UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

DENTAL PLAQUE SUBCOMMITTEE

MEETING

FRIDAY
MAY 29, 1998

The meeting took place in the Walker and Whetstone Rooms, Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, Maryland at 8:30 a.m., Robert J. Genco, DDS, PhD, Chair, presiding.

PRESENT:

ROBERT J. GENCO, DDS, PhD	CHAIR
RHONDA W. STOVER, RPh	EXECUTIVE SECRETARY
WILLIAM H. BOWEN, PhD, DSc	MEMBER
RALPH D'AGOSTINO, PhD	MEMBER
MAX A. LISTGARTEN, DDS	MEMBER
SHEILA MCGUIRE-RIGGS, DDS, DMSc	MEMBER
EUGENE D. SAVITT, DMD	MEMBER
STANLEY R. SAXE, DMD, MSD	MEMBER
CHRISTINE D. WU, PhD	MEMBER
LEWIS P. CANCRO	INDUSTRY LIAISON REP
FRED HYMAN, DDS, MPH	FDA REPRESENTATIVE
LINDA KATZ, MD, MPH	FDA REPRESENTATIVE
ROBERT SHERMAN	FDA REPRESENTATIVE
R. WILLIAM SOLLER, PhD	SPEAKER

ALSO PRESENT:

MICHAEL BARNETT, DDS
NANCY BUCK
PETER HUTT
BRUCE KOHUT, DMD

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

8:32 a.m.

CHAIRMAN GENCO: This morning we have four items, the culmination, considerations for culminations. We'll finish up dosage and performance standards, the microbiologic testing. And then the directions for use. So I'd like to, again for the record, have each of the individuals at the table introduce themselves. Let's start with Fred.

MR. HYMAN: Fred Hyman, Dental Officer, Division of Dermatologic and Dental Drugs, FDA.

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

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

MR. SAVITT: Gene Savitt, Forsyth Dental Center, private practice.

DR. LISTGARTEN: Max Listgarten, University of Pennsylvania.

DR. RIGGS: Sheila Riggs, Oral Epidemiologist, Iowa.

CHAIRMAN GENCO: Bob Genco, University of

Buffalo.

MS. STOVER: Rhonda Stover, FDA.

DR. BOWEN: Bill Bowen, University of Rochester.

MR. SAXE: Stanley Saxe, University of Kentucky.

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

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

MR. CANCRO: Lew Cancro, IRR.

CHAIRMAN GENCO: Thank you. And now Rhonda, you'll make a statement.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. For the next several months the Subcommittee will review information on ingredients contained in products bearing anti-plaque and anti-plaque related claims to determine whether these products are safe and effective and not misbranded for their label 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 United State Code 208B, waivers have been granted to each member and consultant participating in the Subcommittee meeting.

A copy of these waiver statements may be obtained from the Agency's Freedom of Information Office, Room 12-A-30, Parklawn Building. In the event that the discussions involve any other products and 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 who's products they may wish to comment upon.

CHAIRMAN GENCO: Are there any comments?

(No response.)

CHAIRMAN GENCO: Okay, thank you, Rhonda. I'd like now to introduce Dr. Bill Soller, who will discuss combination anti-plaque, anti-gingivitis ingredients. Good morning, Bill.

DR. SOLLER: Good morning Dr. Genco, members of the panel. It's on I believe. Can you hear me? Now that we have the technics down, good morning, Dr. Genco, members of the panel. I'm Dr. Bill Soller, Senior Vice President and Director of Science and Technology for the Non-Prescription Drug Manufacturers Association. And I'm here representing the NDMA/CTFA Joint Oral Care Task Group. And it's a pleasure to return to the three-day plaque-a-thon.

(Laughter.)

DR. SOLLER: We're here to talk about OTC combination policy and I will make a brief remark relating to my use of the term anti-plaque/anti-gingivitis. I won't go into the description of that, but it's the same remark I made yesterday about referring to this as anti-gingivitis. Or anti-plaque/anti-gingivitis or anti-plaque.

Now what I'd like to talk about is FDA's combination policy, the types of combinations that are permitted, examples from the OTC Review, our recommendations and then I'll circle around to the statement of identity on combinations, because that wasn't really dealt with yesterday and we'll have similar slides to what I presented yesterday, though they don't appear in this particular set of handouts that you have.

We sent you materials last week pertaining to our comments on the combination policy. We have handouts here and I've provided you with a brief presentation at the last meeting regarding our recommendations on the combination policy and combination products in this rule making. FDA's OTC combination policy appears in 21 CFR, Section 331-0. An OTC drug may combined two or more safe and effective active ingredients and may be generally recognized as safe and effective with three provisos.

And those are, when each active ingredient makes a contribution to the claimed affect. When the combining of the active ingredients does not decrease

the safety or effectiveness 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.

And all of this, in the context of the definition of effectiveness and that is a reasonable expectation that in a significant proportion of the target population the drug will provide relief of the type claimed. FDA's OTC Combination policy is long-standing. It's supported by companion FDA guidelines, supported by previous OTC Advisory Panels that have all considered this and then acted upon this particular policy creating their own particular recommendations for OTC combinations per those rule makings.

And is supported by the inclusion of many different types of combinations in a wide variety of OTC review rule makings. And I might add, also supported by the successful marketing experience of these drugs over their 25 year or so history of this particular combination policy. Let's take a look at

some examples from the OTC review. Here in the upper left hand corner, Cough/Cold Products, where there are four different pharmacological categories.

And the combination policy allows you to pick one analgesic from this category, a nasal decongestant, a cough suppressant, antihistamine, so you might have dextromethoraphan, pseudoephedrine, aspirin and chloropheniramine. Or it might be dextromethoraphan, phenylpropanolamine, acetaminophen and brompheniramine in that kind of construct. Products you've probably used at one time or another.

Internal analgesics. Two internal, different internal analgesics plus an analgesic adjuvant. For sunburn, three sunscreens. So here you have one pharmacologic class picking three different actives from that one class. Or a sunscreen, skin protectant in the lower left and here it would be taking from two different monogram rule makings a particular active ingredient.

And the top of the topical ophthalmics may be the pinnacle of the application of this policy, and I won't run down these, but there are many different

types of mix and matches that are permitted per the OTC policy. So in some, FDA's long-standing policy allows us to see that there's precedent in the OTC review for many different types of combinations.

From combining ingredients from different pharmacologic categories, or taking ingredients from different monographs. And that's what we'll be talking about in a moment. Provided that each active contributes to the claimed affect, that by combining you do not reduce the safety and effectiveness of each of the actives. And that the combination provides rational, concurrent therapy.

All of this, in the context of the definition of effectiveness, a reasonable expectation of effective and remembering that the OTC combination policy is supported by a remarkable record of safety across all OTC categories spanning some 25 years. So our recommendations are for an anti-plaque, anti-gingivitis agent plus an anti-caries agent. Anti-plaque, anti-gingivitis plus a tooth desensitizer, potassium nitrate in this case.

Anti-plaque, anti-gingivitis plus anti-

caries plus tooth desensitizer and the combination of an anti-plaque, anti-gingivitis active ingredients, though not reviewed or recommended rather for category one status here, mainly a theoretical consideration at this point.

Let's go ahead and take a look at these one at a time. The anti-plaque, anti-gingivitis plus anti-caries agent, here our rationale is that caries and gingivitis are distinct pathological entities. They can be treated by different active ingredients. They affect consumers throughout their lifetime. Just by way of example, we included the epidemiologic study by Hand and the clinical trials by Jensen, Kohout and Lu describing dental caries being a continuing problem in the adult population.

And that significant reductions in caries incidents can be achieved with fluoride-containing dentifrices in adults. Of course on the gingivitis side, the many studies that have been submitted to you and we've talked about this a couple of times over the last two days, mainly in an adult population. So that a stannous fluoride product, in this particular rule

making recommended as category one combination, is actually a combination in one, having intrinsic fluoride, anti-caries activity through that mode but also an anti-gingivitis affect.

But in the rinse category, a fluoride rinse plus CPC, or a fluoride rinse plus a fixed combination or by way of another example, a fluoride plus CPC dentifrice would be appropriate combinations. Thinking now about an anti-plaque, anti-gingivitis agent plus a tooth desensitizer. Descriptions by Flynn and Dowell about a eight to 30 percent prevalence in adults. Usually in the younger age group. Usually on the facial surfaces, canines, pre-molars. And common stimuli such as tooth brushing, digital probing, hot and cold, acids and sweet causing considerable discomfort for the sufferer.

Orchardson has talked about a 68 percent incidence of hyper-sensitive teeth having significant gingival recession. Usually a chronic condition with acute episodes. So our rationale in thinking about the four week duration of use for the category one labeling for OTC tooth desensitizers would be that the

proposed combination would allow continued anti-gingivitis, anti-plaque treatment during episodes of dental hyper-sensitivity.

And then looking at the third combination, the anti-gingivitis, anti-plaque, anti-caries plus tooth desensitizing agent. Here the rationale is very similar to the one I just gave. It would allow recognizing the four week duration of use for the tooth desensitizer. It would allow the proposed combination to provide continued anti-gingivitis, anti-plaque and anti-caries treatment during episode on dental hyper-sensitivity.

These are not included in the hand out packet that you have now, but were shown to you yesterday. And what I'd like to do is just take a brief sojourn back to the issue of statement of identity as it would be applied to combinations, and I mentioned this yesterday. Here again is the Summary of Recommendations for the anti-gingivitis, anti-plaque plus anti-caries. Anti-gingivitis, anti-plaque plus tooth desensitizing. Anti-gingivitis, anti-plaque plus anti-caries plus tooth desensitizing

combinations that I've just talked about.

And I showed this slide yesterday. Remembering as we went back to the statement of identity for single ingredient, it would be the established name of the drug, anti-gingivitis toothpaste. So it would be cetylpyridinium chloride, anti-gingivitis mouth rinse, for example. And that's what you looked at yesterday. Here when you combine a statement of identity from another monograph, you have to sort of fit it in from a rational, English construct standpoint either before or after your particular statement of identity here.

And let's take a look at an example. So that for the combination policy where you do not have to express, per regulation, the established name of the drug, but the principle intended action as the statement of identity. And recognizing that the active ingredient listing would be there on the label so that you're not having a label that would not express what the active ingredient is.

It would be there, probably first among the information on the information panel with FDA's

new proposal. But here, if we took an anti-cavity, anti-plaque, anti-gingivitis dentifrice, which might be a fluoride CPC dentifrice, by way of example. Or an anti-cavity, anti-gingivitis toothpaste for sensitive teeth. Taking that same example, the fluoride CPC plus potassium nitrate dentifrice.

Or perhaps a fixed combination, not shown here, plus fluoride, which would be anti-cavity, anti-plaque, anti-gingivitis mouth rinse. And that's how the statement of identity would appear per the current regulations for statement of identity pertaining to combinations. So in conclusion, just returning, these are there basic combinations that we are requesting the panel review and affirmatively include in your panel report. Thank you very much.

CHAIRMAN GENCO: Thank you, Dr. Soller. Are there any comments or questions from the panel?

(No response.)

CHAIRMAN GENCO: Okay, shall we proceed then to Page 15, the Summary that was presented to us. Any comments about the anti-gingivitis, anti-plaque, anti-caries combination.

DR. LISTGARTEN: Bob.

CHAIRMAN GENCO: Yes.

DR. LISTGARTEN: Can you just refresh our memories about some of the debate from yesterday when we discussed the terminology, anti-plaque, anti-gingivitis. Are we going to use that terminology? Are we going to only use anti-gingivitis? I'm still a bit in the fog about what the outcome was.

CHAIRMAN GENCO: With respect to the statement of identity, we had two categories, anti-gingivitis and anti-plaque, anti-gingivitis. It was turned, yeah, it was anti-gingivitis, anti-plaque, right. So let's first discuss the culminations that might be rational for advice and then the statement of identity, which is how it's expressed.

MR. SHERMAN: I just want to say, determine which combinations would be rational and then --

CHAIRMAN GENCO: And then what --

MR. SHERMAN: -- apply your statement of identity.

CHAIRMAN GENCO: Okay. So let's talk

about the anti-gingivitis, anti-plaque, anti-caries. That's the first combination. Is there any, this is not the statement of identity, but the combination of anti-caries, anti plaque -- anti-gingivitis, anti-plaque plus anti-caries. Any problem with that?

DR. RIGGS: Was there some discussion yesterday that the slash was confusing. We wouldn't want to in any way say you could have anti-plaque plus anti-caries agent?

CHAIRMAN GENCO: Yeah. Let's, let's talk about first the combinations.

DR. RIGGS: Okay.

CHAIRMAN GENCO: And not the english. The english would be in the statement of identity and we'll talk about that next, if you don't mind. So agents which have anti-gingivitis, anti-plaque activity, combined with an agent which has anti-caries activity. That's the combination, I guess, we're advising the FDA. Is that a reasonable combination given that fulfills all the criteria of safety, efficacy and the efficacy isn't compromised by making the combination?

(No response.)

