of children swallowing it. But I think

that should be really the only caveat because if you are looking at the benefit, not the risk -- that's a different part of the equation -- it is justified certainly on the basis of dental maturity that these conditions exist. It's pretty well documented. I think Gene, who obviously has seen the condition in children below 6, indicates there's a need. Particularly if there is a need, you're looking at an inability to brush and to clean, and that's exactly where these agents are intended to promote their benefit.

DR. GENCO: Gene?

DR. SAVITT: There's another aspect to it in that a lot of the products that we've looked at have been designed not so much to deal with gingivitis once it's established, but many of them have been -- or a lot of the data that has been put forth has been designed in such a way to prevent the gingivitis from occurring or to reduce the amount of gingivitis. I'm concerned that we may end up mixing apples and oranges at least about the particular products that we've reviewed. In a theoretical sense I can understand it, but for a lot of the products we've looked at, they've been designed in such a way to prevent the gingivitis or to reduce the amount of gingivitis that ends up occurring as opposed to curing the gingivitis per se.

DR. GENCO: Is there a reason for this age 6? Bill, you brought it up and it's also in the question from

Bob Sherman and Debbie.

DR. KATZ: The reason for age 6 really comes down to the way the labeling has occurred for over-the-counter products. That's been a cutoff. That's one of the ages.

DR. GENCO: Okay. So, the target populations often are age 6 and above.

DR. KATZ: They can be. That's right.

Now, we don't have to be locked into that. There have been exceptions or changes in products that have gotten over-the-counter --

DR. GENCO: Oh, I see. In general, over-the-counter is for age 6 and above.

DR. KATZ: That's right.

DR. GENCO: Thank you.

DR. KATZ: As a general over-the-counter labeling so that it's to be consistent with other products that are there, but that doesn't necessarily mean that you're bound by that age.

DR. GENCO: Right. Okay, thank you very much. That was useful.

Bill?

DR. BOWEN: There's also a specific concern about over-ingestion of fluoridated toothpaste by children, specifically under 6. Many of the manufacturers now make

recommendations on the labeling to use "a pea-sized" portion of toothpaste. Personally I think that doesn't go far enough, but that's, as I said, another day's discussion.

DR. GENCO: What is the monograph for fluoride? Is it over 6?

MS. LUMPKINS: Yes.

DR. GENCO: It is, okay. So, it wouldn't be inconsistent if we also used that as the target population, over 6.

Gene?

DR. SAVITT: While gingivitis is seen in children under 6, you could also ask the question, of what significance is it?

DR. GENCO: Dr. Soller?

DR. SOLLER: Yes. I think the fluoride labeling goes down to 2, if I'm not mistaken.

DR. GENCO: Surely we can clarify that, not that we dispute that, but just to get the proper, let's say, wording, under supervision, pea-sized. It's obviously an important issue, and since 95 percent of toothpaste has fluoride then this becomes very relevant.

DR. LISTGARTEN: One could adapt a little tip to the toothpaste tube so it only squeezes out a very tiny, little bit of toothpaste for children. That would be one

way to dispense a very small amount by squeezing a little bit through a small hole, instead of the regular sized portion.

DR. GENCO: All those with children are smiling, knowing how well they can get around all of those precautions.

(Laughter.)

MR. CANCRO: I only want to comment with respect to Max' suggestion, that when I have to open up a bottle of medicine, I look for a young child to get into it. Sometimes I can't open it.

(Laughter.)

DR. GENCO: Okay. That was very useful.

Bill, further comments?

DR. BOWEN: Is there any concern about the use of agents that have an anti-inflammatory effect? Many of those are clearly being adsorbed through the mucus membrane and one could argue, maybe not legitimately, that this in fact is a systemic effect and not a topical effect. Should we be concerned about that, again in children or in young adults?

DR. GENCO: Comments? Max?

DR. LISTGARTEN: Specifically which anti-inflammatories are you thinking of? Not corticosteroids surely.

DR. BOWEN: Well, again, there has been a lot of work done in Scandinavia, for example, with triclosan where significant amounts clearly are be adsorbed through the mucus membrane. I'm not picking on triclosan. There are probably others also that you know equally well, but that's the one where a lot of work has been done.

DR. GENCO: With respect to the Rx and triclosan, is there an age limit? This might be instructive too. Is that 6 and above or is that a concern for children? Fred, do you recall?

DR. HYMAN: Well, triclosan --

DR. GENCO: It's OTC.

DR. HYMAN: It is OTC, right, but it was considered under a new drug application, so it was an entirely different process.

DR. GENCO: But what was the result of that? A different process, but is it restricted to 6 and above?

DR. HYMAN: The labeling? Actually -- Paul?

DR. BARNETT: It's 6, yes.

DR. GENCO: Thank you. Sorry to put you on the spot. That's how I make my living.

DR. SAXE: Just as another point to get off onto the adults, the first part of that question is, what populations would benefit from these products? Since gingivitis is ubiquitous in the adult population, but those

adults who have limited function and limited in self-care, this obviously would be sort of a target population where it would be an important adjunct for oral health. So, rather than limiting it where somebody may have some systemic condition or chronic illness, this is really of greater value to such a population because of chronic illness or limited in self-care.

DR. GENCO: That's an interesting issue. Let's say a large percent of the population, age 6 and above, has gingivitis. It might be 75 to 95 percent. But there's gingivitis more severe in certain populations. Over-the-counter in this instance wouldn't be targeted to just the severe. It could be for all because it's so prevalent. Is this correct?

So, that doesn't preclude some advertising maybe, or whatever, for a high risk population, but certainly we wouldn't want to restrict it to just that. I think that's the issue.

Linda?

DR. KATZ: What I was going to say is that if you decide that for whatever product that you want to label down to age 6, that implies that the product is safe and recommended for everyone age 6 and above. It doesn't hone in on any specific target population unless there's something specific that there is a specific warning or a

specific indication that would make it different for that particular population, such as, if for an older population, let's say -- this is obviously not for this type of a product, but a preventative type of a claim, that may be applicable only to one segment of the population that's being targeted. Therefore, the indications would be for that particular targeted population only, whereas for general use, the product would be available to a larger-aged spectrum.

DR. GENCO: So, in the labeling -- Dr. Soller gave us several possibilities -- there could be for prevention of gingivitis in home-bound or something like that. That particular claim could be targeted.

DR. KATZ: It could be targeted. Probably an example would be if you look at some of the other products that are out there in other areas, particularly H2 blockers, that the claims may be different depending upon which population they're targeting themselves for and the labels accordingly as to how to take the product.

DR. GENCO: So, we should be concerned with that at the labeling level.

Christine?

DR. WU: How about the population with hyposalivation?

DR. GENCO: I'm sorry. What did you say? The

combination --

DR. WU: No.

DR. GENCO: Oh, the population with hyposalivation.

Bill, do you want to comment on that?

DR. BOWEN: Well, again, that issue came up repeatedly when we were reviewing agents, and I think for the most part, we got satisfactory answers when we asked for data concerning the effect on persons who had hyposalivation. So, again, I think a lot of these products are certainly applicable to people who have hyposalivation without risk of irritation.

DR. GENCO: Further comments then on these issues in number 5, the target populations, age?

(No response.)

DR. GENCO: Let's proceed now to 6.

Specific recommendations. Any other specific recommendations regarding these combination products? Is there anything else, unique aspects of these combination products that we haven't touched on?

(No response.)

DR. GENCO: Let's proceed to the last question then. What data should be required to support combination drug products containing ingredients with antiplaque/antigingivitis claims?

Are you after any unique aspects of the experiments that we haven't dealt with, for example, proving that each ingredient contributes to the total activity? Is there anything else that you're after here?

DR. KATZ: It's actually more general. If you feel that for combinations -- actually it's both. It's a general question as to say whether or not the data that have been given would -- that you have enough data right now to say that specific combinations would be okay or the general broad category would be okay. If not, what additional kinds of information you would like to see to be to be able to state that in general or for a fixed combination what kinds of things you would want to have to be able to assess --

DR. GENCO: As compared to single-ingredient.

DR. KATZ: That's right.

DR. GENCO: Okay. Does anybody want to address that? Lew?

MR. CANCRO: Yes. I just want a point of clarification, Linda. From my perspective, just the interpretation, you're saying that this question relates to the ingredients which this panel has proposed as Category I and then relative to all the other Category I ingredients from different pharmacologic classes. So, the decision regarding data has already been judged for each of the

individual components. You're now asking if additional data --

DR. KATZ: Not for the individual, but as a combination, so that if people are now comfortable with combining ingredients that have already been categorized as Category I, would you want additional information to make you comfortable to make that combination, a Category I type of a combination. Do you see what I'm trying to say?

As individual ingredients, you've already determined which ones you're comfortable as being Category I, but right now in the theoretical or hypothetical conversation you've had, there has been some concern whether or not combining some of these ingredients would be an appropriate thing to do. What we're asking is, do you need any other information? What other kinds of information would you need?

DR. GENCO: So, let's just review. We have already voted on cetylpyridinium chloride and stannous fluoride as Category I single agents. You're saying if somebody wanted to put them together, unless that was addressed in the monograph, they could.