CHAIRMAN GENCO: Okay, so I take that as affirmation. Essentially it already exists with the Colgate product. Okay, with respect to now the second combination. An agent which has anti-gingivitis, anti-plaque activity and combined with an agent which is a tooth desensitizer. Reasonable combination? Any comments, objections?

(No response.)

CHAIRMAN GENCO: Okay. The third category is all three of those, anti-gingivitis, anti-plaque agent combined with an anti-caries agent, combined with a tooth desensitizing agent.

(No response.)

CHAIRMAN GENCO: And I take this to mean one of each category. We'll get to the possibility of multiple, of single categories. Bill.

DR. BOWEN: I have a question for the staff of the FDA or anyone else who can answer. What are the obligations if I add a desensitizing agent to a proven anti-caries, fluoride toothpaste? Do you have to go through the testing, the animal testing,

the fluoride uptake. Okay, thank you.

CHAIRMAN GENCO: Of the final formulation? Okay. So presumably also, Bill, the final formulation with the tooth desensitizing agent would also have to be tested for anti -- the performance standards for anti-gingivitis, anti-plaque that we discussed? Okay. Sheila.

DR. RIGGS: Would there be any claims about root caries versus caries in enamel with that?

CHAIRMAN GENCO: What's the present status of the anti-caries claims? Although we haven't really dealt with that. That would be in the monograph.

MR. SHERMAN: Those would be the same. It would be the same as in the final monograph for any caries.

CHAIRMAN GENCO: Okay, whatever is allowed now.

DR. SOLLER: Right. Do you want me to read it? Would you like me to read it?

CHAIRMAN GENCO: Sure.

DR. SOLLER: Bill Soller. Aids in the prevention of dental select one of the following,

cavities decay, caries bracket decay or caries bracket cavities.

DR. LISTGARTEN: So it doesn't specify.

CHAIRMAN GENCO: So the root surface versus enamel is not part of that. Okay let's get back to the anti-gingivitis, anti-plaque, anti-caries and tooth desensitizing, those three, one of each in that three-fold combination. Any problem with that, any comments, questions?

(No response.)

CHAIRMAN GENCO: Okay. One that we haven't really talked about is this combinations of two or more anti-plaque, anti-gingivitis active ingredients. Stannous fluoride with CPC for example. We haven't really discussed that. We're being asked to make some comments about that. Again --

DR. LISTGARTEN: Well, I think if the combination is rational and this may be a rational combination since one provides fluoride and the other one acts in a different manner. If in fact the two are additive or synergistic, I guess that would be acceptable. They would have to be at least additive.

CHAIRMAN GENCO: Okay. What is the, what is the FDA policy to combinations of single class, two or more of a single class. Do you they have to show superiority to either used singly?

DR. KATZ: They have to show a benefit.

CHAIRMAN GENCO: A benefit from being used as a combination.

DR. KATZ: That's right. But there has to be some benefit for having both of them together --

CHAIRMAN GENCO: Okay.

DR. KATZ: -- to be allowed.

CHAIRMAN GENCO: Okay. Yes.

MR. SAXE: When you say benefit, you mean that there is just a rationalization of their use as a benefit, or you mean a benefit shown in some sort of a study invitro or invivo that there is an enhanced benefit to the consumer.

DR. KATZ: A benefit in a study. Whatever study is deemed appropriate for those particular products. But it's felt that in order to combine two from the same category, that there clearly has to be a benefit from each of those ingredients that are

combined.

CHAIRMAN GENCO: Okay, so the --

DR. KATZ: And again, it has to be a demonstrable benefit.

MR. SAXE: But this some benefit does not have to exceed that which could be achieved by any single ingredient?

DR. KATZ: That's correct.

MR. SAXE: Each simply has to contribute in some fashion.

DR. KATZ: To contribute to it and you have to be able to demonstrate that each has a benefit. So that if by combining the two of them, but there is not a benefit, that if you have a benefit demonstrated from one but not from the other, then the two could not be combined. Or if combining to of them, one as a detrimental affect on the other, they could not be combined.

But if you're able to demonstrate they both have a benefit then they could be combined. It doesn't, the, for the OTC it doesn't specify that it has to be a significant benefit above that, but it

just has to have a benefit. And the two together, you have to demonstrate have a benefit in the, when they're combined together.

CHAIRMAN GENCO: So, let me see if I understand that.

DR. SOLLER: Page 4 of the handout has the policy. And it's Point 1 that you're talking on. Makes a contribution to the claimed affect. But contribution isn't specifically defined.

DR. RIGGS: Does the benefit have to be above the benefit of one product?

DR. KATZ: No, it doesn't. Unless of course in, when you are designing the trial that's what you're asking them to do. But the regs don't specify it that way. They just specify that they have to demonstrate a benefit. So that you have to be able to show that each ingredient has a benefit.

CHAIRMAN GENCO: So Max's question about the additive affect, it's not an additive or synergistic affect.

DR. KATZ: No, it does not.

CHAIRMAN GENCO: It's a benefit as however

defined as a benefit. I mean you can look at a population and one agent may work on the young and another on the older, but if you looked at the total population, you may not see a difference in the two together. Except inasmuch as you looked at individuals, for example. I'm just trying to think of what a benefit would be that isn't additive or synergistic.

Working on different populations or different times in the life span. Or different stages of disease.

DR. KATZ: It could probably, I don't think it's ever been really defined that way. But it's basically been defined that, again, for an OTC that there has to be some rational for putting the two together. And that you have to demonstrate that both of them together would have a benefit.

Unfortunately, I think this where it always gets confusing with the combination policy because the regs don't specify that you need to have a synergistic benefit.

CHAIRMAN GENCO: Okay.

DR. KATZ: You just need to have a demonstrated benefit.

CHAIRMAN GENCO: Okay. So the company has to be able to convincingly argue that there is a benefit and define what that benefit is and show it in a clinical study, whatever that benefit is.

DR. KATZ: That's correct.

CHAIRMAN GENCO: And it could either be a numerical, synergistic or additive affect.

DR. KATZ: That's correct. And there has to be a rationale for combining them.

CHAIRMAN GENCO: Okay. A rationale and a clinical trial?

DR. KATZ: That's right. Well actually there has to be a rationale because otherwise why would you combine them.

CHAIRMAN GENCO: Right.

DR. KATZ: But there, so that the two would go sort of hand-in-hand.

CHAIRMAN GENCO: Okay, fine. That's helpful. Yes.

MR. HUTT: Bob, I think it, rather than,

pardon me, talking about each having a benefit, it's each has to make a contribution to the claimed effect. Let's go back to one that Bill Soller used yesterday, the antacid monograph. All that is required is that each one of the combination of antacid ingredients contributes significantly to the antacid effect.

There's no requirement of added benefit, greater synergistic or any other type of reaction among them. Frequently there has been more than one active ingredient from the same pharmacological class we're talking about, not different pharmacologic classes, in order to reduce exposure to individual ingredients. And that isn't a "benefit" in the classic sense of effectiveness. But there has never been a requirement that you show that two are better than one.

DR. KATZ: I think we're having a semantic argument versus what the terminology, contribution versus benefit. Because from the Agency's perspective we, what you're describing as a contribution we look at as under the terminology of benefit. And we are saying the same thing, we're just using a different

word and it's a semantic difference.

Because basically what I was saying was the same thing you were except I used the word benefit and you used the word contribution. And that's actually the way that it's interpreted is that we're not asking for a synergistic benefit, but we are asking for a benefit, which is the word that you are using as a contribution.

MR. HUTT: In other words, Linda, to go back to the antacid, the benefit is it acts like an antacid?

DR. KATZ: That's correct.

CHAIRMAN GENCO: So to paraphrase or so that we understand what you've said, if one agent used at effective concentration has a side effect, if it's used at half the concentration and another agent is used to supplement and you get the same effect on the gingivitis but you reduce the side effect by reducing one agent, then you have a benefit.

MR. HUTT: Well --

CHAIRMAN GENCO: Or, or with --

MR. HUTT: You have a contribution.

CHAIRMAN GENCO: You have a contribution, right.

MR. HUTT: Each one --

CHAIRMAN GENCO: It's a beneficial contribution.

MR. HUTT: -- is an effective agent.

CHAIRMAN GENCO: I think I, I think, is that clear? In other words, you can combine two to reduce the side effect of one that would be, have a side effect at its full concentration, you can halve it --

DR. KATZ: That's correct, but you --

CHAIRMAN GENCO: Okay.

DR. KATZ: -- but you don't necessarily have to do that either.

CHAIRMAN GENCO: Okay.

DR. KATZ: Because there may be some circumstances where you will put them in at their, the same dose that they might be used singly and that whatever --

CHAIRMAN GENCO: Okay.

DR. KATZ: -- for whatever desired

rational effect that you want, that there is deemed to be a benefit from combining the two.

MR. HUTT: I think the critical thing is there doesn't have to be, and I think Linda and I are saying the same thing, an additional benefit.

CHAIRMAN GENCO: Additional, okay.

MR. HUTT: Just, it has to be "effective".

CHAIRMAN GENCO: Okay.

DR. RIGGS: I need a clarification.

CHAIRMAN GENCO: Surely.

DR. RIGGS: The, let's just hypothetically say Listerine gives you 30 percent reduction in gingivitis and you add CPC and they now each can give 15 percent toward that reduction to equal that 30 percent reduction? Is that, so it's exactly the same reduction.

CHAIRMAN GENCO: But there's a benefit that you can use less alcohol or something like that.

DR. KATZ: There would have to be some benefit for doing it.

CHAIRMAN GENCO: Right.

DR. RIGGS: Now then how does that, the

second line on Page 4, the second bullet, when combining the active ingredients does not decrease the effectiveness. Well it did. It --

DR. KATZ: However, it may not have. Because what you may have done is that there may be something else that you would be able to reduce as a result of combining the two ingredients. So that you've not lost effectiveness and that the end result is still the same. So the product may still be as --

DR. RIGGS: Right, the end result is still 30 percent reduction, but --

DR. KATZ: So that your end point, which was whatever your reduction wanted to be is still the same so that the product may be viewed as being effective.

DR. RIGGS: Will that decrease the effectiveness of any of the individual active ingredients.

DR. KATZ: Right, but there would have to be some rationale for doing it. Now if the rationale for doing it was to reduce something else that may have gone into the component, let's say alcohol. So

that by combining the two, you could then reduce the alcohol by half. That might be deemed a significant enough benefit to allow the combination to occur. However, if everything else remains the same, I'm not sure whether that combination would be able to fly unless there is some other reason or rationale for having them.

CHAIRMAN GENCO: So, what is the process then? Let's say that after we're finished, a company comes up with some combination of these, two of these three category one agents. They would have to present to the FDA the rationale and the studies?

DR. KATZ: No. If these, it would depend. If these are allowable combinations, then they would not. They would just again have to show to the FDA that they've combined them in a way that the FDA has allowed and then label it accordingly. However, if there's some deviation and that these are not allowable combinations --

CHAIRMAN GENCO: Okay.

DR. KATZ: -- then they would have to go through and do the clinical trials to show that they

are effective.

CHAIRMAN GENCO: All right, so right now we have no basis to say anything other than theoretically they may be combined because nobody has combined them. I mean so this panel can't really judge whether a combination would be effective.

DR. KATZ: That's correct. Unless of course you feel that from the information that has been presented to you and the rationales that you can think of as to why these products might, ingredients might be combined, that if there is a rationale and you can think of a good reason to do it, then this would be the time to let us know --

CHAIRMAN GENCO: Okay.

DR. KATZ: -- that this seems to be something that we would want to see or we would not want to see occur.

CHAIRMAN GENCO: Okay. Let's get, let's answer that question. We have comments first.

MR. HUTT: I there's still some confusion. And let us go back to the antacid example because it is a very clear policy that's now been established for

20 years. You can use three antacid ingredients, perhaps even four, in an individual product. You're not required to show any "benefit" other than that each makes a contribution to the claimed antacid effect.

You do not have to show a rationale as to why you're including them in there. Each one is effective. And that is the only thing you must show. You don't have to show greater safety, greater effectiveness. Sheila, in answer to your question, obviously if you will just take two, if you put two, each one is in at a lower level and each one makes its own effectiveness. If you, three, you put them in at still a lower level, what the provision in the regulation refers to is that one doesn't block the action of the other.

That was the only concern of why that regulation was written the way it was. You didn't want to add one that literally prevented the other from being effective. But there was no and is no requirement that there be a, and some benefit rationale for having two rather than one. That was

never a requirement, and to my knowledge, FDA has never said so to this day.

DR. KATZ: That is not a requirement. But for the purposes of this discussion it would be. In the sense of that if there's no rationale for doing it now, then one may not want to allow those combinations. But once the decision has been made, you're correct. That if the decision is made to allow two from the same category, then you are right at beyond that, the rationale isn't needed. But for this discussion, I think that people need, the panel needs to entertain if there's a rationale or a basis for combining those products or ingredients.

MR. HUTT: Well, I'm not sure in the -- this may be a lot about nothing, because I'm not sure that any, at least I haven't seen and perhaps people in the audience will correct me, anyone requesting the opportunity for a combination. But to go back to the antacids. At the time of that monograph and I could name other monographs as well, the sole question was it a manufacturer wants to put in two rather than one, that is enough benefit. There was no other

requirement of any kind.