DR. KATZ: No, no, no. They could not. They could not be put together unless the monograph states that they can be put together in a combination.

DR. GENCO: Okay.

DR. KATZ: So, what we're saying is that if you say it's fine to put them together as a combination and you feel you have enough data, that's fine. If you feel that you don't have enough information to be able to make that assessment, we're asking what additional information would you need to be able to be comfortable to put it into the monograph that the combination --

DR. GENCO: So, we're not discussing the data for the express combinations that we're reviewing, but in the event that we ought to discuss what someone could do with these combinations. All right, good.

Max, do you want to address that?

DR. LISTGARTEN: It seems to me that if you're going to mix two ingredients that individually work and you don't know whether there's going to be an incompatibility between the two, that you need to do the same kind of clinical trial that you would for a new combination. Basically you need to show that the combination works. In other words, if you're going to claim that product A plus product B reduced caries and reduced gingivitis, you have to show me that they do.

DR. GENCO: Yes.

DR. BOWEN: As far as fluoride is concerned, I wouldn't go quite that far. If you came up with a combination, I'd be prepared -- that's me -- to accept the

data from a well-controlled animal study comparing with and without.

But in addition, which is not particularly popular at the moment, I'd like to see clearance data of the fluoride from the mouth, that that's not affected also and that's comparatively easily carried out. That falls well short of a full-scale clinical study.

Similarly, if there was an antibacterial agent, again I personally will be prepared to accept the data if you showed me clearance curves from the mouth comparable with and without the extra additive. But I certainly wouldn't accept it, as you clearly won't either, as a blanket, well, 1 and 1 equals 2 always. It doesn't we both know.

DR. GENCO: So, let me just try to understand what you're saying. Max, you said obviously the two agents, cetylpyridinium chloride/stannous fluoride, you can't willy-nilly put them together and just assume they're going to work. You have to test them just like you would any other combination. All the safety/efficacy concerns, individual activity concerns would be addressed. So, those are for the antiplaque/antigingivitis.

But we have another category of combination here and that is combination with proven agents like fluoride which have already been combined with other

agents. There isn't such uncertainty about that combination. And Bill is saying in that instance, for the fluoride, he would accept lesser evidence than the final preparation activity that the ADA requires.

DR. LISTGARTEN: I guess the issue is how much additional testing do you need for a combination of two active ingredients. I'm willing to retreat from a full clinical trial. I just didn't want to leave the impression that you could just mix them. I'm with Dr. Bowen in that respect.

DR. BOWEN: I think it's comparatively easy to determine whether, if you mixed two ingredients, you get a new product formed. I think if you had evidence that there is a new product formed, then I think it's a whole different situation. Then you're looking at toxicity in full scale clinical studies. But if it was clear that the two products remain separate from each other, then I would be prepared to accept lesser evidence.

DR. GENCO: For either condition? Two singly approved antiplaque agents or antigingivitis or one of these antiplaque agents with a proven anticaries.

DR. BOWEN: Correct.

DR. GENCO: Either instance.

Lew?

MR. CANCRO: Well, I concur. It would seem to

me that if you add one of these Category I antiplaque/antigingivitis agents to a fluoride dentifrice, to go to a three to four-year clinical trial to prove that the fluoride is still effective is unnecessary because there are conditions which are predictive for that fluoride. I agree with Bill.

DR. GENCO: But what about mixing stannous fluoride and cetylpyridinium chloride, two singly approved Category I agents, for antigingivitis? They're both for antigingivitis.

MR. CANCRO: For the same indication?

DR. GENCO: Yes.

MR. CANCRO: Well, again, you got to refer to your combination --

DR. GENCO: Then that becomes a combination. It has to go through all the steps of proof of the combination. It's a new combination.

MR. CANCRO: If you accept the proposed policy that the FDA has indicated, then those contributions have got to be shown.

DR. GENCO: So, the discussion is any new combination obviously as a new combination has to fulfill all requirements of a combination. But a combination of either a single agent or an approved combination, if we do come to that for antigingivitis, with a known, proven

anticaries or anti-hypersensitivity, requires a lesser level of evidence in everyone's mind.

DR. LISTGARTEN: What do we know about -- what's the word?

DR. GENCO: Cetylpyridinium chloride, CPC.

DR. LISTGARTEN: What do we know about CPC -- CPF? What do we know about CP fluoride?

DR. GENCO: CPCF?

DR. LISTGARTEN:

DR. BOWEN: No, no. CP fluoride.

DR. BOWEN: I agree with the point that Max is making. We're getting a bit specific here, but let's take stannous fluoride, as people want, and CPC. If you have evidence that there's a new compound formed as a result of mixing that -- and that would be obviously the first thing you would do -- then a new set of rules apply because you're now looking at a new compound. It's neither stannous fluoride nor CPC. It's stannous CPC, if you prefer, if such a thing can exist. Then it's a different set of rules.

But if you can show that the stannous fluoride, which by the way also has got anticaries effect, that that remains separate and the CPC remains separate, then I would be prepared to take lesser evidence than the full-scale clinical study, but if there's a shred of evidence that

there's a new compound formed, to my mind that's a different ball game.

MR. CANCRO: Exactly.

DR. GENCO: Lew?

MR. CANCRO: Well, that's precisely why you have GMP. All these materials, whatever the combinations are, have to meet GMP requirements. They have to show availability right after they are made. You're right, Bill. If the entity is lost, it's not the same thing anymore. So, it's simply a case --

DR. BOWEN: Or a new entity formed.

MR. CANCRO: Or a new entity forms. But that's what your stability studies are really intended for, to establish that these things are not happening literally on a production basis, batch by batch.

DR. LISTGARTEN: So, basically we're coming up with the answer to the problem, and the answer to the problem is to demonstrate that there are no chemical interactions and no new products formed and that each product works independently from the other. Basically you need to establish that.

DR. GENCO: Works. That's the key term. They're active. They're bioequivalent, and we'll get into that later tomorrow.

DR. LISTGARTEN: And they don't interact.

DR. GENCO: So, some sort of measure of in vitro or in vivo bioequivalence is what you'd want.

DR. BOWEN: But you also want to show that the materials do behave in the mouth in a small scale study as they do normally, i.e., what sort of salivary levels and what sort of plaque levels do you get? That would be, I would imagine, not too difficult to conduct.

DR. GENCO: So, we're getting into the final formulation testing of these combinations which the discussion will occur tomorrow in some depth, the details of that.

Christine?

DR. WU: I have a question about adjuvant. Correct me if I'm wrong. I think I've read somewhere in the monograph, Bob, that an adjuvant, when it's combined with an active ingredient, if it enhances the activity of the active ingredient, it is considered an active ingredient also. Now, then in that case, does one have to do all the studies to prove that an adjuvant itself is also safe and effective when it's combined with another active ingredient?

DR. GENCO: The feeling is if it's defined as an active ingredient, then it would be tested as an active ingredient.

Andrea, do you want to make a comment?

DR. NEAL: I just wanted to comment that unless you speak into the microphone, it's not going to get recorded into the transcript.

DR. GENCO: Dr. Listgarten, do you want to make a comment for the transcript regarding that issue?

DR. LISTGARTEN: Well, it seems that if it's going to be -- if an adjuvant is going to be considered as an active ingredient, then its interaction with whatever the other product is must be considered in the same way as if it were an active ingredient.

DR. GENCO: Further comments then about this issue of these combinations both of single ingredient, antiplaque/antigingivitis and antiplaque/antigingivitis combined with known active ingredients that are already maybe in monographs?

(No response.)

DR. GENCO: Okay, that finishes the morning agenda. Are there any comments from the audience relative to this issue? Cliff, the ADA has dealt with this and do you want to say any more than what you said about the final formulation testing? You have taken a very clear stand on that apparently. Dr. Whall?

DR. WHALL: No, I don't really have anything else to say, but I'll say it anyway. No. That has always been the issue, just exactly what you're talking about,

that you don't know when you mix ingredients or adjuvants or whatever, what's going to happen to the end product. So, that's the position the Council has been able to take over the years. We just want to see the tests done on the end product. Now, whether they're clinical tests or laboratory tests depends upon how much is known about that particular kind of product and its combination. So, we've been able to do that.

DR. GENCO: So, you would take an antiplaque/antigingivitis agent new, test it alone and then combined with fluoride and maybe ask for fluoride equivalency laboratory tests or enamel uptake rather than full clinical tests for the final formulation with both.

DR. WHALL: Yes. For fluoride that has not been our position before. We've wanted clinicals. I think the Council is reevaluating that as we speak now because of everything that is known about fluoride now. I think we might be going in that direction.

DR. GENCO: Okay. Thank you. I didn't mean to put you on the spot again, but you got an A already in the beginning of the morning. So, don't worry.

Yes, Christine?

DR. WU: One last question. In reading the established monograph, there is limitation of ingredients in the combination products. It says that one shouldn't

combine two or more active ingredients from the same therapeutic group with the same mechanism of action. So, should there be a limitation on the numbers of active ingredients in the combination in our case?