CHAIRMAN GENCO: I think you're right. We clearly don't have any basis, scientific basis, experimental basis for the combinations. They haven't been tested, period. And I think what Linda is saying is, she's really stretching us while we're here, is there even a rationale? And on the basis of a real strong rationale, would this committee say yes, you know, it's reasonable that you combine one with three. And I think that's what we're being asked. And I just wonder if that's the case. Max and then Bill.

DR. LISTGARTEN: I just, the one thing that puzzles me a little bit is that if someone decides to make some eight ingredients they just have to argue for rationale. But don't they have to demonstrate the middle bullet that there is no decrease in the safety or effectiveness of any of the individual active ingredients.

They have, it hasn't been done so we don't know. So if somebody all of a sudden comes along and says, I want to do it, it behooves someone to show that there is no decrease in the activity of one of

the ingredients.

MR. HUTT: Well again, Max, there has to be if you're adding two antacids, obviously the total neutralizing capacity of the final product remains the same, but the activity of each one, because it's in at a lower level --

DR. LISTGARTEN: I think it works very nice for antacids, but let's take the anti-plaque agents. We need a fixed oil combination to have activity. You need all of these in a gold package.

MR. HUTT: Correct.

DR. LISTGARTEN: Okay, I'll buy that. Now let's say I'm going to add fluoride to this. Now I don't know what fluoride is going to do to this. Maybe it will do nothing. Maybe it will totally neutralize the activity of the four oils? I don't know that.

MR. HUTT: Well clearly, that's why the provision is in the regulation that prevents that. That is the one thing that is crystal clear.

DR. LISTGARTEN: But who has to demonstrate the fact that --

MR. HUTT: The manufacturer.

MR. HUTT: So there is, there is an obligation on the part of someone who wants to mix ingredients to demonstrate that there is no interference.

MR. HUTT: Yes, correct.

DR. SOLLER: Dr. Genco. Could I make a comment.

DR. LISTGARTEN: That wasn't very clear.

CHAIRMAN GENCO: Bill and then I'm going to go right back to the panel, because I think we can resolve with fairly easily.

DR. SOLLER: That's what I'm trying to convey here and offer perhaps some clarity. I had mentioned that it was principally a theoretical discussion. You haven't been presented with that.

CHAIRMAN GENCO: Right.

DR. SOLLER: I think it would be helpful, in the interest of R&D, if we had the kind of resolution to this discussion that didn't foreclose that possibility. And as long as we see that the manufacturer, if in this rule making was to petition

for an amendment, that there was a basis within this panel to say that as long as this is met, that it would seem to be an appropriate way to go.

CHAIRMAN GENCO: Okay. So at the present time, does anybody on the panel think there is a rationale for combining any one, excuse me, two or more of the category one anti-plaque, anti-gingivitis agents? In other words, it's our rationale for combining stannous fluoride, Cepacol and/or the fixed Listerine. Is there a rationale?

DR. LISTGARTEN: I think there's a rationale. I mean we're dealing with different conditions. If we can have a product that hates caries and gingivitis and it helps to desensitize teeth in a person who happens to have sensitive teeth, I don't, probably I don't see any particular problem. I mean, is that what you're asking for us to give you our opinion?

CHAIRMAN GENCO: That's right. So this would be a direct --

DR. LISTGARTEN: I don't have a problem with it.

CHAIRMAN GENCO: We can't say much more than that. There's a theoretical rationale. I mean there's no scientific basis, though, for doing it.

DR. BOWEN: There might be a biochemical basis for not doing it.

DR. LISTGARTEN: Well, this was the nature of my earlier question. There might be some, a biochemical basis for not doing it.

CHAIRMAN GENCO: So it's not a clear cut example as the antacids. It probably doesn't matter which of the antacids you mix as long as they neutralize acid. But we don't have such a simple situation here.

DR. LISTGARTEN: But I don't have, I don't have a problem with a product that has shown to be effective against gingivitis and reduction of caries and at the same time desensitize teeth. I think it's a wonderful thing. Why not?

CHAIRMAN GENCO: But it has to be tested.

DR. LISTGARTEN: But it has to be tested so that in fact it does all these things and --

CHAIRMAN GENCO: So the theoretical

rationale but there's some reservations, require testing. Bill and then Lew.

DR. BOWEN: I think there's no problem with the concept. We might have a problems with specific details. I have a question also for the FDA staff. What's the status of tooth desensitizing agents?

DR. KATZ: There's one ingredient that's allowed and that's, it's in a tentative, final monograph, potassium nitrate as a tooth desensitizer.

DR. BOWEN: And I have one additional question. What if you combine a product or an agent that has a cosmetic effect, namely anti-calculus? Presumably a fluoride toothpaste, for example, would have to be retested again in the animal model and the fluoride uptake.

DR. KATZ: Yes, that's right.

CHAIRMAN GENCO: Okay how, Lew and then let's come to a resolution of this combinations of anti-gingivitis.

MR. CANCRO: I want to make two points. The first is when you jump between pharmacological

classes, in other words go from one category to another, such as fluoride and anti-gingivitis, the obligation is to meet the standards of each, of each of the categories. So for fluoride, you must now go through all the performance tests and additionally in this category, the manufacturer also has to go through additionally the tests that you're proposing.

So that's independent of the, of this issue of combining materials in the same pharmacological class. And here, since nobody has given you a combination, the issue on the table is the principle of whether or not this could be rationale. And it could be rationale. Less stain, better taste, less side effects, more facility in formulating. So potentially, one could rationalize that there are many, many benefits to combining this. But nobody has put forth to this panel a combination at this time. So it's the principle of --

CHAIRMAN GENCO: So the problem is that each of these is a different pharmacologic class.

MR. CANCRO: Well, you --

CHAIRMAN GENCO: And it's not like the

fluorides where you have three possible fluorides that have anti-caries and you can mix and match those possibly. We don't have a simple situation like that.

MR. CANCRO: Yeah, I'm --

CHAIRMAN GENCO: So it's complicated by the fact that they're in three different pharmacological classes. So that the rationale is less clear.

DR. RIGGS: On Page 15, we've signed off on the first three. It's this one we're discussing.

CHAIRMAN GENCO: Right, no, we're talking about the combinations of anti-plaque --

DR. RIGGS: Right. And Linda, can we make a recommendation that the rationale be if you combine two within the, from this monograph, they have to have more benefit than --

DR. KATZ: No. Basically what the recommendation would be, would be to say that a combination, that you would allow combinations from the anti-gingivitis, anti-plaque. Combinations of ingredients, category one ingredients. That you can't specify that it has to be better than --

DR. RIGGS: Okay.

DR. KATZ: That it just has to, basically, if you're allowing the combinations to exist, they would have to be, the combinations would basically have to demonstrate that they, when you combine the two together, that it fits into what the combination policy says. Such that there's a benefit, but you can't specify what kind of benefit you want to see.

CHAIRMAN GENCO: Okay. So does the panel think we can just allow that? Is there a rationale to allow that or not? To allow combinations of anti-gingivitis agents, simply to allow them?

(No response.)

CHAIRMAN GENCO: No?

DR. BOWEN: Before I say yes or no I have another question for the staff of the FDA. What are the obligations of toxicity on combinations?

DR. KATZ: Again, through part of the testing, it's the same as one would look at for anything to make sure that when you're combining things that there is no significant toxicity that would preclude allowing it to be available.

DR. BOWEN: So the submitters have to go through a whole battery of new toxicity studies?

DR. KATZ: Well, it would, basically, there would be a standard that they would have to go through. And in that one would look at toxicity.

CHAIRMAN GENCO: So there's no basis, there appears to be no basis to allow the combinations, as there was in the case of the fluorides or as there was in the case of the antacids. Combinations of anti-gingivitis agents.

DR. LISTGARTEN: I'm not sure how you came up with the fact that there is no basis.

CHAIRMAN GENCO: I'm just, I'm putting a position on the table.

DR. LISTGARTEN: I think if you can, if you can kill two birds with one stone --

CHAIRMAN GENCO: That's a rationale. I'm saying --

DR. LISTGARTEN: That's a rationale.

CHAIRMAN GENCO: I think what they need to know is do we think that now there is rationale evidence --

DR. LISTGARTEN: There is no evidence. If there is jus -- the only thing we can discuss here, since we have absolutely no information about combinations, is the rationale.

CHAIRMAN GENCO: Okay.

DR. LISTGARTEN: There is a rationale.

CHAIRMAN GENCO: Okay. All right, would you make a motion to that effect?

DR. LISTGARTEN: Sure, I'll make a motion. Whoops.

MR. HUTT: Bob, can I just clarify one thing.

CHAIRMAN GENCO: Sure.

MR. HUTT: Because I have the feeling, listening out here, that different people around the table are talking about quite different things. And I think there are two different types of combinations. One type of combination is where you take more than one active ingredient from the same class, i.e., only a combination of anti-gingivitis agents. A second kind of combination is where you take active ingredients from different types, different

pharmacological categories, e.g., an anti-cavity and an anti-gingivitis.

CHAIRMAN GENCO: I don't think we're talking about that at all.

MR. HUTT: Well, some people were and some weren't. And Max was talking about the second category and you were talking about the first.

CHAIRMAN GENCO: No.

MR. HUTT: All right.

CHAIRMAN GENCO: I think we're all talking about combinations of anti-gingivitis agents. I haven't heard anybody say anything --

DR. LISTGARTEN: And I was talking about the other kind too.

CHAIRMAN GENCO: Okay. Now --

DR. LISTGARTEN: I wanted to reduce caries and reduce sensitivity --

CHAIRMAN GENCO: Within the anti-gingivitis, Lew brought up the point there are different pharmacologic types. There are oils, there's stannous fluoride and there's CPC. These are different. They all have the same effect of anti-

gingivitis, but maybe different mechanisms.

MR. CANCRO: No, by pharmacologic class, it would be anti-gingivitis and anti-plaque.

CHAIRMAN GENCO: Right.

MR. CANCRO: The materials --

CHAIRMAN GENCO: Oh, all right.

MR. CANCRO: -- have different basis of chemical activity.

CHAIRMAN GENCO: Okay.

MR. CANCRO: But it's all the one class of material.

CHAIRMAN GENCO: Okay, I used the wrong term. I apologize. But they're different classes, I mean stannous fluoride is a very different chemical class than Listerine, etcetera.

MR. CANCRO: Yes.

CHAIRMAN GENCO: So it's not like different antacids, sodium bicarbonate, magnesium carbonate, whatever, which could very easily be thought to be combined. We have groups that are not easily thought to be combined brought up. There may be chemical interactions. But there is a rationale

for combining them. In other words, do you want to hear from us that, sure, it looks like you can easily combine these and there will be no problem.

Like that antacids or like the fluorides. Or there is a rationale, but it really is going to require quite a bit of testing for safety efficacy before this can be done.

MR. CANCRO: Bob, you already have, you already have in place the safety net that they can't interact because you're going to test for the chemical integrity of the material and the biological activity of the material. So that's, that's in place. If two materials from the same class interact, they'd fail those tests. So that's an aside issue. They, you couldn't put out a combination that had a chemical interaction. I mean it would fail the test.

CHAIRMAN GENCO: Yeah, I think we've also discussed that. Any of these combinations would have to be tested in the final formulation for safety and efficacy. But we're not saying, I don't think anybody here says, that we think that that's not going to be a problem if you combine these two.

DR. LISTGARTEN: Nobody is saying that.

CHAIRMAN GENCO: Nobody is saying that. So that's the message. Maybe we can go on to the next topic. There are none of these combinations that we think are going to be completely free of problems in the performance testing.

DR. LISTGARTEN: But that's not, that's really not our business. Our business is to determine, it seems, whether in principle, whether in principle we can allow mixing of active ingredients, let's say just to fight gingivitis. If in principle we can allow the mixing of ingredients that have different pharmacological effects so we can combine anti-gingivitis with an anti-caries agent.

And it goes without saying or it's understood that for any of these combinations, whether it's just for gingivitis or whether it's to fight caries and gingivitis, that for any of these combinations, the manufacturer is going to be held responsible to show that the final combination is stable, is safe, is effective and that's none of our business, because at the moment we don't have any data

to even discuss it. But it's assumed that somebody is going to have to take that responsibility.

CHAIRMAN GENCO: Bill, do you want to make a comment?

DR. BOWEN: Just very briefly. I agree with Max, we're not discussing the agents that we've been reviewing. We're discussing concepts, as I understand it. And as I understand it also that the obligation remains with the submitter to show that the combination they submit is safe and effective.

CHAIRMAN GENCO: Okay, fine. Maybe that ends it then. Is there further discussion?

MR. SAXE: Well, I was just going to say that we do have three class one agents at this point. And I think it could be expressed as the feeling of this panel, of this committee, that there is no indication you could just say, yes, that's fine, any combination of these certainly would be acceptable. Because there is hesitancy since these three class one, category one agents are vastly different in their composition.

So I think the concept is fine, sure. But

as far as we have information to date, there's no blanket approval of the existing category one.