DR. GENCO: You're suggesting that we discuss that as a general guideline for these particular products?

DR. WU: Yes.

DR. GENCO: Is there any reason from the data that you've heard to make that as a general suggestion?

DR. WU: I'm just reading what's established in the monograph. It says that it's better not to combine more than two. So, are we going to do that for our discussion?

DR. GENCO: Is there reason to do that? We have heard that maybe combining antimicrobial agents might make sense if they have different spectra of activity against different organisms. So, our example -- the one example anyway of Listerine -- there might be a justification for combining. Even though they're the same pharmacologic class, they do have different spectra of activity.

DR. LISTGARTEN: I'd like some clarification from the FDA representatives. I wasn't sure whether this limitation of two or three referred to certain things we were trying to deal with. For example, one could

conceivably deal with caries, gingivitis, hypersensitivity, and something else. Is that too many things, or should we just have two of these four?

DR. GENCO: Dr. Katz and then Dr. Soller.

DR. KATZ: You can have more than two, and there are combinations that are out there that have as many as four active ingredients. Some of the cough/cold preparations exist with up to four. So, depending upon the nature of what it is that's being combined and why it's being combined, it may be appropriate to have more than two provided that each again is contributing to show effectiveness and safety is not being compromised.

DR. LISTGARTEN: Okay, so there is no upper limit if one can justify it.

DR. KATZ: That's correct. However, again, the more active agents you add in, the more you risk the safety as becoming a potential problem, but there have been up to four active ingredients that have been approved and do exist.

DR. GENCO: Dr. Soller?

DR. SOLLER: I was going to say a very similar thing, but I would just point to the combination policy itself where it says two or more and then go further down in the policy and it's rational concurrent therapy. That should be the driver for you to make your therapeutic

judgment.

DR. GENCO: Thank you.

Further comments or discussion of the questions posed to us by the FDA?

(No response.)

DR. GENCO: Bob and Debbie and Linda, does that help?

MR. SHERMAN: Yes.

DR. GENCO: Okay, fine. Thank you.

Andrea?

DR. NEAL: I just wanted to say one thing before we break for lunch. If anybody spoke today who wasn't listed on the agenda, could they please give their information to the transcriber because that does get included in the official record. So, just state your name and degree I think is what she needs and where you're from.

DR. GENCO: Okay. Let's reconvene at 1 o'clock at which time I'll give a progress report on the topics and ingredients we've discussed. Then we'll get into a discussion of a couple of single-ingredient and possibly combination-ingredient to be classified. Thank you.

(Whereupon, at 11:55 a.m., the subcommittee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:07 p.m.)

DR. GENCO: I wonder if I might have your attention. It's getting to be a little after 1:00, so we should start.

I'm going to give a very brief progress report of our discussions over the last 11 meetings. Specifically, we have discussed the possible relationship of alcohol-containing mouthrinses to the development of oral and pharyngeal cancers. As you recall, the recommendation was more studies needed, that the concerns were less serious than we originally thought based upon the epidemiologic studies we saw, their lack of reproducibility and the lack of a dose response. But there was concern that that be pursued. As we understand, there are several studies ongoing now. So, we await the results of those studies.

Another topic. We talked about the general guidelines for determining the safety and effectiveness of antiplaque and antigingivitis drug products, and I think that we have made real progress there and have applied those. I'll summarize the votes that we've taken.

We spent a lot of time on definitions and general information related to antiplaque and antigingivitis drug products.

We discussed the drug versus cosmetic status of antiplaque products and labeling claims.

Then some general recommendations for antiplaque combination ingredients which began last meeting and continued this meeting and, I'm sure, will continue the rest of today and possibly tomorrow.

We have reviewed 17 products, included stannous fluoride, zinc citrate, peppermint oil, sage oil, cetylpyridinium chloride, aloe vera with enzyme blend, the amylase/protease/lipase combination; hydrogen peroxide, sodium bicarbonate, hydrogen peroxide/sodium bicarbonate combination, sanguinaria extract, sodium lauryl sulfate, Xylitol, C-31G Therasol, the menthol/thymol/eucalyptol/methyl salicylate combination, Microdent, hydrogen peroxide/povidone iodine, and hydrogen peroxide/zinc chloride/sodium citrate/sodium lauryl sulfate combination.

We have classified 11 of those 17 agents so far, and of those 11, 2 single ingredients are in class 1 both for safety and efficacy. Cetylpyridinium chloride we recommended classification as Category I for plaque and gingivitis; and stannous fluoride, Category I for gingivitis.

In Category III, we voted and our recommendations are for Category III aloe vera with enzyme

blend, hydrogen peroxide, Microdent, peppermint oil, sage oil, sanguinaria extract, sodium bicarbonate, and sodium lauryl sulfate.

We have discussed and recommended classification of one combination product, hydrogen peroxide/sodium bicarbonate as Category III.

Any comments, discussion about that summary?

(No response.)

DR. GENCO: So, of those ingredients that we have been assigned that are not yet classified, there are three single ingredients and three combination ingredients yet to vote on. The single ingredients are C-31G which is Therasol, zinc citrate, and Xylitol. The combination ingredients are menthol/thymol/eucalyptol/methyl salicylate. The second combination of ingredients is hydrogen peroxide/povidone iodine, and the third is hydrogen peroxide/sodium citrate/zinc chloride/sodium lauryl sulfate.

It appears that among the single ingredients, Xylitol was not voted on for several reasons. The main reason was that the company was going to present additional data. So, we'll discuss that later. We'll defer that.

A combination ingredient, hydrogen peroxide/sodium citrate/zinc chloride/sodium lauryl sulfate, we'll defer until the next meeting for new data

also if it comes in.

So, that leaves then single ingredients C-31G and zinc citrate to consider today, and combination ingredients menthol/thymol/eucalyptol/methyl salicylate and hydrogen peroxide/povidone iodine to possibly consider today also.

So, on the agenda then for this afternoon will be to review and/or vote on C-31G. Dr. Bowen will discuss that; Listerine, which is the menthol/thymol/eucalyptol/methyl salicylate, Dr. Saxe; zinc citrate, Dr. Saxe; and then hydrogen peroxide/povidone iodine, Dr. Savitt.

Does anybody want to add anything to that very brief summary? But I think that gives the present status of the committee's activities. Lew?

MR. CANCRO: Bob, I would only add the footnote that all of the ingredients -- generally you provided the Category I proposal for their safety. As you recall, you know we split that up into a vote on safety and a vote on effectiveness. So, I'd like the minutes to show that that's what you meant.

DR. GENCO: For Category III, yes. So, for aloe vera, hydrogen peroxide, Microdent, peppermint oil, sage oil, sanguinaria, sodium bicarbonate, and sodium lauryl sulfate, as well as for the hydrogen peroxide/sodium

bicarb, they're all recommended to be Category III for efficacy but Category I for safety. Yes.

MR. SHERMAN: I think that's true as far as I know. We didn't do that breakdown. We were just talking about Category III for safety and/or effectiveness at this point, but we can get that for you.

MR. CANCRO: Well, maybe the summary is incorrect, but indeed we did vote in that direction on many of these ingredients.

DR. GENCO: Yes. So, let's get that sorted out clearly for which ones we did vote on, and I think we voted on most of them that way. Right. And if we've not, then we'll have to revisit that. Thank you.

Bill?

DR. BOWEN: Bob, could you clarify the status of Xylitol again please?

DR. GENCO: Okay. The Hershey Company had just bought the company that was making Xylitol. They were going to present data at this meeting, as I understand. Bob or Andrea, do you have further information?

MR. SHERMAN: They were going to. There's a possibility that they may decide not to do that, but in any case because Dr. McGuire is not present, we're just going to defer that issue until next time before we vote on it.

DR. GENCO: Yes. She was assigned Xylitol.

Further comments?

(No response.)

DR. GENCO: Any comments from the audience with respect to that summary? Is that a reasonable summary of what you understand we did?

(No response.)

DR. GENCO: Okay, thank you.

Let's proceed then to discuss Therasol, C-31G. Dr. Bowen?

DR. BOWEN: As you may recall, I presented my report several meetings back. For those of you who need other copies, I have a couple of spare copies here. I understand my instructions are not to go through the whole report.

Just to remind you, C-31G is a combination of alkyldimethylglycine and alkyldimethylamine oxide. I'll just read a couple of paragraphs pertaining to the toxicity, and you'll get the sense of my opinion.

A series of dermal toxicities have been carried out. Again, some of these are difficult to evaluate because the concentration of the liquid used is not stated. In one study, the dermal toxicity of 3 percent solution was evaluated in abraded skin of rabbits. 2 of the 20 animals displayed minimal reaction. An additional study reported a 3.6 percent of the applied dose was absorbed through the

rabbit's skin.

Two dermal sensitization studies were carried out using guinea pigs and appeared to reach diverse conclusions. In one, it concluded that there was no evidence suggesting that C-31G can act as a sensitizer in guinea pigs. That's a quote. However, it's unclear what concentration of test material was used.

In a second study, where a 3 percent solution was used, it was concluded that repeated topical exposures of guinea pigs to 31G 3 percent liquid had the potential to induce mild dermal sensitization.