MR. CANCRO: But Bob, there is the potential, the potential for all of these other category three agents to ultimately demonstrate effectiveness, meet monograph conditions and hence, within that repertoire of 19 ingredients, there may well be the ability to combine them and get a benefit. So again, it's the concept and nobody's dealing with specifics here.

CHAIRMAN GENCO: Okay, so that, that I think sums it up nicely. The concept of combination is certainly reasonable and rational, theoretically. But in practice they would have to be tested very rigorously because there's no, we don't have practical certitude that any of these combinations would reasonably meet all the safety and efficacy testing as may be the case for the antacids. Okay, yes.

DR. WU: I have a question for Linda. I remember I read somewhere in the combination policy that it says two or more agents from the same therapeutic groups with same mode of action should not

be combined. So in our case, we may be able to combine the three different agents from the category one in the product?

DR. KATZ: You may be able to, that's correct.

CHAIRMAN GENCO: Okay, let's go on to the other rational combinations. I think Bill has already brought one. That is with the anti-calculus agent. Bill, do you want to summarize that or make some sort of a comment with --

DR. BOWEN: No, basically I wanted clarification on when you add a substance that is mainly in there for cosmetic reasons, what are the obligations on the effect on the product? And that was answered to my satisfaction in that the combination has to be, go through same testing as the original agent.

CHAIRMAN GENCO: Okay, so any other comments about other rational combinations?

(No response.)

CHAIRMAN GENCO: The feeling is that they're theoretically possible, may be quite

desirable, show benefit, complement each other. But of course the performance testing of the final formulation would have to be carried out with respect to efficacy and safety.

DR. RIGGS: Do you keep --

CHAIRMAN GENCO: There's no, yes.

DR. RIGGS: I'm sorry. Do you keep, when you combine it with a cosmetic ingredient, do you keep that totally out of the indications and on the labeling? I mean I wouldn't want to give false legitimization to the cosmetic thing by inserting them into the indication.

DR. KATZ: It's not part of the indication. It is separate from that. If you look at some of the products that may have both drug effect and cosmetic effect, that even in terms of on the packaging they are kept separate so that the two don't get intermingled to create confusion with consumers.

CHAIRMAN GENCO: Okay, Peter.

MR. HUTT: Bob, I wanted to again clarify your most recent question. I assume that you have not yet begun to take up the question of combinations

among different classes. For example, anti-gingivitis and anti-cavity.

CHAIRMAN GENCO: We did that first.

MR. HUTT: Oh, that's all done. Those are all done. All you are talking about here was the combinations of the three --

CHAIRMAN GENCO: Right.

MR. HUTT: -- category one ingredients.

CHAIRMAN GENCO: Peter, pick up Page 15 and we're taking Bill Soller's outline.

MR. HUTT: All right.

CHAIRMAN GENCO: We've already done that and we're on the fourth, which is combinations of anti-plaque, anti-gingivitis within that category.

MR. HUTT: Thank you.

CHAIRMAN GENCO: And now we're talking about other rational combinations besides the anti-caries, anti-gingivitis, anti-plaque. Anti-calculus for example. And so we've said there is a rationale for doing that, of course, subject to final performance testing, final formulation performance testing.

MR. HUTT: Well, let me simply reiterate what I hope has, is understood. The way that the FDA has always handled the combination of any aspect of a cosmetic --

CHAIRMAN GENCO: Right.

MR. HUTT: -- component is to exclude that completely from this over-the-counter drug review because this has never been a cosmetic review, it is solely an over-the-counter drug review.

CHAIRMAN GENCO: Okay, so Sheila's question was --

MR. HUTT: But, again Bill, please understand, the final formulation must meet the requirements. And must be tested in that way.

DR. LISTGARTEN: I think one could have, I have a slight concern with the, I have a slight concern between this division between the cosmetics and the drug effect. Let's say you want to have an anti-calculus agent and you want to have a desensitizing agent in the same, in the same combination. You may run into a problem because the two are very likely to work against one another.

MR. HUTT: Well, there are two requirements --

DR. LISTGARTEN: If we don't consider, if we don't consider them in the same, in the same breath, you know, how do we deal with this potential conflict.

MR. HUTT: Well, there are two requirements that would prevent that. The first is the combination policy clearly states that you can't add an ingredient that would take away from the effectiveness of the other.

DR. LISTGARTEN: Even if it's a cosmetic?

MR. HUTT: That's right.

DR. LISTGARTEN: Okay.

MR. HUTT: And the second is that any final performance testing must be conducted on the final formulation. And if, for example, you added something that would result in the product flunking the final formulation testing, than automatically the product is illegal. It can't be marketed.

CHAIRMAN GENCO: So it's all final formulation performance testing that takes care of any

cosmetic that may be added. Chris.

DR. WU: I would say if there's a product that comes, that has a combination of stannous fluoride and oil so in the final performance testing does this product have to go through both, let's say the Listerine test, which is the anti-gingivitis test and have to go through the PGRN and the whole bit.

CHAIRMAN GENCO: Right. The final performance testing for all the, all the drug claims.

DR. WU: Right.

CHAIRMAN GENCO: But since they have the cosmetic, which may affect the drug claim, of course you're testing the effect of the cosmetic on the drug. Okay, can we proceed now to the statement of identity for, and let's go back on Page 15 of the anti-gingivitis, anti-plaque, anti-caries combination. The suggestion Bill Soller made is that the statement of identity by anti-cavity, anti-gingivitis (toothpaste or dentifrice), anti-cavity anti-gingivitis (toothpaste or dentifrice) or mouth rinse, whatever. Is that reasonable?

DR. RIGGS: What was our statement of

identity for, did we end up with for the anti-gingivitis, anti-plaque? It was a little, little bit longer than that wasn't it? Rhonda, what did we decide yesterday? It seems quite a bit shorter than our statement of identity for just --

CHAIRMAN GENCO: Yeah, for, for, no, the indication was longer. The stannous fluoride, for example, was the anti-gingivitis, that's it. The statement of identity is anti-gingivitis.

DR. RIGGS: Okay.

CHAIRMAN GENCO: You're thinking about the indications.

DR. RIGGS: Okay.

CHAIRMAN GENCO: That was the longer.

DR. RIGGS: Okay.

CHAIRMAN GENCO: And we don't have to get into that now.

DR. RIGGS: Okay.

CHAIRMAN GENCO: We only have to deal with statement of identity for these combinations. For example, Colgate Total, anti-cavity, fluoride and anti-gingivitis toothpaste. That's the statement of

identity. So we're saying that statement of identify for a product like that would be anti-cavity, anti-gingivitis, dentifrice or toothpaste. Now they've added the fluoride to it, but I guess that's probably just wordsmithing.

MR. HUTT: It's permitted in the monograph.

CHAIRMAN GENCO: Okay, good. Okay, so the monograph for the anti-cavity allows the fluoride, okay.

DR. RIGGS: Should we put that parens in also?

CHAIRMAN GENCO: I think we should. In other words, we should be instructed by that monograph. I mean we can simply tell that that, obviously that's what you're going to do. The addition we're making is space anti-gingivitis. Any comments, any problem with that?

DR. LISTGARTEN: I just had a question or clarification.

CHAIRMAN GENCO: Sure.

DR. LISTGARTEN: Which, what are we

working on?

CHAIRMAN GENCO: Okay, Bill gave anti-plaque, anti-gingivitis products, OTC combination policies, it's Page 15.

DR. LISTGARTEN: Okay, we're still on the same page?

CHAIRMAN GENCO: Yeah. Would it help to put that slide up. Maybe, Bill, would you mind, it's your summary slide.

DR. SOLLER: Just by way of, just by way of referring to what we just talked about, the statement of identity from a different monograph would appear either before or after the statement of identity that you came up with. And I didn't redo the slide from your discussion the other day, but that would be anti-gingivitis space anti-plaque. And I think we went through a discussion, Bill, whether it would be a slash or an and. And my recommendation would leave that up to the manufacturer. It's inconsequential.

But to at least separate it would probably be preferable. So anti-gingivitis, anti plaque or

anti-gingivitis including all the dosage forms and now thinking about, are you going to put anti-cavity here and for sensitive teeth down here.

CHAIRMAN GENCO: Would you put the previous one up? Your combination -- that's it.

DR. SOLLER: Yeah.

CHAIRMAN GENCO: Let's look at that first combination, anti-cavity, anti-gingivitis toothpaste. That's the one we first discussed. And I think we agreed that that would be anti-cavity, the statement of identity would be anti-cavity space anti-gingivitis (toothpaste, dentifrice, mouth rinse). Okay, any comments? Let's go on to the middle one.

DR. LISTGARTEN: Yeah. I have a comment.

CHAIRMAN GENCO: Yes.

DR. LISTGARTEN: There a whole bunch of those formulations, toothpastes, sprays, gels, what have you. Suppose I have an anti-cavity, anti-gingivitis product and it's proved to be effective as toothpaste and I want to sell it as a spray.

CHAIRMAN GENCO: As a spray?

DR. LISTGARTEN: As a spray. Or as any,

yeah.

DR. RIGGS: Then we go back to the --

CHAIRMAN GENCO: That's a different formulation.

DR. LISTGARTEN: When I'm dealing with a different formulation.

DR. KATZ: Right, and actually that's going to be part of the next discussion.

CHAIRMAN GENCO: Right.

DR. KATZ: When we go back to address the formulation issues. But depending upon what you decide, since we never really came to grips with Wednesday's discussion about formulation, final formulations themselves, is if you decide in the monograph that you want to specify the formulation, then if you specify that it can be a toothpaste or a mouth rinse or what have you, then the spray itself would need to come in through an NDA as a new drug to be assessed.

It would not fall under the monograph. Or one could petition the monograph to see if it could come under the monograph. That would be the two

avenues. But that it would not be automatic. And that will be a part of the discussion that we come back to later this morning.

CHAIRMAN GENCO: Should we talk only about the products that have been tested that we've been presented with? Because if that's the case, then that first statement, anti-cavity, anti-gingivitis would only be a toothpaste.

DR. KATZ: At this point in time --

CHAIRMAN GENCO: Because the only anti-gingivitis agent we've heard was toothpaste, strictly anti-gingivitis.

DR. KATZ: You could it that way or you can just leave it sort of at that part open. And then we can fill in that part --

CHAIRMAN GENCO: It will be obvious.

DR. KATZ: -- of the blank after, right after they get the rest --

CHAIRMAN GENCO: If these other formulations are approved?

DR. KATZ: That's correct.

CHAIRMAN GENCO: So that the --

DR. KATZ: But remember --

CHAIRMAN GENCO: -- toothpaste could be dentifrice, mouth rinse or whatever formulation is proven.

DR. KATZ: Right. But remember under the anti-caries monograph that there are a different variety of dosage forms.

CHAIRMAN GENCO: Okay, thank you. Let's go to the next one. Anti-cavity, anti-plaque, anti-gingivitis. Here we have added the other two agents that have shown anti-plaque activity. And as I recall we reversed the order. So that the statement of identity for this group, the middle group would be anti-cavity, anti-gingivitis, anti-plaque (dentifrice, mouth rinse, toothpaste). Okay.

Now the fourth category would be anti-cavity, anti-gingivitis, toothpaste, dentifrice, mouth rinse for sensitive teeth.

DR. SOLLER: Bob, again I was using anti-plaque, anti-gingivitis --

CHAIRMAN GENCO: Right.

DR. SOLLER: -- to be quotes.

CHAIRMAN GENCO: So there is a possibility there would be a fourth --

DR. SOLLER: Anti-cavity, anti-gingivitis, anti-plaque toothpaste or dentifrice, whatever for sensitive teeth.

CHAIRMAN GENCO: Okay. So any objection to that?

(No response.)

CHAIRMAN GENCO: So the fourth one, Bill.

DR. BOWEN: Just a clarification. Anti-plaque would not be ever substituted for anti-gingivitis?

DR. SOLLER: Correct. Under what you have recommended.

CHAIRMAN GENCO: So to make that clear, what would not be allowed would be an anti-calculus or an anti-plaque only statement of identity.

DR. RIGGS: In combination with anti-cavity or sensitive teeth.

CHAIRMAN GENCO: In combination with these others, right.

DR. RIGGS: Right.

CHAIRMAN GENCO: Well, in combination with anti-cavity or tooth desensitizer.

MR. SAVITT: Well, not anti-calculus. Calculus isn't an --

CHAIRMAN GENCO: Right. Just to make it absolutely clear for the record. Okay, is everybody pleased with that? Any comments?

(No response.)

CHAIRMAN GENCO: Good. Thank you very much.

DR. RIGGS: But we, we also will allow like fluoride.

CHAIRMAN GENCO: Be instructed by the anti-caries monograph.

DR. SOLLER: You would be putting that in per the anti-caries monograph, so remembering --

CHAIRMAN GENCO: Per the monograph.

DR. RIGGS: Yeah.

DR. SOLLER: -- that when you start combining ingredients --

DR. RIGGS: Monographs.

DR. SOLLER: -- from one monograph to the

other, you have to --

DR. RIGGS: Right, you have to --

CHAIRMAN GENCO: You have to be instructed by the --

DR. SOLLER: -- be informed by the statement of identity of that other product.

DR. RIGGS: Right. Is there anything in brackets for the sensitive teeth? Just point of information. It's not a final.

CHAIRMAN GENCO: It's a tentative monograph.

DR. RIGGS: Okay.

CHAIRMAN GENCO: Okay. I think we've covered the combination ingredients. Good.

MR. CANCRO: Bob, are you going to formally vote on this or what happens? Are you just proposing it or what's need?

CHAIRMAN GENCO: Are we going to vote on this?

MR. SHERMAN: No I think, we have your recommendations, I don't think we need to go around and --

MR. SAVITT: I think it was unanimous.

CHAIRMAN GENCO: It's pretty much unanimous. I think --

MR. CANCRO: Okay, so the --

CHAIRMAN GENCO: -- for each of the items I asked --

MR. CANCRO: No, but I -- from a procedural point of view, I want to be sure that the record reflects it's the unanimous recommendation of this panel.

CHAIRMAN GENCO: Okay, does anybody object to all of the things that we discussed with respect to the combinations and the statement of identity? Is there any objection, or is it unanimous? Okay, I see all positive --

MR. SAXE: Clarify again under other rational combination where the role of the anti-calculus was coming in? You said that there could not be --

CHAIRMAN GENCO: We said that, in the statement of identity, we went on record to say that anti-plaque alone, in the absence of anti-gingivitis

or anti-calculus would not be appropriate in the statement of identities for any of these combination agents.

MR. SAXE: Anti-calculus would not be included --

CHAIRMAN GENCO: Included at all, right. Maybe that doesn't have to be said, but I think for the record. Okay. So let's proceed now to the, to finish up the performance standards, there were two issues. One was the representative of microbiologic listing for anti-gingivitis products. And Dr. Listgarten has proposed a list of organisms for invitro testing, culture testing, I would take that from clinical islet, culture testing. And then morphotype account for the clinical studies.

And I would take this as example and representative, but not prescribed. Okay, so the wording would be as part of performance testing, for example in the invitro aspect of testing an anti-gingivitis, anti-plaque agent or anti-gingivitis alone, you would do, in the laboratory, invitro testing of antimicrobial activity to this, to a

representative set of bacteria, oral bacteria, including Fusobacterium nucleatum, Porphyomonas gingivalis, Prevotella intermedia, Bacteroides forsythus, candida species and gram negative enteric rods.

Again, this is a, for example. It is not prescribed that these are the absolute only or all of these have to be tested. Comments, questions? And I can give you this list.

DR. LISTGARTEN: I just want to clarify why the manufacturer would have to do this if we won't allow them an anti-microbial claim? Because yesterday we went around --

CHAIRMAN GENCO: Oh, it's very simple.

DR. LISTGARTEN: Okay.

CHAIRMAN GENCO: If somebody mixes the four essential oils or makes a new prep of stannous fluoride, they may inactive it chemically. One measure of the lack of activity is that it kills these bugs. Whether that's the mechanism or not is not the issue. It's a measure of activity. It's a marker for activity predictive of, but not definitely proving

mechanism of anti-caries, anti-gingivitis effect. That's the way I view it. It's a marker. It's a convenient laboratory test to say that this preparation is completely buggered up.

DR. LISTGARTEN: Okay, so you're basically using this performance test --

CHAIRMAN GENCO: Right.

DR. LISTGARTEN: -- without having to go through a clinical, is that what you're saying?

CHAIRMAN GENCO: No, no. Realize that anybody who makes the formulation of the fixed oils also has to do a two-week experimental gingivitis study. So there's two things that they have to do. One is the invitro laboratory anti-microbial testing of the prep. And the other is the invitro, excuse me, invivo human two-week inhibition of experimental gingivitis.

Those two would say that this company can now go to the FDA and say we have a product that's essentially comparable to Listerine and we want to sell it because we think that these two tests are indicative of its effect in a six-month gold standard

clinical trial. Not that these tests are necessarily, get to the essence of mechanism. Only that they're predictive of the clinical trial. Okay, that's for the fixed combination. Mike.

DR. BARNETT: Yeah, but you know Max raises this interesting point though. Because unless there's the presumption that in fact these formulations are killing these organisms, these very same organisms invivo, then it really doesn't matter which organisms you select. It could be the ones we proposed. So, you know, in selecting these, I think there is a presumption that these organisms are pathogens or potential pathogens and that these formulations, the expectation is that these formulations are going to kill these organisms in actual use.

And therefore that's one mechanism by which they were acting. So there's --

CHAIRMAN GENCO: No, I don't follow the therefore. I say, all the terms you used before were, you know, it makes sense, provisional, presumptive, that all, but to prove mechanism is a very different

situation. You're not going to test soilmethano bacteria. That doesn't, that's not even logical or reasonable.

You are going to test the bugs that are associated with gingivitis. That's logical or reasonable, but it doesn't prove that that's a mechanism. I think it's a very different situation.

DR. BARNETT: Well, I'm glad, Bob, we're at a point where we agree perhaps 80 percent and what, no, no, I'm not being facetious.

CHAIRMAN GENCO: These are for industry, these are short cuts to the six-month clinical trial.

DR. BARNETT: No, no, but we're talking about two different things. One is the performance test.

CHAIRMAN GENCO: That's what we're talking about. We're only talking about that.

DR. BARNETT: And, right. And what, the only point I bring up is to follow up on Max's point with respect to consistency with yesterday's discussion. So what I would suggest is rather than prolong this here, because that's not really the issue

of the day, is that we come back and maybe discuss this further next time.

CHAIRMAN GENCO: Oh, I think we need probably a one-week conference to discuss mechanism. That would be fascinating. And as a Scientist, I would welcome that. What I think this morning, what we're talking about is expedient, efficient, predictive tests that companies can use and not go broke.

DR. BARNETT: No, I understand.

CHAIRMAN GENCO: To show that a product is comparable. That's all we're talking about. We're talking about final --

DR. BARNETT: Yeah, but Bob, Bob, we're talking about, I agree, that's what we're talking about this morning. I only brought that up because Max raised the issue and it had to do with the claims discussion of yesterday and it sounds as through perhaps that ought to be addressed further. And what I'm suggesting is that we consider that at the next meeting.

CHAIRMAN GENCO: Oh surely. Okay, shall

we proceed now. We've discussed this invitro culture test and Chris would also, handed in her homework too. And she said that we should note in the protocol to add that the starting inoculum size should be at least at an ocular density of 1.0 at 650 nanometers. Is that, did I read it right?

DR. LISTGARTEN: I don't think they may work for all the organisms. Some maybe difficult to grow and, for example, b-forsythus might best be detected by aminofluorescence. So I wouldn't presume on telling the manufacturers how to test for them. They have to use an acceptable method of monitoring and show that there is a significant reduction.

CHAIRMAN GENCO: Okay, so actually what Max is suggesting is that this list be for invitro testing and/or clinical testing. So it may make sense not to include the b-forsythus in the cultural tests because they are so difficult to grow. But to include them in the second test, which is the, which is the invivo.

Let's just talk about the invitro first. So this is a suggested group of organisms. And for

that suggested group --

DR. LISTGARTEN: I mean let's, you know, let's not sort of regulate every last little thing.

CHAIRMAN GENCO: Okay.

DR. LISTGARTEN: Let's just say, for example, you can do this. Leave it up to the manufacturer to find an appropriate way of doing the monitoring.

CHAIRMAN GENCO: Is there some reason why the one, you know, this OD is critical. Are we going to be misled or is anybody going to be misled if they use a .5?

DR. WU: Because in the protocol it doesn't specify what is starting cell consistency fu per mil, starting cell concentration. If you start out with a ten to the eight cells and we go through the protocol and by the time you dilute it you've ended up with 200 cells. And if a company comes and do the testing they don't know what the starting concentration is. And if they start with a .OD.2 which could be ten to the five cells, by the time they go through the protocol they end up with no cells when

they've played it out.

And they would think that the agent is totally effective because they don't have any growth. So they have to give a control starting concentration in a controlled experiment and that's what I don't see.

DR. LISTGARTEN: Well, I hope they have a good enough Microbiologist on hand that they won't just dilute themselves out of existence.

(Laughter.)

DR. WU: I don't know. Because if I were to follow this protocol, I'm not sure, you know, where would I start with the initial inoculum. It's a fool proof thing, that's what I'm trying to say.

CHAIRMAN GENCO: Let's say that final formulation testing is going to submitted to the FDA and the FDA Microbiologist would look at it so they would determine if it was adequately done. Is that the way this is?

DR. KATZ: No. Basically what's done with the final formulation testing is that the manufacturer is obligated to do it but the FDA doesn't necessarily

get the results back to review. So that the only time that they are reviewed is at the time of inspection. So that we may not see --

CHAIRMAN GENCO: Right.

DR. KATZ: -- the final formulation testing, even though the manufacturer is required to do it, that we may not get it back to review.

CHAIRMAN GENCO: But it's at risk for being reviewed at the time of inspection?

DR. KATZ: That's correct.

CHAIRMAN GENCO: So, in fact, it must be done right.

DR. KATZ: That's correct.

CHAIRMAN GENCO: Because nobody knows when the inspection is going to occur. So I think that the answer is that it is subject to review, therefore, it has to be done right. So I think we can, we can, Chris, would you agree that we can be too prescriptive and shouldn't at this point because it's subject to review. Okay. Bill and then Lew.

MR. CANCRO: I was only going to add that you have to remember that this has to match a sample,

the gold standard in a sense, which has to perform in the test. So, you know, this is profile matching of the chemical and biological activities of each of these things. As you, according to the tests you propose.

CHAIRMAN GENCO: So, so far all we've recommended is a suggested list for cultural testing. Okay. Any problem with that? Bill.

DR. BOWEN: I don't want to prolong this, Bob, but I'm appalled by the four organisms. There's gram negative and there's no gram positive organisms included. And it's well recognized -- sorry?

DR. LISTGARTEN: It's gingivitis. They are periobugs.

DR. BOWEN: Yeah, but it's the periobugs that have to exist in a plaque matrix. And a plaque matrix, for the most part, is made up of extracellular polysaccharides derived from sanguous mutans and actinomyces. So one or more of those should be included. But I know we revisit this issue, so I just wanted to get it on the record.

CHAIRMAN GENCO: Well, we could do that

now. If you'd like to add, and representative gram positives such as step mutans, strep sanguous?

DR. BOWEN: Yeah.

CHAIRMAN GENCO: Would you object to that?

DR. BOWEN: No.

CHAIRMAN GENCO: Okay. Okay, any further comments about that suggested list of organisms? Okay, let's go now to the two-week experimental gingivitis. What's recommended here is that a differential morphotype count be carried out including the coccoids, spirochetes, motile rods, other morphotypes and that also the cultural studies, for example, of these organisms be carried out. So the experimental gingivitis would of course look at plaque, gingivitis and the microbes.

The microbes being looked at include Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, candida species, gram negative enteric rods and gram positive representative organisms such as strep sanguous and strep mutans. Either by culture or by some other appropriate technique, PCR, immunofluorescence.

DR. LISTGARTEN: Probably no PCR.

CHAIRMAN GENCO: Okay, immunofluorescence.

DR. LISTGARTEN: Or DNA probes.

CHAIRMAN GENCO: So culture or alternate technique, because we don't know what the future is going to hold for these tests. And then also morphotypes should be looked at. Mike.

DR. BARNETT: Yeah, I just, could we discuss, Max, the rationale for this extensive, because this is all done in the six-month trials and now we're showing comparability --

DR. LISTGARTEN: These are just examples. I don't think these are, I mean, maybe it's not, maybe it's turning out to be too strong a list. I think that originally this was supposed to be a laundry list of the type of organisms that might be included. It doesn't mean that anyone is held to that. And perhaps that hasn't been emphasized enough, Bob, that this is, for example, this is a for example list.

CHAIRMAN GENCO: Right. And these are representative.

DR. BARNETT: Yeah, I was wondering since

we've included many of these or some of these organisms in the invitro test, whether the morphotype analysis and the cultural determinations for the invivo may be overkill. And whether, for example, the morphotype analyses by themselves would be sufficient to answer the questions about comparability of formulations on an invivo basis.

MR. CANCRO: Is the purpose of this additional testing invivo safety or efficacy? Remember, remember the model that the company is proposing has an end point of plaque and gingivitis.

CHAIRMAN GENCO: Right.

MR. CANCRO: And this type of testing was really looked at, I think, originally from the perspective of whether or not you are getting shifts in the oral flora. So remember the profile testing is to ensure that some formulation change, other than the active ingredients in the concentration being proposed has changed. And hence, you want to be sure that they are delivering the efficacies.

So is this necessary or is this really thought of as looking at some ecological shift in the

bacteria.

DR. RIGGS: But if industry wants to, they can do the six-month clinical trial instead of these steps. Is that correct? It's either or? So if this is onerous, then they can go back to the six-month clinical trial?

MR. CANCRO: The industry, and I'm sure the FDA would agree, can always go to the full-term clinical trial. I mean anybody can do that.

DR. RIGGS: Right.