And then there are a whole series of other irritation tests carried out reaching essentially contradictory results, often with total inadequate description of how the studies were conducted.

In one study of particular concern, the effects of C-31G on mammalian cells were examined using a chromium release assay from human leukemic cells. The release of chromium occurred at concentrations of 0.025 to 0.005 percent, and the report notes -- and I quote -- these findings are of some concern since the effective window approximates the MIC for several bacterial species. So, it's clear that there are some concerns concerning the toxicity of this material.

The clinical studies that have been done in

many instances are inadequately described, but basically in none of them was gingivitis assessed.

So, basically my conclusion and recommendation is that there are some questions concerning the toxicity, and the clinical effectiveness has not been demonstrated.

DR. GENCO: Thank you, Bill.

Comments, questions?

(No response.)

DR. GENCO: Do you want to make a recommendation?

DR. BOWEN: I recommend Category III.

DR. GENCO: For both safety and efficacy?

DR. BOWEN: Yes.

DR. GENCO: We can vote on them separately, or we can vote individually. What's your pleasure? One for safety and one for efficacy, or together?

MR. SHERMAN: Do it individually.

DR. GENCO: Okay. For safety then, the recommendation is Category III for C-31G.

DR. LISTGARTEN: For safety?

DR. GENCO: Excuse me? For safety, yes. Safety.

Gene, do you want to start?

DR. SAVITT: So, if the recommendation is for Category III, I vote yes.

DR. GENCO: Max?

DR. LISTGARTEN: Yes.

DR. WU: Yes.

DR. SAXE: Yes.

DR. GENCO: Bill?

DR. BOWEN: Yes.

DR. D'AGOSTINO: Am I a voting member on this, Andrea? I'm never clear.

DR. NEAL: You are.

DR. GENCO: Oh, I'm sorry.

DR. D'AGOSTINO: I've been jumped over but I want to vote.

(Laughter.)

DR. D'AGOSTINO: Yes.

DR. GENCO: So, it's six yeses.

With respect to efficacy, recommending Category III for efficacy.

DR. BOWEN: Category III also for efficacy.

DR. GENCO: Okay. We'll start here. Bill?

DR. BOWEN: Yes.

DR. GENCO: Stan?

DR. SAXE: Yes.

DR. GENCO: Ralphs?

DR. D'AGOSTINO: Yes.

DR. GENCO: Chris?

DR. WU: Yes.

DR. GENCO: Max?

DR. LISTGARTEN: Yes.

DR. SAVITT: Yes.

DR. GENCO: Let's proceed then. Any other comments, discussion?

(No response.)

DR. GENCO: Let's proceed then with Listerine. Dr. Saxe, do you want to give us a summary of your two reviews, one for safety and one for efficacy?

DR. SAXE: Yes.

Two meetings ago, I reported on efficacy of Listerine and had some criticism related to the studies, chiefly in which the data was presented or the statistics, and the concern was chiefly in terms of quantifying the findings, that is, who and how many in the study group were affected and by how much and that the data could be presented with what are called appropriate indicators of measurement error and uncertainty, essentially confidence intervals. I felt that there was essentially a reliance solely on statistical hypothesis testing with the use of p values which don't give us that important quantitative information.

At our last meeting, Dr. Barnett came back and did a presentation of the data with some additional data

which satisfied that critique.

Also at the last meeting, I presented the review of the safety of the Listerine on the four essential oils. My opinion was that that was a safe combination.

So, I came to this meeting prepared to suggest that the product be Category I for efficacy and Category I for safety. I have in the efficacy, however, a question which was prompted by the material which came today which perhaps we could clarify, and that is in the presentation today and in the printed material in the minus-one study, I need some clarification now on the role of the vehicle. Perhaps you can help me with this at this time. It shows that the vehicle itself is having an effect on the bacteria that are surviving treatment in the bound volume which was presented today, which is Warner-Lambert Research Report 946-1107.

MR. CANCRO: What page is that, Stan?

DR. SAXE: On pages 6 and 7 where the tables are presented, bacteria surviving treatment. For example, on page 7, at the Actinomyces viscosus bacteria surviving treatment, it shows that the vehicle -- for example, vehicle, 4.2 times 10 to the 3rd; without thymol, 6.1 times 10 to the 3rd.

DR. LISTGARTEN: Those are the standard errors.

DR. SAXE: Okay, looking at the mean column

instead, yes. Okay.

I'd ask the other members of the committee who have also reviewed this then if they have any concern about activity of the vehicle.

DR. GENCO: Chris, do you want to explain your concern?

DR. WU: I think I brought it up this morning. On page 6, the vehicle control for P. intermedia, if you take a look at the surviving organisms, it's 5 times 10 to the 3rd. Sorry. It's the other one.

For A. viscosus on page 7, the vehicle control treated A. viscosus. The survival count was 4.2 times 10 to the 3rd. It's lower than what Listerine shows.

DR. BARNETT: Christine, if I may interject for a second. I'm sorry, Bob. Mike Barnett from Warner-Lambert.

That's the standard error column.

DR. WU: Oh, I'm sorry. Okay. I got it. So, that was my mistake then.

DR. GENCO: So, in the mean column, the vehicle on page 7 is 2.1 times 10 to the 5th organisms remaining, whereas Listerine itself was 2.8 times 10 to the 4th. That's about a log difference between Listerine and the vehicle.

DR. WU: Yes, that's correct.

DR. GENCO: But there is a statistically significant difference. In other words, the vehicle itself is different from Listerine. That's the interpretation.

DR. WU: Yes.

DR. GENCO: Your question is, is the vehicle different from another negative control? In other words, is your question does vehicle itself have activity?

DR. WU: I looked at the wrong column.

DR. GENCO: Okay. The issue is, does the vehicle itself have activity? And where is that data?

DR. LISTGARTEN: No. The issue stays the same. Even if you look at the mean column, it says vehicle -- well, let's take page 6 which deals with Prevotella intermedia. It says vehicle survival is 2.4 times 10 to the 5 cells. Without thymol, it's approximately in the same ball park. In other words, thymol doesn't seem to be significantly different from the vehicle alone. I think that's the issue.

DR. GENCO: Whereas, both are different from Listerine. In other words, Listerine has more activity than the vehicle and has more activity than the without thymol. So, that's the issue.

It looks like without thymol, it's equal to the vehicle. If the vehicle is a negative control, you're saying without thymol, it looks like the negative control.

I'm trying to understand. I don't want to put words in your mouth.

DR. LISTGARTEN: No. What I'm saying is, if you test the vehicle, it has a certain amount of antibacterial activity, but it's considerably less than the whole combination.

Now, if you just test the entire thing without thymol, the activity is basically the same as the vehicle control.

DR. GENCO: Bill?

DR. BOWEN: Presumably the vehicle is, what, 20 something percentage alcohol. Is that correct?

MR. CANCRO: 26.

DR. BOWEN: 26 percent alcohol. Well, it's well-known that alcohol in various concentrations has antibacterial effects. Of course, the optimum is at 70 percent. Of course, here you're seeing different effects on different microorganisms, which is hardly a big surprise.

The question I have, however, is could we get a sense of, for want of a better term, the percentage kill with the vehicle and, say, Listerine?

DR. GENCO: That's a question to Dr. Barnett?

DR. BOWEN: Yes.

DR. GENCO: Mike, do you want to address that?

DR. BARNETT: Bill, I'm not sure in this context what the question means. Clearly the differences are statistically significantly different between the vehicle and Listerine.

I think if the question is does the vehicle have any effect, again the real test is what happens clinically. You recall that two of the studies that we had presented compared the total formulation to a vehicle control cell and to a sterile cold water control cell. Those were the earliest studies we had done. In those studies, there was no difference in antiplaque or antigingivitis activity between the vehicle control cell and the sterile water control cell. I think that's really the ultimate question in terms of whether the vehicle is exerting any effect.

DR. GENCO: I think it's still a legitimate question to know how many bacteria did you start with? Something like 10 to the 5th or 10 to the 6th? It says that the complete formulation produced a 2 to 3 log reduction in total CFU. So, the complete formulation on page 6 is 1.2 times 10 to the 2; 3 logs would be 1.2 times 10 to the 5th. Is that what you started with, 10 to the 5th organisms? In which case the vehicle would have probably very little activity at 2.4 times 10 to the 5th. It sounds like the error. I think that's what Bill is

asking. Is it a 10 percent, 20 percent reduction, or is it a log reduction for the vehicle?

DR. BARNETT: No. Pauline can answer that.

DR. GENCO: What's the input organism level? That really would help us understand this a little better.

DR. PAN: Mr. Chairman, members of the Plaque Subcommittee, I guess this is something that's very simple but it seems to be bothering all of you.

DR. GENCO: Yes. Let me just say that we were given this this morning.

DR. BARNETT: May I just comment on that?

DR. GENCO: So, you have to bear with it. We're trying to understand it. There's no challenge here. We're just trying to understand it.