MR. CANCRO: What we're proposing here is have you changed the conditions under which the drug is being delivered. And the manufacturer, and you have agreed, has proposed a certain way to do it. Now what I'm asking is you're monitoring the microbes during this two to three-week trial and to what purpose?

Is it to convince yourself that there's no shift in the actives? Because you've already been convinced of that in the six-month trial. Or is it a measure of efficacy? And I don't think it's the latter. I don't think --

CHAIRMAN GENCO: I think that what the original intent was, was for the invitro testing to add a more up-to-date group of organisms, that's all.

MR. CANCRO: Invitro.

CHAIRMAN GENCO: And I think what has happened is we've had the suggestion now to also do this in the gingivitis. And I think we could discuss that. I think the original intent was to add more, you know, the bugs that are representative of gingivitis that would be, the reasonable bugs don't, not proving anything, but the reasonable bugs to look at in the invitro testing.

So Max, would you think that's reasonable that we don't put the microbiology as part of the experiment with gingivitis?

DR. LISTGARTEN: I'd be quite happy --

CHAIRMAN GENCO: Okay.

DR. LISTGARTEN: -- to leave it out. I mean I --

CHAIRMAN GENCO: So then we made a representative list of organisms modified by Bill to include some gram positives.

MR. CANCRO: Invitro, invitro.

CHAIRMAN GENCO: Invitro.

MR. CANCRO: Fine.

CHAIRMAN GENCO: As markers for potential activity in six-month trials.

DR. LISTGARTEN: And if you are going to use invitro, it may not be appropriate to even include differential morphotype counts.

CHAIRMAN GENCO: Yeah.

DR. LISTGARTEN: Because of, that's something that could only be used in invivo studies and --

CHAIRMAN GENCO: So the recommendation is --

DR. LISTGARTEN: I think this could be only for --

(Both are talking at once.)

CHAIRMAN GENCO: Here is a list of representative examples of organisms that could be used. Okay. Any disagreement with that then? So there will be no comment with respect to the clinical study and microbiology. Okay, thank you. Now with

respect to dosage, let's go back to that issue. Bruce Kohut would like to make a presentation. Are you read Bruce?

MR. KOHUT: Good morning Dr. Genco and members of the panel. Thank you for the opportunity to again comment further on the issue of suitable dosage forms for category one anti-plaque, anti-gingivitis active ingredients. I will keep my comments very brief. During your discussions following our presentations on Wednesday, questions were raised on the safety of the higher fixed combination concentrations required for different dosage forms.

These questions were what is the acute soft tissue safety of the higher concentrations, even though the actual, the absolute amounts are the same. And what is the potential fixed combination exposure levels from these products. These are very important safety issues and we appreciate the subcommittee's questions. We believe, however, that each question has been or can be addressed.

Safety can be assured by limiting the

dosage form to those not intended for ingestion. Requiring the milligram dose in any dosage form to be no greater than the mouth rinse milligram dose. And requiring specific attention to specific soft tissue reactions as part of the performance test. What is the acute soft tissue safety? Regardless of the same milligram dose, higher concentrations, as Dr. Bowen pointed out, can carry a potential risk of acute soft tissue irritation.

We agree. And as part of our dentifrice development program, we extensively assess the safety of these higher concentrations in dentifrices. We initially hypothesize that the higher concentration would be rapidly diluted intra-orally during use. This was based on the generally accepted premise that a dentifrice is diluted three to one during use. Duke and Forward published in the British Dental Journal that following 30 seconds of brushing, the dentifrice was diluted to 22 percent of its original volume.

Theoretically, the ten time concentration of a fixed combination would be expected to be diluted to only 2.2 times, that of the mouth rinse, during a

30 second brushing. We next tested this irritation potential clinically. We conducted exaggerated use irritation studies on the dentifrices containing the fixed combination at both eight times and ten times the concentration in the mouth rinse.

This exaggerated study design is an industry standard and evaluates acute soft tissue irritation and sensitization potential of dentifrices when subjects brush five times a day at hourly intervals over a period of five days. Examinations are performed on days one, three and five. Both the eight and ten times concentrations were found to be safe under the exaggerated use conditions of these studies.

Beyond these specific safety studies and to finally assure safety, we have recommended that a clinical trial of six-month duration be required. And soft tissue assessments will be conducted at each exam period. In addition to compliance, in addition, in compliance with good clinical practices, there would be in the protocol extensive instructions on the definition, handling and reporting of any adverse

events.

We believe that the expected intra-oral dilution, the completed irritation studies and the recommended six-month trial or assure the acute soft tissue safety of these higher concentrations of the fixed combination. There were additional questions on dose, on total exposure. During Mr. Hutt's presentation on Wednesday, he listed three fundamental points when considering suitable dosage forms.

His second point involved the exclusion of dose forms for safety concerns. Additionally, Dr. Katz clarified the scope of the dose forms by recommending that only traditional dose forms be considered. We agree with Dr. Katz. We therefore recommend for the purposes of this monograph, dose forms be limited to only those intended, excuse me, only those not intended for ingestion, thus excluding products such as chewing gums and lozenges.

This restriction, along with limiting the milligram dose to that in a mouth rinse or 51.7 milligrams per dose, would control the fixed combination systemic exposure and in deed align the

potential total body exposure with that of the accepted long term safety of the fixed combination mouth rinse. Dr. Bowen when discussing safety, expressed concern over the differences in intra-oral retention of mouth rinses and dentifrices.

While we agree with Dr. Bowen on these expected differences and retention rates, we feel that there still is sufficient data to support the systemic safety of fixed combination dentifrices. During the Subcommittee's previous deliberations, the safety of the fixed combination was determined in part by evaluating total body exposure using a conservative estimate of mouth rinse retention of 20 percent of the dose.

In reality, mouth rinse retention is less. The expected dentifrice retention is certainly within this 20 percent and thus the previously reviewed data supports the safety of fixed combination dentifrices also. In conclusion, we believe that safety can be assured for fixed combination dentifrices by restricting a monograph to any oral dosage form not intended for ingestion, requiring products to deliver

no more than 51.7 milligrams per dose. And requiring a six-month performance study with specific safety assessments. Thank you for your attention and I or any of my colleagues would be glad to answer your questions.

CHAIRMAN GENCO: Okay, thank you, Bruce. Any comments, questions? Bill.

DR. BOWEN: I would agree with everything you've said, Bruce. But I still have one more additional concern that I have raised on other occasions. There's a growing segment of the population who lacks saliva for one reason or another. Mainly as a result of prescription drug activity. And I would suggest that the, paced with the eight to ten times elevated concentration of a fixed oil be tested in a subgroup of that population for irritation.

If I understand you correctly, you did carry out the exaggerated use test in persons who had normal salivary flow.

MR. KOHUT: That's correct, Bill. That's a very good point and I would agree with your recommendation.

CHAIRMAN GENCO: Chris.

DR. WU: I have a question. Now when the mouth rinse is formulated, your ingredients, the oils are dissolved in alcohol so they are readily available. Now when you come up with the toothpaste formulation with the same concentration of the oils, do you test for availability of how much your combination of oils is released or available in the oral cavity when it's in a different formulation.

MR. KOHUT: Yes, as part of GMP we have to do assessments of the chemical availability of the essential oils and they will meet GMP requirements. And the clinical testing also demonstrates that. I mean that certainly is the advantage of the, of the performance test within our recommendation.

CHAIRMAN GENCO: Further comments, questions? So it appears then that you're suggesting that this monograph limited to those that are not, those dosage forms not intended for ingestion?

MR. KOHUT: That's correct.

CHAIRMAN GENCO: Which means topical use.

MR. KOHUT: No, forms such as a chewing

gum or a lozenge. Restricting it to dosage forms which are expectorated.

CHAIRMAN GENCO: Okay. Any comments about that issue. Is the panel in agreement with that?

DR. RIGGS: Linda, what was the term you used yesterday about standard?

DR. KATZ: It's actually referred to tradition dose form. But I guess one other point and I guess maybe I can sort of make the point now, because I was going to wait later in terms of the discussion, but it seems like this might be the time to do it. Is that also when considering dosage forms and traditional dosage forms, one also has to remember what was presented in terms of what, going back to the discussion on Wednesday, what was voted on for category one types of ingredients.

Then in some cases test form may be important in terms of what it is the data has been presented, what's been available. So that in those cases, monographs have specified a specific dosage form. In other cases, a traditional dosage form may be used because it's felt that one form may be

substituted with another form going back to do the required testing. And that once the required testing is done and the standards are met, that there's really, that one form may be substituted for another.

And that was actually part of the point that I was trying to make on Wednesday and I'm not sure that it actually got made. Is that when we're trying to decide, since we didn't actually decide on dosage forms and our discussion was kind of free floating back on Wednesday as to different possibilities, is to go back and look at what it is that you've assessed for category one and whether or not you feel a traditional dosage form is acceptable for what one has put into category one, or whether or not any of these a specific dosage form needs to be specified.

For example, whether or not it is important to say that something should be a gel or a paste or whether or not. Does it make a difference if it's a mouth rinse or another type of a dentifrice. Because what you're going to allow and what you're going to say is acceptable will then go into the

monograph and then these products will be substituted provided that they can meet the accepted standards.

If one feels that there is an issue that arises, that something needs to go back to be tested because this was not looked at by what you've put into category one, then that becomes either a new drug or needs to be a petition into the monograph to be allowed. And I'm not sure that that point was made clear.

CHAIRMAN GENCO: Linda, with respect to the specific dosage form and the traditional dosage form, just so that we're clear, in the case of this monograph we have, we've only looked at two specific dosage forms, a mouth rinse and a dentifrice. So if it was the, the monograph was limited to category one status for those agents that have been tested in either of those two forms, then that would be the most extreme limitation?

DR. KATZ: That's correct.

CHAIRMAN GENCO: Okay. Now the standard, traditional dosage form could be any of the three agents in either of those two dosage forms.

DR. KATZ: That's correct.

CHAIRMAN GENCO: That would be the traditional.

DR. KATZ: That's correct. Otherwise what will --

CHAIRMAN GENCO: But this, that is more restrictive than what Bruce was suggesting is non-ingested.

DR. KATZ: That's correct.

CHAIRMAN GENCO: That's even more liberal.

DR. KATZ: That's correct.

CHAIRMAN GENCO: Okay. So we have that in mind. So the more specific is the anti-gingivitis would be the dentifrice, stannous fluoride and the mouth rinse would be other two. And the monograph could be limited to that. Or, the next step would be to log the traditional dosage form, any one of those three category one agents in either of those dosage forms, dentifrice or mouth rinse.

DR. KATZ: That's correct.

DR. RIGGS: Where does gel fit into that? That's not a traditional?

CHAIRMAN GENCO: That's not --

DR. KATZ: That's not considered a traditional, however under the other, the proposal we heard this morning, the gel would fall into that. So that that would be, if you were looking at topical forms, non-ingested topical forms, a gel would fit into that category.

CHAIRMAN GENCO: So that's the third category that the non-ingested would include the gel. That would be the only other type?

DR. KATZ: I can't think that there's anything else that would fall there.

MR. KOHUT: I can't either, Linda.

CHAIRMAN GENCO: And that gel would be as a dentifrice on a toothbrush or in a tray or applied as a paint to the tooth?

DR. KATZ: It could be any of the above.

CHAIRMAN GENCO: Any of those.

DR. KATZ: That's right.

CHAIRMAN GENCO: Regardless of application, okay. So I think the panel now, is it clear, the three possibilities? Specific, traditional

and traditional and not for ingestion, which would include the gel.

DR. KATZ: That's right.

CHAIRMAN GENCO: Okay.

DR. LISTGARTEN: And just to, for clarification one more time. If what we've reviewed has only been marketed as a rinse and someone wanted to market it either as a toothpaste or as a gel, they would have to come back, with an MDA, to do this.

MR. KOHUT: No. What we're suggesting is that a six-month performance test should be done to demonstrate the efficacy of that product.

DR. LISTGARTEN: Okay, but a six-month performance test would have to be done?

MR. KOHUT: Yes, that's correct.

CHAIRMAN GENCO: All right, that scenario would be that any three of these category one agents could be used in any of the two, three forms, gel, dentifrice, mouth rinse. But if the previous, what we've reviewed wasn't that form, the new form would have to have one, six-month clinical trial safety and efficacy, for safety and efficacy.

In other words, if Listerine came in as a dentifrice it would have to have one six-month trial as a dentifrice. Is that, I mean that's a scenario. And that could be a recommendation from the panel.

DR. KATZ: Let me go back one more time.

CHAIRMAN GENCO: Okay.

DR. KATZ: Depending upon, now in terms of, from the last scenario, in which way would you, if you voted Listerine for example, since you used that example. What, in terms of, how would you, what would you put into category one?

CHAIRMAN GENCO: Okay, it's in category one as a mouth rinse.

DR. KATZ: Umm hmm.

CHAIRMAN GENCO: We're saying if the traditional form would include a dentifrice for any of the category two, as well as a mouth rinse, but if it hadn't been previously tested, let's say Listerine, as a mouth rinse. Not it's being tested as a dentifrice. It would have to, the performance test would be the six-month trial, which should satisfy the issue of concentration that Dr. Bowen brought up. Maybe it

does, maybe it doesn't.