DR. BARNETT: I just want to clarify. I know that it was given you this morning. In all fairness, I should comment that this actually had been sent for submission to you guys a couple of weeks ago. So, there was a little bit of a lapse in terms of how you got it. And I appreciate that you haven't had time to look at it in detail.

DR. PAN: I guess I have three things to say, which I hope will make things much clearer for everyone in this room.

The first is it's well-known from many

investigators and in our own laboratories at Warner-Lambert that the full formula of Listerine, if one exposes it under usage conditions of 30 seconds, all representative microorganisms in in vitro tests will be killed completely. Therefore, using undiluted Listerine, one would not be able to discern and show contribution of the individual actives.

In the report you have in front of you, several microbes were selected and it's not by any chance that these were selected. These were selected, as Mike reported this morning, to be representative of plaque and gingivitis. These were also selected for their inter-bacterial contribution towards plaque and gingivitis development.

Now, putting all this into context, how would one look at this in a most direct and meaningful manner?

The most direct manner that is presented in this report is to set all the cells at the same percent transmission. Granted, that would mean that they all have somewhat slightly different CFUs. For instance, a larger organism would give you greater turbidity, but there would be fewer organisms.

Having set all these organisms to the percent transmission, one dilutes this Listerine and then looks at a trial to see what is the relative contribution for each of the ingredients.

It is entirely possible from an academic perspective to keep on adjusting dilutions of cells and their relation and adjusting the dilutions of Listerine until what one gets, as I would describe from my previous work at Princeton, is a perfect academic number which is a great spread. That spread would be an entirely so-called in vitro model to show it. To show similarities, all these organisms were tested under as similar conditions as possible.

The next point is to your question about the vehicle. I think under the combination consideration that we're discussing today, one has to look at not just one organism, for instance, the Strep or the Actino, but one has to look at the panorama of all the organisms that were presented. If one looks at all of this across the board for vehicle effects and total Listerine effects, one can see very clearly that the full combination of Listerine is the most effective germ kill formula, more than each of the n minus-one contributions and the vehicle is, after all, just a vehicle. Over and above this, each one of the ingredients contributes to the activity.

I hope that this clarifies things for you and makes it easier.

DR. GENCO: What would be the count of the positive control with no vehicle? Is it in the range of 10

to the 6th?

DR. PAN: For each organism, of course, it would be different. There was no negative negative. There is just a vehicle. The most direct is, is there a difference between vehicle, n minus-one, and total Listerine?

DR. GENCO: So, you didn't measure the actual killing by the vehicle.

DR. PAN: No.

DR. GENCO: Just versus a broth.

DR. PAN: Correct.

DR. GENCO: I think that's what Dr. Bowen was asking. So, you didn't measure that.

DR. PAN: No.

DR. GENCO: Okay.

DR. PAN: Thank you.

DR. GENCO: Further comments, questions? Dr. Listgarten?

DR. LISTGARTEN: I'm a little confused about how killing organisms affects turbidity. Was turbidity the criterion for microbial survival?

DR. PAN: The criteria for survival were plate counts.

DR. LISTGARTEN: They were plate counts.

DR. PAN: Right.

DR. LISTGARTEN: So, these mean values --

DR. PAN: Are plate counts.

DR. LISTGARTEN: Those are plate counts.

DR. PAN: These are plate counts.

DR. LISTGARTEN: Okay.

DR. GENCO: Just so we understand, the turbidity was how you established the input dose of bacteria by turbidity.

DR. LISTGARTEN: Turbidity was used to standardize the suspensions.

DR. PAN: That's correct.

DR. LISTGARTEN: And then survival was measured in terms of colonies on plates after treatment.

DR. PAN: That's correct.

DR. LISTGARTEN: Okay, fine.

DR. WU: Now, if you start out with testing with the same turbidity, then you're actually starting out with testing -- I mean, each sample would not consist of the same amount of cells. Right? Usually we do an MIC or MBC test. Usually the cell number is defined and we look for a difference.

DR. LISTGARTEN: I guess if you had to, you could give us how many organisms were found at a certain turbidity for each species. Presumably Prevotella intermedia may not be the same size as Fusobacterium

nucleatum. So, given the same turbidity, they would give you different cell counts.

DR. PAN: Yes.

DR. LISTGARTEN: But you know what that cell count is.

DR. PAN: For each organism, of course, if you have the same turbidity for each organism, the cell count may be slightly different because of large or small size cells.

DR. LISTGARTEN: Yes, but it would be in the same ball park.

DR. PAN: Right.

DR. LISTGARTEN: Do you have any idea what that cell count is that corresponds to a certain turbidity for the various species?

DR. PAN: These were not counted. They were just adjusted to the turbidity. But what is known very clearly, the cells that were used for the test, these are logarithmic cultures, very vibrant and active. So, one would expect fully that when one is testing for germ kill, if one sees effect, it would have worked against fully viable cells.

DR. GENCO: Is the issue then the effectiveness of thymol? In other words, we're given in vitro data to show the essentiality of each one of the ingredients. Are

you questioning to try to understand the role of thymol? Because on page 6 with Prevotella, the mean for thymol is about the same as the vehicle. The same for page 7 for Actinomyces viscosus and the same for Strep. sanguis. They're comparable. Is this what you're challenging?

But for Fusobacterium, it looks like there is some reduction.

DR. D'AGOSTINO: This may not help but if this were a clinical trial setting and you had a vehicle, in some studies for example, you ask the question is there down-side sensitivity. Do the ingredients beat out the vehicle, do they beat out the placebo? After you've resolved that, then you ask how do the drugs compare among themselves.

I think our problem here is that looking at this for the first time, we're not convinced that they're beating out the vehicle. Is that what the problem is, that some of these formulations look like the vehicle? And do we want them all to beat out the vehicle before we can go on to looking at the individual ingredients?

DR. SAVITT: I think the problem is, as Bill pointed out, that we'd like to know what numbers they started out with, and they don't have that. So, it's just a question of whether the vehicle is active, and the way to resolve that is to find out how many cells they started out

with and they don't have that info.

DR. GENCO: But to pursue Ralph's comment, assuming the vehicle is active -- and that probably is the case -- could be the case -- and it looks like the total Listerines are active against all five bugs. So, the total product is active.

The next question then, I'm rephrasing it. The minus-one, are each of them active? One of the questions is the minus-thymol -- or excuse me -- without thymol. It looks like four out of five are not beating out the vehicle. Am I interpreting that right? Regardless of what the vehicle is, active at some level. If the vehicle was 90 percent active, you'd be concerned, but it probably isn't.

DR. D'AGOSTINO: If I read this, we're going to be making a jump from this type to what would have happened in the clinical. So, we'd have to be somewhat convinced that things are really sharp, I would think, in this or not. We aren't going to go to clinical trials, obviously, so how much of this can we infer would happen in the clinical? How much confusion, how much delineation would have appeared in the clinical?

DR. GENCO: So, I think Ralph has helped us focus. It's clear from the in vitro that the total product is active against all five organisms, and it looks like the

minus-menthol/methyl salicylate/eucalyptol is active, beating out the vehicle, but the question is the thymol. Have I rephrased that again? Does everybody see the same thing I'm seeing or that was pointed out by Max and Christine?

DR. SAVITT: It's the other way around. The thymol is the one that appears to be active, and when you take the thymol out --

DR. GENCO: No. W/O, without, thymol is not beating out the vehicle.

DR. SAVITT: Right, okay.

DR. GENCO: Mike, do you want to address that?

DR. BARNETT: Yes, I'd like to comment about a couple of things.

First with regards to whether or not the vehicle is active, I think it should be recalled that in the just handling of these organisms in the tests, since some of them are rather anaerobic, there will be a certain amount of kill, loss of organisms just in the course of running these tests. So, I think that should be borne in mind in terms of asking the question is the vehicle active or not.

The second thing which Pauline mentioned was that this test was done in such a way as to increase the sensitivity of what would normally be a bond test, to be

able to tease out, to demonstrate differences among these various formulations, and that in fact the level of oils in all these formulations, although they started out as a level in Listerine, have been diluted to some extent in order to be able to have organisms survive in order to show differences.

So, if you were to look at these same combinations at the levels that one would find it in Listerine, in fact you would be beating the vehicle in every single case. That is, you would have a sufficient degree of activity. I think that should be borne in mind, that there's a difference in levels between what we're looking at here in order to be able to show these differences and in fact what would happen if you were using them at full strength.

DR. GENCO: Before you leave the mike, could I just ask a question? What is the final dilution? Is it 40 percent?

DR. BARNETT: It's in the range of 40 percent, Bob.

DR. GENCO: So, it would be comparable to what's happening in the mouth. You take 30 cc's of mouthrinse and stimulate salivary flow, and you're going to get at least a two-fold dilution probably within seconds?

DR. BARNETT: Yes. Bob, of course, the

difference in the mouth is that we're not using combinations of only three. We're using --

DR. GENCO: No, no, I understand. I'm trying to think about the model in vitro, how well it reproduces what happens in the mouth. And you're convincing me that it does reproduce reasonably well what's going on in the mouth.

DR. BARNETT: Well, I guess to some extent --

DR. GENCO: There is some dilution.

DR. BARNETT: Yes. The fundamental question in the mouth, of course, is what happens with the total combination.

DR. GENCO: Well, nothing in vitro is ever going to reproduce completely what goes on.

DR. BARNETT: That's right.

DR. GENCO: But at least it's not two logs dilution versus a one to two dilution.

DR. BARNETT: Yes.

DR. GENCO: Okay.

DR. LISTGARTEN: If I understand correctly, if you were to use the product straight from the bottle, you would kill everything. Even if you took out one ingredient at a time, there would be nothing surviving for you to assay relative effectiveness. Is that correct? And so, you have to dilute it in order to create something that you

can measure.

DR. BARNETT: Yes. I think what we've seen as a result, of course, is in fact there are different susceptibilities of different organisms, and this is one way of demonstrating that.

DR. LISTGARTEN: Yes, but you understand what bothers the panel, that having diluted it to the point where you can actually see differences, it turns out that the vehicle has exactly the same activity as the whole thing minus thymol, suggesting that thymol is contributing little, if anything, to the formulation.

DR. BARNETT: No, no. It's just the opposite, Max. It's just the opposite; that is, if you take the thymol out, the effectiveness is reduced.

DR. LISTGARTEN: No. If you take the thymol out, it doesn't kill as well.

DR. BARNETT: That's right, which suggests that the thymol in fact has a rather significant contribution.

DR. LISTGARTEN: No, no. Listerine in its full formulation, you end up with about 120 cells, 1.2 times 10 to the 2. That's your most effective formulation, the full concentration. You end up with 100 measurable cells surviving.

If you take out thymol, you have 2.3 times 10 to the 5th cells surviving. So, it's not as effective.

DR. BARNETT: That's right.

DR. LISTGARTEN: Okay. Now, the vehicle all by itself has the same effect. All by itself the vehicle will kill to the same extent as the full formulation minus the thymol.

DR. BARNETT: For that particular organism.

DR. LISTGARTEN: For that particular organism.

So, what does the thymol contribute beyond the vehicle?

DR. BARNETT: Max, Max, the thymol contributes, in this case looking at it simplistically, the difference between the vehicle and the complete formulation. It's just the opposite.

DR. LISTGARTEN: Okay, all right.

DR. GENCO: So, are you comfortable with that? The interpretation then is the thymol contributes to the effect beyond the vehicle. If you take it out, it doesn't beat the vehicle in, what, four out of five or five out of six cases, and really close in the sixth. With Fusobacterium, it's 9.3 times 10 to the 5th, and with the thymol out, it's 8.1. That may not be statistically different. It's a log, but it may or may not be.

DR. LISTGARTEN: I'm happy.

DR. GENCO: Lew?

MR. CANCRO: If Max is happy, I don't have a

comment.

(Laughter.)

DR. GENCO: Bill?

DR. BOWEN: I think that it's a kind of a pity that you didn't standardize on the numbers of organisms because I think by not doing so, you may well have underestimated the effectiveness of the product because clearly the more microorganisms you have in there, the more product you're going to need to kill them off. You've already indicated correctly that it was diluted 1 in 4. So, my guess is that in all probability that in some instances -- obviously I don't know because I don't know the number of organisms -- you're actually underestimating the effectiveness of the product.

DR. PAN: That's entirely possible, but nonetheless they were standardized this way in order to provide a uniformity across the board.

DR. GENCO: Further comments, questions? Christine?

DR. WU: I have a question for Mike. If I remember correctly, your clinicals that were done using the vehicle control, wasn't the vehicle control made of hydro-alcohol, or was it the true vehicle, the 27 percent alcohol?

DR. BARNETT: Yes, it was the true vehicle,

Chris.

DR. WU: Okay.

DR. GENCO: Fred?

DR. HYMAN: I'm still a little unhappy with this. Again, this is the first time that I've seen this too, but when I look at these tables, I'm starting to think that the thymol is really the effective component and the others are inhibiting it. That's one way of concluding about this data, that if you had just thymol, you might be just as effective as the Listerine. Every time you add these eucalyptol, menthol, or methyl salicylate, you're less effective than the Listerine, but without the thymol, it's the same as the vehicle. I find this data very confusing.

DR. GENCO: Does anybody want to address that? Dr. Barnett?

DR. BARNETT: Yes. Could I just make one comment? I think we're maybe getting a little bit off track here. The question that was originally raised by Stan I think had to do with effectiveness of the total product, and that I thought we had demonstrated quite clearly in all the eight clinical studies that we had presented, Stan.

So, I think what we're talking about here is a continuation of this morning's discussion where we're

really asking the question not whether the total formulation is safe and effective for clinical use, but rather what the combination -- this is really an extension of this whole question of combination.

We had approached it from the other extent this morning in terms of asking the question, if you look at the effectiveness of the total fixed combination in terms of killing organisms, what happens when you begin to take out individual components? Does it change? Is it significant? Are the differences significant?

I think we saw this morning that in fact thymol was responsible probably for the bulk of activity, but certainly not all the activity, because when you took out other components as well, it was still significantly less effective than the total formulation.

I just reiterate what I said before in terms of a comparison in this context to the vehicle and that is one of dilution, looking at these ones where you would expect to have less effectiveness because the thymol was out.

Basically I think the assumption is not that each of the components contributes equally to the effectiveness of the formulation, but each makes some contribution with some making a greater contribution than others. This is not surprising, particularly in view of some of the data we presented last time looking at some

clinical studies in which we looked at single-ingredient formulations compared to the total formulation.

Now, with respect to activity of these oils, I think if we looked at saturated solutions of each oil individually, the kill times for three representative organisms -- we have it up on the slide here. This was actually in one of the research reports presented to you -- was certainly within 2 minutes and, in some cases, within 1 minute.

If you look at the level of the oils within the fixed combination which are approximately one-tenth or so of the levels of saturated solutions, the fixed combination in fact has a kill time within 30 seconds. So, there's a dramatic difference in terms of activity when you put them all together as opposed to looking at them individually even at higher concentrations.

So, really I think the question that's being asked is whether or not -- this is again a continuation of this morning's discussion -- each of the four oils contributes to the total formulation. I think all the bodies of data we have presented suggest that in fact each of them does contribute, although admittedly some contribute to a greater extent than others. In fact, if you were to look at the phenol coefficients of these various oils, you would not be surprised to see, for

example, that thymol has a higher phenol coefficient than any of the others. So, all this is very consistent in terms of effectiveness.

DR. SAXE: Yes. Jack, could you put that last overhead back on again please?

You said I was concerned about the efficacy of the fixed combination. That wasn't my concern. My concern was what role? We're talking about the four essential oils as ingredients, and I just wanted to point out that my opinion today was then that perhaps the vehicle is playing a greater role than we thought it did and that was my concern. It wasn't the full combination.

If we look at this slide, the test solutions with the four essential oils, as you pointed out, Mike, the kill time in minutes is less than 1, less than 2. Now, with the fixed combination, it isn't simply that the four ingredients are now pooled together or put together in a fixed amount, but there's also a vehicle in there. Isn't that correct? So, it may well be the vehicle is contributing in some fashion, and that of course may be all to the good except that the magical element may not simply be in the full combinations but also the vehicle itself which plays a role. It's fine in a fixed combination.

DR. BARNETT: I'm informed here that the same vehicle was used in each of these solutions.

DR. SAXE: Okay.

DR. GENCO: Dr. Barnett, is this study summarized in the handout, the kill time study?

DR. BARNETT: It is not in this one. I think it was in the original submission to this panel.

DR. GENCO: Further comments, discussion? Christine?

DR. WU: Would it be possible that you obtain a standard suspension of all of your organisms and then determine the viable counts and then give us a percent kill and so forth, give us that kind of data? Is that possible?

DR. GENCO: Does somebody want to answer that? Jack?

DR. VINCENT: Jack Vincent from Warner-Lambert.

Christine, for these particular studies, I can't give you those numbers today. However, as you recall, we presented some data last time on the Staph. aureus that was tested in the same model. In that one we reported surviving counts that were incubated in sterile distilled water, the vehicle, the four minus-one formulations, and the complete formulations.

The difference between sterile distilled water and the vehicle, as I recall, was .03 log, and I may be in error there. It may have been .07 log, but it was between .03 and .07, a very, very, very small difference. Whereas,

the difference between either sterile water in the complete formulation or the vehicle in the complete formulations, as I recall, was in the neighborhood of 3.95 logs.

So, in one you're talking about the difference -- I think it was in the area of, let's say, 1.3 times 10 to the 7th survived in water; 1.25 times 10 to the 7th survived in the vehicle, and then it was 1 times 10 to the 3, roughly, in the complete formulation.

DR. GENCO: Further comments, questions? Lew?

MR. CANCRO: Yes. I think the issue is that this is what the combination is. It has been on the market for 100 years. Data has been presented regarding its clinical efficacy against appropriate controls, and the manufacturer has now gone to a series of tests to demonstrate that none of the components taken out individually, put together equal the total product. So, the burden now of suggesting that one of these ingredients may have more activity than another, or what would happen if the concentrations are increased I believe is irrelevant.