Because you'd look at, maybe you'd want exaggerated testing to, but just to get that on the table as a scenario.

DR. KATZ: Right, no that is correct. That is correct.

CHAIRMAN GENCO: Okay.

DR. KATZ: Let me go back a little bit because this may also clarify or help to clarify for different types of products that have been allowed or the formulation, the formulations of them. For the anti-caries drug products, basically what's been allowed for it to be is a dentifrice, toothpaste, tooth polish, tooth powder, gel and so, rinses, rinse powder, rinse effervescent tablets, mouth wash. So these are all things that have come in through that traditional guise.

CHAIRMAN GENCO: But presumably most of those have been tested. There have been experience with those. Whereas we're looking at products with not, I mean I don't know of anybody that's put Listerine in an effervescent tablet or that sort of

thing. We're not looking at it.

DR. KATZ: No.

CHAIRMAN GENCO: We're, for us those are theoretical. For the caries group that was probably based upon experimental evidence.

DR. KATZ: That's correct.

CHAIRMAN GENCO: Okay. Peter.

MR. HUTT: I'd just like to again put this very briefly in context. The way that the majority of monographs have been handled is to permit, in effect, any appropriate dosage form without trying to, and I've never seen the word traditional used in any monograph. I may be wrong. Linda, are you --

DR. KATZ: No, no, you're right.

MR. HUTT: All right.

DR. KATZ: Okay. Because we had used the category on Wednesday so I was trying to hone back to what we meant by traditional from Wednesday's discussion.

MR. HUTT: Okay, but I think that crystallizes the issue. Because there is no list of traditional dosage forms and in deed the industry is

constantly coming up with new ways of applying active ingredients to the teeth. In a sense they are traditional in that they are all applying it to the teeth, but they are using new mechanisms of application to make it more effective, safer, perhaps more easily used by the consumer.

Now if you try to come up with a list, what you're telling the industry is give up that research because you need a new drug application. It's going to take you five or ten years to do it. And that's why FDA has, over the last 25 years gone to a broader characterization and the actual characterization used at least in the first section of the anti-cavity monograph was in any dosage form suitable for application to the teeth.

But adding Bruce's qualification, and not intended for ingestion. That cuts off the ones that are intended for ingestion. It leaves the ones that, as you pointed out Bob, are expectorated, but doesn't limit technology. Because if we think, well, okay, a gel is one type of existing, maybe traditional, way of applying it. I think if we sat down we could think up

50 more that no one has ever looked at but that could be major advances not worthwhile going through an NDA, but would pass the performance test.

And that is the key to the whole thing. It has to pass the performance test. It has to pass Bill's concern about being irritating in too high a concentration. It has to pass all these tests to assure both safety and effectiveness. So I would urge, cut out that traditional category, which in a sense is meaningless. It really is in any form suitable for application to the teeth or just list them.

CHAIRMAN GENCO: Thank you. So the and other scenario is the more liberal, a more liberal, is dosage forms not for ingestion which would include dentifrice, mouth rinse, gel and x.

DR. LISTGARTEN: Could it include a spray?

CHAIRMAN GENCO: Well, that's the problem. When you get into that then you might have, you know, other safety issues. So I think that's a good, excellent question.

DR. KATZ: A chewing gum is not meant to

be ingested, but --

CHAIRMAN GENCO: The ingredients are.

DR. KATZ: That would be --

MR. HUTT: Yes, yes.

CHAIRMAN GENCO: So we'd exclude the chewing gum or lozenge or pastille.

MR. HUTT: Yes, yes.

DR. KATZ: And a spray would probably be excluded as well for a variety of other reasons that it just would not fall into one of those categories.

CHAIRMAN GENCO: But there may be x that we haven't thought of. This is what Peter was saying. That would be consistent with not ingested, but not have the problems associated with a spray or anything, a powder or what have you.

DR. KATZ: It's possible. It's possible.

MR. HUTT: There are, there are dozens of additional possibilities. Some have been used in the past. Some are obviously in the laboratory today and the critical issue is, are they intended to be applied to the teeth. And are they expectorated, i.e., not intended for ingestion.

CHAIRMAN GENCO: Right.

MR. HUTT: Those, and do they pass the performance, the two performance tests that we've talked about.

DR. RIGGS: The two-week and the six-month.

MR. HUTT: That is correct. They must --

DR. RIGGS: And Bill's

MR. HUTT: They must --

CHAIRMAN GENCO: No, not the two-week, excuse me. We're mixing performance tests. Let me just clarify that, excuse me.

MR. HUTT: All right.

CHAIRMAN GENCO: The performance test is for the category one agent if you want to make a new Listerine. You know, another mouth rinse, you have to pass the invitro and the two-week. We're talking about a six-month clinical. That's the only thing that's been discussed now for going from a dentifrice to a mouth rinse, a mouth rinse to a dentifrice or mouth rinse to a gel. Or a mouth rinse or dentifrice to x.

DR. RIGGS: Right. But what about Bill's point --

CHAIRMAN GENCO: Six, so far the only performance test is the six-month trial. And what I'm asking now, would there be other performance tests. The problem is we probably wouldn't know. For x there may be a unique performance test that's very important. But because of that mode of application, we wouldn't know about that.

MR. HUTT: But because it is for application to the teeth, the same performance test would apply. No matter how you apply it to the teeth, the question is whether you get the reduction in gingivitis that is required and --

CHAIRMAN GENCO: Let's say it's a powder, which brings up a whole other set of safety issues, inhalation, etcetera. That's what I'm --

MR. HUTT: Okay. This is covered under the protocol. I checked it personally as a matter of fact to make certain that that issue would be covered. There are four or five pages that require under the protocol that people and that the investigators check

to make sure there is no untoward effects in the mouth to make certain that if there are any they are immediately reported to the sponsor and the study is stopped and a full examination is done. A n d I personally was satisfied that this was --

CHAIRMAN GENCO: That the six-month trial would --

MR. HUTT: Would solve Bill's problem, yes. Now if you wish to see that, we have those five pages here and there's no reason why you wouldn't -- you could write that write in the monograph. We would obviously have no objection. That is what Bruce referred to as good clinical practice.

CHAIRMAN GENCO: So the greatest comfort level may be with, whatever you want to call it, those applications such as dentifrice, mouth rinse and gel, period. Because those, those we all might feel comfortable about. That's one scenario.

MR. HUTT: Now, as you point out, you're then cutting off --

CHAIRMAN GENCO: Exactly. But I'm just clarifying so that we can discuss the two.

MR. HUTT: Yes.

CHAIRMAN GENCO: The other possibility is the, those three plus x, which would be the non-ingestible.

MR. HUTT: Yes.

CHAIRMAN GENCO: I guess the question is that, what is your feeling? Which scenario, the first or the second. The first would be the dentifrice, the gel, the mouth rinse and that's it. The second scenario is those three plus x, as long as it's non-ingestible, expectorated. Bill.

DR. BOWEN: I'm in favor of the second one because again we are to some extent hide bound by the manner in which we deliver therapeutic agents to the mouth. On the one hand, frequently we're trying to clean the tooth. On the other hand, trying to deposit material that is clinical effective. And I think it would be a pity to restrict innovation in delivering products that are effective. And I feel reassured in that any, for the want of a better term, reformulation or new method of delivery is going to be subject to a six-month test with all the attendant safeguards and

I would support the second proposition.

CHAIRMAN GENCO: With a single six-month test as the performance standard for the final formulation of this new formula.

DR. BOWEN: Correct.

CHAIRMAN GENCO: Okay.

DR. LISTGARTEN: I would exact that.

DR. WU: I support that. Now if someone come up with a different delivery system, would that be considered dental device?

CHAIRMAN GENCO: I think that, for example, we discussed a little plastic pellet that's attached to the tooth and releases this agent. That would most likely be a device.

DR. KATZ: It would probably fall under the combination. And depending upon what the intended mechanism of action is would determine whether it's categorized as a device or whether as a drug.

CHAIRMAN GENCO: So this brings up another issue. There is an obvious level of control at the FDA. In other words this, they would have to apply to you with their six-month, results of the six-month

trial for this new dosage form. And you'd have to make a judgement that it in deed fell within the context of the monograph or didn't.

DR. KATZ: That would be correct.

CHAIRMAN GENCO: Okay, good. So that if some, some questionable dosage form or delivery form came up, the FDA obviously would make a ruling whether it fell under the monograph or not.

DR. LISTGARTEN: If you have a slow-release capsule sitting on your tooth, you're going to swallow it. It's not designed for expectoration.

CHAIRMAN GENCO: Well, I've used that as a, just to answer the question. Okay, should we take a vote on that or is there any disagreement with the suggestion then. Okay, so the suggestion is that the monograph cover dentifrice, mouth rinse, gels and other non-ingestible forms meant to be expectorated of agents, anti-plaque and anti-gingivitis agents.

But that these new dosage forms be subjected to six-month clinical trial in which efficacy and safety is assessed. And the details of that protocol, I think we should look at between now

and the next meeting or two, if you'd like to do that.

MR. KOHUT: I'll be glad to submit that.

CHAIRMAN GENCO: Okay, thank you. Yes.

MS. BUCK: Nancy Buck, representing Pfizer. I have a question about the linkage between Wednesday and today. I had understood that the different dosage forms and the protocol that Dr. Kohut had proposed today were applicable only to the four essential oils, the fixed combination.

CHAIRMAN GENCO: No, no. That was if somebody else wanted to make another fixed combination mouth rinse, they had to do two things. Invitro testing in the laboratory, antimicrobial. And a two-week anti-gingivitis trial.

MS. BUCK: I would simply ask the question, do all three products that are now proposed for category one share the same characteristics such that such an extensive testing program for a change in dosage form, any change in dosage form, is really necessary?

CHAIRMAN GENCO: Okay.

MS. BUCK: Because I, it is, it is wildly

unconventional to have a six-month clinical trial as the basis for changing a dosage form within broad limits. And so I would seriously ask the question, in fact I know of no other where such extensive performance testing has been required for a change in dosage form in the OTC Review. I don't believe there is any precedent for that whatsoever.

And it may be necessary for the combination known as Listerine, but I would ask, is it really necessary to have such extensive testing? I mean that's a lot of testing for the OTC Review. It's been down played as performance testing, but that is a major big deal and I would ask whether the other two require the same kind of testing.

CHAIRMAN GENCO: That is if CPC was put into a dentifrice.

MS. BUCK: For example.

CHAIRMAN GENCO: If stannous fluoride was put into a mouth rinse.

MS. BUCK: For example.

CHAIRMAN GENCO: If any of those were put into a gel.

MS. BUCK: For example.

CHAIRMAN GENCO: If any of those were put into x.

MS. BUCK: Right.

CHAIRMAN GENCO: Ask the committee, what are your feelings? I think one of the problems is we haven't seen that done. And --

DR. LISTGARTEN: We don't have anything to go by. We have no precedent. If we had a precedent it would be easier to say we don't need a six month.

CHAIRMAN GENCO: All we've seen done is one abstract where a mouth rinse at one-tenth the concentration has been made into a dentifrice at ten times or eight times the concentration. The company has gone through great extent to look at concentration of this dosage. So I think that's, that's what we're being advised by, we're learning from that. I would have to agree to some extent that maybe going the other way is not such a problem, going from the high concentration dentifrice to a mouth rinse. But we haven't seen the data either.

And it maybe that getting it into solution

in a mouth rinse would cause all kinds of problems, so.

MR. HUTT: Bob, I'd just like to remind you that, and Bruce has made this point before, that Warner Lambert certainly agrees that as shorter term tests are validated, as standards become available against which you can test the newer forms, everyone is in agreement that the shorter term testing should be substituted for the six-month. The only reason that Warner Lambert suggested the six-month study was because of the lack of a standard at this moment for the dosage forms other than the mouth rinse.

So no one suggests that the six-month is perfect. It's a, if you will, an interim solution to a difficult problem and will assure safety and effectiveness.

CHAIRMAN GENCO: And I think the spirit of the committee is to make a shorter term where it's more reasonable when you're going from one formulation of a mouth rinse to an identical formulation just handled by a different company. Then of course that test if going to be much less onerous. And I think

that's what the performance tests reflect. And in fact I think the performance tests for stannous fluoride and for CPC are quite minimal. Bill.

DR. BOWEN: Oh, I just want to make the point that changing it, this isn't simply a change in dosage form, it's a change in concentration. And change in dosage form isn't necessarily the same as change in concentration. And that the standards that were applied in the past don't necessarily apply to increasing the concentration of a topical application.

CHAIRMAN GENCO: Okay, further comments on Ms. Buck's discussion. Okay, I'd like now to address the last point. And that is the total maximum daily dose. Bruce recommended that it not be more than the single application in the proven application. Let me rephrase that. In the case of, I'm talking like a lawyer now I think.

(Laughter.)