DR. GENCO: That last comment we dealt with this morning. I asked the question and it was dealt with. We're only talking about the fixed combination, not if one or another were increased.

MR. CANCRO: Okay.

DR. GENCO: We have to make a judgment here. The law says that each one of these has to be active, otherwise we can't really say that they should be in the monograph -- that contribute to the activity. I'll read it. We read it several times this morning. So, I think that's what we're groping with.

MR. CANCRO: Yes, they have to make a contribution.

DR. GENCO: Contribution to the activity. So, that's what we're groping with.

We've got one in vitro experiment and a previous experiment of kill time. It seems that there's at least two experimental approaches that have been used in vitro. One is the kill time and the other is this static, constant time comparison, minus-one experiment. So, I think that's where we are. We're trying to understand those experiments.

Max?

DR. LISTGARTEN: I guess what's probably most confusing on these tables is the fact that there's a role called vehicle which in a way confuses the issue here. I think if you just ignore the vehicle for the time being and just look at the rest of the data, surely enough every time you remove one active ingredient, the killing power is decreased compared to the full combination. So, on that

basis each one contributes something even if you assume that thymol does most of the killing, the fact is if you keep thymol in and only take one of the other ones out, eucalyptol, menthol, methyl salicylate, it does decrease the killing power of the whole combination. So, they must be contributing something to the killing power.

Now, testing the vehicle alone, I'm not sure if that's relevant to this particular experiment here. I think it just helps to confuse the issue because you can't remove the vehicle all by itself. The vehicle role here really doesn't belong to that experiment is what I'm trying to say. It tends to confuse the issue.

DR. GENCO: Bill?

DR. BOWEN: Although I might have done the study a little differently, I think the evidence shows to me, at any rate, fairly convincingly that each ingredient is making a contribution to the killing of specific microorganisms. And clearly they are individually more effective against some microorganisms than others and that comes hardly as a big surprise. It's clear also that the total product is more effective than any combination minus-one. So, I think the data is convincing.

DR. LISTGARTEN: And the vehicle role is really confusing because you have nothing to compare it to. It's like a fish out of water here.

DR. SAXE: I think the vehicle alone does have some killing power. So, it is significant to include it because if the vehicle was entirely innocuous -- but it isn't. So, the vehicle in combination with thymol -- because none of the studies were done -- only one was taken out at a time. If you took the vehicle with thymol, maybe in terms of killing power, which is just some kind of a surrogate measure which we don't know how effective it is of what we're really concerned about the clinical result, but if you just took the vehicle with thymol, maybe if you looked at killing power, it's even better. Maybe the methyl salicylate or the menthol or eucalyptol really diminishes it a little bit. We can't tell that, but that's okay.

What we're looking at is the whole product effective clinically, and it appears to be so. Here in the laboratory if you're trying to find out which of the ingredients is the one with the most zing, it certainly appears that thymol is. In this study, one could find out maybe these other things are inhibiting thymol a little bit instead of enhancing it, but the product as a whole is efficacious and the product as a whole has the best killing power.

DR. LISTGARTEN: So, it's less effective if you remove one of the ingredients at a time. That comes back

to the discussion we had this morning. Anybody is free to go out there and create a new formulation of vehicle plus thymol if they want to. Then they have to run these clinical trials all over again.

Now, this is not what we're here to discuss. The way the data looks in these tables, each ingredient does in fact contribute something when compared to the whole mixture regardless of what the vehicle by itself shows which, as I said, seems to be irrelevant to this experiment.

DR. GENCO: Ralph?

DR. D'AGOSTINO: I guess if you thought that it's only the combination minus-one to resolve the problem, but one could have asked the question, the combination minus-two. I guess you'd want to see something compelling with the combination minus-one. At least I guess for some of us, there's some questions about letting it rest on combination minus-one as being the final way of handling the problem.

DR. LISTGARTEN: I think we'd like to know some answers which don't seem to be relevant to the task at hand. I think that's what we're beginning to discuss. The minute you're saying, well, I'd like to see what happens if you remove two, I'd like to see what happens --

DR. D'AGOSTINO: But in any other arena --

DR. LISTGARTEN: Those are very interesting questions.

DR. D'AGOSTINO: But in any other arena that I know of in drugs, that's what's done. It's not combination minus-one. If you have four ingredients, you ask how do they individually act. Then you ask how they act together, how do they act as threes. And I'm not arguing that it's not a way of doing it, but we're making an assumption in this group that the total minus-one is somehow rather sufficient for what would otherwise be asked, all possible combinations.

I'm not sure I understand why the menthol would inhibit something, but if we thought that it had an effect of inhibiting, then there's a question that isn't resolved by this experiment.

DR. LISTGARTEN: Would we go about it differently -- if we were reviewing a brand new product, one which is now being submitted with four active ingredients, that's never been used before, would we be reviewing this differently from a product that has been around for 100 years and where we want to --

DR. D'AGOSTINO: I think that's a different answer. I think that's a good question, but I think that's a different answer to saying that we have sufficient data with the four minus-one. We can say because it's been

around 100 years, we want to look at it in a somewhat different fashion, and I'm not averse to that argument. But I am averse to the argument saying that somehow or other this is sufficient for all the possible combinations.

DR. GENCO: Dr. Barnett?

DR. BARNETT: I wonder if I can make two comments. One is in terms of the appropriateness. I'd just like to remind you of something I mentioned this morning and that was mentioned last time, and that is that with respect to this same combination but perhaps a different monograph, the FDA had in the past made the judgment that this was an appropriate way of showing the contribution of each.

With respect to whether some of these ingredients were actually inhibiting thymol -- I forget who raised that question. But I think if you look at the kill times with saturated solutions of individual oils where the kill times were in some cases 2 minutes or less, in other cases 1 minute or less, and then look at the total formulation where the kill times for these same organisms within 30 seconds, I don't understand how anybody could conclude that in fact something is inhibiting the thymol. If anything, it would seem to be helping the effect from those data.

DR. GENCO: Fred and then, Bill, did you want

to make a comment?

DR. HYMAN: I think I had actually raised the question about inhibiting. I think now that I've looked at this a few more minutes, I think one of the problems is that these five tables actually raise a lot of questions. I think that you really could have different arms, different combinations to get more information.

I think what this also raises to me, it indicates to me that the vehicle probably has a relatively strong activity.

In answer to the question of how would we do this if this were a new drug coming in now, I review new dental drugs and I can say I would probably have a real question about what's in the vehicle. So, it would be done differently than this task.

DR. LISTGARTEN: Could you pursue this and tell us whether we should review this differently?

DR. HYMAN: No. I'll turn that over to someone from OTC if they'd like.

DR. GENCO: Linda, do you want to make a comment?

DR. KATZ: I think given the precedent with what has been done for OTC and what has been done with this product and some of the prior comments that have been published in the Federal Register regarding this

combination, to go back and have it looked at as if it were a new drug I'm not sure is entirely appropriate.

I agree with Fred, if it were to come in under an IND and later go on to an NDA, things may be done differently in that arena.

DR. GENCO: Bill?

DR. BOWEN: Weren't we asked to judge on whether the individual components in this mixture make a contribution to the effectiveness of the overall product?

DR. GENCO: Yes.

DR. BOWEN: While I don't think that's possible clinically, I think the submitters have in my opinion shown that each individual ingredient does indeed make a combination to killing these microorganisms.

When I look at the data, I'm not too sure how one can conclude that the vehicle is making a contribution. I kind of suspect that it is, but I don't think one could conclude it from the data that was presented here in the absence of a complete negative control.

DR. GENCO: Chris?

DR. WU: Now, if I look at your report, Mike, page 4, it says how the test solution was diluted. So, they were diluted anywhere from 20 to 50 percent, and on page 5, a different concentration of the test solution was used for different organisms, if I understand correctly.

Now, if the mouthrinse was diluted 40 percent and 30 percent, when you did the vehicle control, was the vehicle also diluted to that similar concentration or was that a straight vehicle?

DR. BARNETT: No. Everything was diluted to the same concentrations.

DR. GENCO: Ralph?

DR. D'AGOSTINO: I'm all caught up with the discussion of the individual components and so forth, but I'd like also -- and maybe it's inappropriate, but I'd like also that there's a statement to be made about the product as it is too. We've had an awful lot of data about the effectiveness of the product as it is, and we don't necessarily want to get too carried away with all these individual components.

DR. GENCO: Is the issue from the FDA's standpoint -- what's the rationale for the law requiring that each in a combination be active? This goes to your comment here. If a combination is active for 100 years, safe, does it really matter -- I'm not saying this is the case here, but one is not really contributing very much to the activity or at all?

DR. KATZ: The intended purpose for the policy was basically to prevent ineffective active ingredients from being combined or to prevent products together that

would not be safe if they were combined.

The policy itself, as the guidelines, give somewhat of a leeway as to what is the measure of effectiveness. It doesn't really say you have to be better. It just says equivalent. It's up to the determination, in a sense, of this panel to say that, yes, it would be equivalent in terms of effectiveness and safety and also weighing in the risk/benefit profile and the intended purpose and the target population. So, there are a variety of factors that would go into it rather than just is it more effective than or is it as effective or is it effective. That is sort of a degree of interpretation.

DR. GENCO: Thank you.

I have a suggestion. It's almost 2:30. I suggest that we take a break and then come back and further discuss and, if appropriate, take a vote.

Does anybody want to comment before we do that?

DR. D'AGOSTINO: Yes. If we do that, which I'm all for, we as panel members can't caucus to decide on what we're going to do.

DR. GENCO: Cannot.

DR. D'AGOSTINO: We cannot. Right.

DR. GENCO: No, I didn't mean that for caucus.

DR. D'AGOSTINO: I know you didn't, but the audience may think we --

DR. GENCO: I was thinking about a physiologic imperative that we all have.

(Laughter.)

DR. GENCO: Thank you. Let's get back here in 15 minutes, which will be 25 to 3:00.

(Recess.)

DR. GENCO: I'd like to welcome you back. Can we start the proceedings?

We're going to have some comments by Andrea Neal, Dr. Neal, regarding a process. As you know, we are now under CDER and there's some minor differences in protocol.

DR. NEAL: I just wanted to clarify that the contact person for CDER meetings is the person who's listed in the Federal Register notice. That was me. I'm sorry that the meeting materials didn't get to people until this morning, but they actually weren't sent to me, nor were they sent by the date that was listed in the Federal Register. So, in the future, just keep those things in mind.

The other thing is that in CDER, the chairman is a voting member, and that may be different from what it is in CDRH. I'm not that familiar with their rules. They run under a whole different set. So, I'd like to go back and actually get Dr. Genco to provide his vote for the last

ingredient that we reviewed.

DR. GENCO: Thank you. For the record, with respect to safety for C-31G, I vote yes for Category III, and with respect to efficacy, I vote yes for Category III. Thank you.

In fact, I recall not voting before, so I think it must be different.

Let's proceed now with the discussion of Listerine and particularly the issue of the minus-one experiments. Does anybody else want to make any further comments about that or anything else that you would like to discuss before we proceed to what could very well be a vote? Stan, do you want to make some final summary suggestion or comments?

DR. SAXE: No. My own opinion would be to move to a vote on efficacy and safety of the four essential oils combination, i.e., Listerine.

DR. GENCO: As you reviewed it, would you share with us your feelings about the categorization?

DR. SAXE: I would suggest that in terms of my recommendation, in terms of efficacy the product Listerine be Category I, that it is efficacious, and second, for safety, Category I, that is demonstrated to be safe.

DR. GENCO: Okay. Are we ready to vote? Any further comments, discussion? Gene?

DR. SAVITT: I'll vote yes on both, or do you want to handle it separately?

DR. GENCO: Let's handle it separately, yes.

DR. SAVITT: For safety, Category I, I vote yes.

DR. LISTGARTEN: Yes.

DR. WU: Yes.

DR. D'AGOSTINO: Yes.

DR. GENCO: Yes.

DR. SAXE: Yes.

DR. BOWEN: Yes.

DR. GENCO: For efficacy, and the recommendation is Category I. Let's start with Stan this time.

DR. SAXE: I vote yes.

DR. GENCO: Bill?

DR. BOWEN: Yes.

DR. GENCO: Gene?

DR. SAVITT: Yes.

DR. GENCO: Max?

DR. LISTGARTEN: Yes.

DR. GENCO: Chris?

DR. WU: I abstain.

DR. D'AGOSTINO: Yes.

DR. GENCO: Yes.

Let's proceed --

DR. D'AGOSTINO: I'd like just to have it somewhere in the record that there is the clarification of this n minus-one or the particular ingredients and that the efficacy vote, at least that I gave, was realizing that that's a discussion point, but I still think the total product is efficacious.

DR. GENCO: Thank you.

Well, Stan has been given quite a workout here.

(Laughter.)

DR. GENCO: Why don't we go out of order here to hydrogen peroxide/povidone iodine and let Gene give us his summary.

DR. SAVITT: To summarize my review from I believe it was the last meeting, the combination of ingredients I felt the submitted information raised a number of toxicity issues, both acute and chronic, neither of which were adequately addressed by the presentation or following discussion by the industry representatives from the company submitting this particular product.

I also felt that the efficacy data was contradictory and did not provide adequate information, nor were the studies adequately designed or appropriately designed to allow for an interpretation in terms of efficacy.

There was a number of comments raised that the product appeared to be poorly designed as an OTC product, and based upon my review, I felt that the safety issues were not adequately addressed to permit anything other than a Category II for safety. I'm sorry. Category III. I'm sorry.

DR. GENCO: And do you want to make some comments about efficacy and a suggestion for categorization?

DR. SAVITT: In the same vein, I felt that the studies submitted did not permit an adequate evaluation of efficacy, and I would also recommend a Category III for efficacy as well.

DR. GENCO: Any comments, discussion?

(No response.)

DR. GENCO: Are ready to vote? I don't want to rush the vote if there are comments or further questions here.

Let's deal with safety first. The recommendation is for hydrogen peroxide/povidone iodine to be in Category III. Do you want to start the vote?

DR. SAVITT: Yes.

DR. LISTGARTEN: Yes.

DR. WU: Yes.

DR. D'AGOSTINO: Yes.

DR. GENCO: Yes.

DR. SAXE: Yes.

DR. BOWEN: Yes.

DR. GENCO: Okay, that's seven yeses.

For efficacy, the recommendation is for hydrogen peroxide/povidone iodine to be Category III. Bill, do you want to start?

DR. BOWEN: Yes.

DR. SAXE: Yes.

DR. GENCO: Yes.

DR. D'AGOSTINO: Yes.

DR. LISTGARTEN: Yes.

DR. WU: Yes.

DR. SAVITT: Yes.

DR. GENCO: Thank you. Seven.

Okay, Stan, you've had your rest.

(Laughter.)

DR. SAXE: Zinc citrate was reviewed by me at the last meeting of this subcommittee on May 8th of this year, at which time I reported that there was fairly extensive study of zinc citrate but basically as an inhibiting agent for dental calculus formation, as we have in the minutes that have been supplied to us today, and that there had been study done on the safety of the use of zinc citrate, and indeed it was extensive and zinc citrate

in my opinion is safe.

However, for efficacy, there simply was insufficient evidence that was in the material which was submitted to this subcommittee to make any determination of its effectiveness as an antigingivitis agent.

So, therefore, I recommend that zinc citrate for safety be Category I; for efficacy, zinc citrate be Category III.

DR. GENCO: Comments, questions about zinc citrate?

(No response.)

DR. GENCO: Okay. I take it you want it to go to a vote. Any objection to that?

(No response.)

DR. GENCO: The recommendation for safety is Category I. Stan, do you want to start?

DR. SAXE: yes.

DR. GENCO: Yes.

DR. D'AGOSTINO: Yes.

DR. WU: Yes.

DR. LISTGARTEN: Yes.

DR. SAVITT: Yes.

DR. GENCO: Bill?

DR. BOWEN: Yes.

DR. GENCO: That's seven yeses for Category I.

Zinc citrate efficacy. The recommendation is Category III. Gene, do you want to start?

DR. SAVITT: Yes.

DR. LISTGARTEN: Yes.

DR. WU: Yes.

DR. D'AGOSTINO: Yes.

DR. GENCO: Yes.

DR. SAXE: Yes.

DR. BOWEN: Yes.

DR. GENCO: That's seven yeses.

We're finished with the official agenda, and as I understand it, we really can't start the next topic until tomorrow morning because of its being announced.

Is there anything that you folks from the FDA would like to say about how we're proceeding or anything that's happened today? Can we be of any further help?

MR. SHERMAN: I just wanted to mention that I've distributed a handout having to do with tomorrow's presentation on final formulation testing -- or tomorrow's discussion, rather. There are a few general questions listed, as well as one submission with a particular point of view about final formulation testing. I believe another one was included in the background package. I just suggest that you review that, if you can, tonight to help with tomorrow's discussion.

Also in the background package that you were supplied with, there were some examples of testing requirements and discussion from other advisory panels. It would be a good idea to look at that too.

If any of you do not have the background package, I'll see if I can get you another copy.

DR. GENCO: Lew, do you have a question?

MR. CANCRO: I'm sorry. Was that distributed, Bob, the background package?

MR. SHERMAN: That should have come to you previously. The one that you got several weeks ago. It was a rather thin package this time. It should be in there. Because there were no new reviews.

DR. GENCO: Lew told me if it doesn't weigh a pound and a half, he doesn't even look at it.

(Laughter.)

DR. NEAL: Before Dr. Genco adjourns the meeting, I'd just like to have the Plaque Subcommittee members stay so that we can talk about future meeting dates. I have a set of dates that I've polled you for, and we need to choose those because I don't think you want to meet seven or eight times.

DR. GENCO: Any further comments, discussion?

(No response.)

DR. GENCO: The meeting is adjourned. See you

tomorrow at 8:30.

(Whereupon, at 2:50 p.m., the subcommittee was recessed, to reconvene at 8:30 a.m., Thursday, October 30, 1997.)