CHAIRMAN GENCO: In the case of, in the case of Listerine, it's 51.7 milligrams per dose. And what we heard was that the maximum daily dose, the maximum daily exposure be that amount, whatever it is,

per dose. In other words, if in a dentifrice the recommendation is to brush twice a day, but people brush four times a day, then the maximum for any of those doses be 51.7 milligrams.

But that we don't really get into the issue of the total dose per day, only the total application time per day. And I think the bind we get into is pointed out by Bill Soller is that some people may use these things four times a day. And if we set a maximum daily dose based upon use twice a day, that may be unrealistic. The problem is we don't have the data.

We have the data on the toxicity, which is done at very high doses, in grams. And the use level is in milligrams. The intermediate, how many milligrams, how many hundreds of milligrams, we don't really have the data. The example of the aspirin is a good one. It's instructive because the rheumatologist had the data on aspirin to make a maximum daily dose of one gram or four grams, whatever it is, before your ears start ringing. They already had the experience. They know the toxicity level is

way higher.

They know the average use is way lower. But the maximum dose could be quite a bit higher, maybe six or seven times the average use and still would not cause serious problems. But we don't have that kind of data, I don't think.

MR. CANCRO: Bob, I think I helped introduce, really, a misconception which is what the dosage, I believe, that Bruce is talking about is the minimum effective dose. The safety dose has to be set on the basis of toxicity issues, what the manufacturer submitted by way of tolerance to ingestion, irritation, etcetera. So the, what, what is being proposed, I believe, is that to achieve effectiveness, the minimum dose is two times 52 milligrams in effect.

That's the dose at which the manufacturer believes the product will deliver an anti-gingivitis, anti-plaque effectiveness. The maximum dose is always set at a higher level because the manufacturer has supplied you with the toxicological consequences of, you know, the upper limit.

MR. KOHUT: A point of clarification. The

dose I'm suggesting is for safety. The maximum dose is for safety.

CHAIRMAN GENCO: It is safety?

MR. KOHUT: Yes, it is. And it's based upon the safety of the product originally evaluated by the subcommittee. In terms of efficacy, we're suggesting that you may not need the same levels as in a mouth rinse when you change dosage forms. Because there are different conditions that would occur in the mouth during that process. And that again is the value of the six-month performance test.

CHAIRMAN GENCO: The presumption is the six-month performance test would not violate the maximum dose of the predecessor product.

MR. CANCRO: Oh, I misunderstood.

CHAIRMAN GENCO: For example, if it's rinsing two times a day, then you'd put that dose in each dose of toothpaste and use it twice a day. And if that's the case, I mean that's one possibility. Bill, do you want to comment?

DR. BOWEN: Yeah, I have a suggestion. How about putting on the label, recommended use twice

daily or three times daily, whatever the manufacturer suggests. For more frequent use consult your dentist or whoever.

CHAIRMAN GENCO: Max.

DR. LISTGARTEN: You know, we're dealing with tremendously large safety margins in these products. And I think that putting an upper limit is almost pointless. I mean nobody is going to clean their mouth 100 times a day. And I would bet that you could clean your mouth 100 times a day and you'd still be okay. I mean the bristles of the toothbrush might tear your gums apart, but the product isn't going to be harmful.

So I think this is a misguided type of conversation because we're dealing -- you know, you could swallow a tube of toothpaste and probably nothing would happen.

CHAIRMAN GENCO: All right. So you're saying that in one of these new formulation, new dosage forms that as long as the total maximum dose is comparable to or maybe identical to the maximum dose of the present product than that's well within the

safety margin.

DR. LISTGARTEN: Absolutely.

CHAIRMAN GENCO: And this Bill's suggestion, if you want to use it more often, see your dentist, is reasonable. Ralph, do you want to --

DR. D'AGOSTINO: No, I think the discussion, you have to put something down as the upper limit, but I think the margin is just so large it's, it really is a sort of discussion that has to fill a number but it isn't really going anywhere.

CHAIRMAN GENCO: Okay, good. Further comments? Is that helpful? I think what we've said --

DR. KATZ: That is helpful. The only other question would be is there a duration, a maximum duration or leave it open-ended.

CHAIRMAN GENCO: The only duration consideration I heard was efficacy and that was for desensitization which isn't really our subject here. The presumption was with desensitization, if you had it, you'd use it for four weeks. And then I don't know what you do after that, change toothpastes

without a desensitizer? But I think that's a presumption. That there's no need to use the desensitizer more than four weeks. Yes.

MR. SAXE: Are we talking about duration of use on a daily basis of any of the agents?

CHAIRMAN GENCO: No, duration over time, months, weeks.

DR. KATZ: Duration over time, exactly.

CHAIRMAN GENCO: Years.

DR. KATZ: Because actually I thought that you did address the duration for the daily in terms of Bill's suggestion with the directions to use twice to three times a day, more often use to consult a dentist.

MR. SAXE: On the daily basis also let's recall that on the four essential oils most all of these studies were done under strict supervision, at least five out of every seven days in the duration of the study. And there was, there was not casual use but directed use, supervised use for a certain amount of seconds, 30 seconds I believe. And I think then that sort of information also then has to be, you

know, within the label. So it's not only the times per day but the duration in which the rinsing, in this case, is to be done in order to, for the consumer to get a sense that they're going to have a chance to be, to be using an effective agent.

CHAIRMAN GENCO: I think we're getting into the next topic, directions. And maybe that's a good segue. Let's finish this one. Now dosage, both dosage per application and maximum dosage. We're comfortable with how that's left then. Okay, fine. I think it's a good time to take a break. Why don't we come back at ten to 11:00 and we'll talk about directions. And I think that plus the calendar will be the two items left. Thank you.

(Whereupon, the foregoing matter went off the record at 10:33 a.m. and went back on the record at 10:52 a.m.)

CHAIRMAN GENCO: I wonder if I could ask you to take your seats for this last half hour or so of our three day meeting. Plaque-a-thon. Okay, we'd like to discuss now the directions. And we have a

template here that we can work from and that was provided to us by Bob Sherman. And I draw your attention to his handout from yesterday, five pages from the end. Safe and effective use of an ingredient or dosage form. And the first issue is instructions for different age groups.

I think it's probably best to take first the dentifrice, stannous fluoride dentifrice and then the mouth rinses. So let's discuss the dentifrice. Let me read to you what's on the FDA approved anti-gingivitis toothpaste. Adults and children six years of age and older brush teeth thoroughly preferably after each meal or at least twice a day or as directed by dentist or doctor.

I think I'd object to the dentist or the doctor, because dentists are doctors. Maybe dentist of physician.

(Laughter.)

CHAIRMAN GENCO: Did you have anything to do with that, Fred.

(Laughter.)

MR. HYMAN: That actually, that wording is

in the anti-caries monograph.

CHAIRMAN GENCO: Is it.

MR. HYMAN: Yeah.

CHAIRMAN GENCO: Take it out.

(Laughter.)

DR. SOLLER: Actually they can be used interchangeably, okay. They are interchangeable terms under the regulations.

CHAIRMAN GENCO: Except that you get into malpractice problems.

DR. SOLLER: It's a review, not the NDA.

CHAIRMAN GENCO: Okay. Is there any comment to that. You don't have that in front of you, let me read it again. Adults and children six years of age or older. That's the first issue. So the age is dealt with there. Adults, children, and children six years of age and older. Any comments on that as an instruction for the dentifrice now.

Brush teeth thoroughly, preferably after each meal or at least twice a day. Thoroughly, preferably after each meal or at least twice a day. Or as directed by dentist or physician. Bill.

DR. BOWEN: I'm not sure what is on the label for children with the stannous fluoride product. But several companies I know put --

CHAIRMAN GENCO: Yeah, it is the next statement.

DR. BOWEN: Well, what I'm concerned about before I read it is the, whether it's a pea-size.

CHAIRMAN GENCO: This is for the low dose and this is for the higher dose.

DR. KATZ: The pea-size is no longer there.

DR. BOWEN: No.

CHAIRMAN GENCO: It was taken out.

DR. BOWEN: Okay. It's still a concern in various parts of the world over the chronic use of fluoride toothpaste possibly, and underline possibly, in being responsible for the alleged increase in the prevalence of fluorosis. And I'm wondering whether a more specific instruction is necessary on the size or the amount of paste put on the brush for children.

CHAIRMAN GENCO: You know, as I read the directions here, it really all relates to the fluoride

issue in caries. But let me read through them.

DR. BOWEN: Okay.

CHAIRMAN GENCO: The next statement, see the first bullet is adults and children six years of age brush teeth thoroughly preferably after each meal or at least twice a day or as directed by a dentist or doctor. Second bullet, instruct children under age 12 years of age in good brushing and rinsing habits (to minimize swallowing). And then third bullet, supervise children as necessary until capable of using without supervision.

And fourth bullet, children under age six of age do not use unless directed by dentist or doctor. So these, these all seem to be related to the caries. How much do we have to get into. I meant there's no, it doesn't appear to be anything specific to the anti-gingivitis, anti-plaque effect.

DR. KATZ: At this point basically, part of what we wanted was whether or not there are any specific directions that need to be for the products that we're looking at, which would be the anti-gingivitis, anti-plaque.

CHAIRMAN GENCO: Okay, not the combination.

DR. KATZ: Not really the combinations because the combinations would actually fall under whatever other guides might already be there.

CHAIRMAN GENCO: Okay.

DR. KATZ: So that if there is a specific directions from fluoride, then they would go back to use the wording that is currently there for fluoride. If there's something specific for anti-caries that again would go back. So that when, right now the question is really more specific to anti-gingivitis, anti-plaque type of products.

CHAIRMAN GENCO: Okay, does anybody have any suggestions for, that would be specific. I mean we know already what I've read is going to be on there or a variant of that.

DR. KATZ: A variant of that.

CHAIRMAN GENCO: So, is there anything additional specific to the gingivitis. Peter.

MR. HUTT: I simply wanted to point out, I have in front of me the monograph for anti-cavity

toothpaste. And what you read, Bob, is identical perhaps with a one or two word slight difference. But it's identical to what is already required on every anti-cavity, fluoride toothpaste for the higher concentration, for the 1,500 PPM fluoride.

CHAIRMAN GENCO: For the single use then, what would be the instructions. In other words, we wouldn't, it wouldn't be this particular, these directions wouldn't be on, let's say, well, wait a minute. Is the stannous fluoride dentifrice also anti-caries.

DR. BOWEN: Yes.

CHAIRMAN GENCO: So it would be. All right. So for the anti-gingivitis dentifrice, it's exactly what is here and the question is, is there anything additional? Okay. Now let's go to the mouth rinses. I don't have in front of me an instruction. I don't have good direction for that, so we're really working in an area of, with no precedent except the ADA seal of approval product, not an FDA approved product.

MR. HUTT: But there is, for an anti-

caries treatment rinse product there is currently in the monograph, in the CFR and if you would like me I would be happy to read it. Adults and children six years of age and older use once a day after brushing your teeth with a toothpaste. This is for use, obviously, under those circumstances. Vigorously swish ten milliliters of rinse between your teeth for one minute and then spit out.

Do not swallow the rinse. Do not eat or drink for 30 minutes after rinsing. Instruct children under 12 years of age in good rinsing habits to minimize swallowing. Supervise children as necessary until capable of using without supervision. Children under six years of age consult a dentist or doctor. That is what is currently used.

It could be used, not in hike verba, but it could be used as a model for the type of labeling we're talking about.

CHAIRMAN GENCO: But it's directed to the anti-caries effect. Also, some of those are specific for anti-caries.

MR. HUTT: That is why I said it could be

used as a model but not --

CHAIRMAN GENCO: Not verbatim.

MR. HUTT: -- not identically.

CHAIRMAN GENCO: Okay. From what you've heard would you want to include or exclude any portion of that or is it a good model?

DR. BOWEN: If I remember correctly, those are all fluoride mouth rinses with no alcohol in them, is that correct?

DR. KATZ: They are all fluoride mouth rinses. It doesn't specify here about alcohol or not, but it does specify that they are fluoride.

DR. BOWEN: And Listerine I think has it on their label, a restriction pertaining to 12 year olds. And I would feel comfortable, as they obviously do, starting at that point with mouth rinses containing significant amounts of alcohol. I'm not particularly worried, as I indicated yesterday, to the actives, I think their safety is so high. I would be a little concerned about the amount of alcohol that is potentially, could be swallowed.

CHAIRMAN GENCO: So that would be

consistent with the indication too.

DR. BOWEN: Yeah.

CHAIRMAN GENCO: So the direction would be, for adults and children over age 12 --

DR. BOWEN: That would be my feeling.

CHAIRMAN GENCO: -- use twice a day. This was, the fluoride was one time a day. Do you have some instruction?

DR. BARNETT: Actually there was a bottle of Listerine floating around this morning. I don't know if it's still here, but basically the directions for use on the label correspond to the usage in our clinical trials. Which is basically rinsing for 30 seconds with 20 milliliters twice a day and I think the label says morning and evening.

DR. LISTGARTEN: I guess if we take the directions for the fluoride rinse, the way it would differ is the fluoride rinse is recommended to be used after brushing. I'm not sure that this would apply for the gingivitis product.

CHAIRMAN GENCO: Would it be instructive for us to say that the directions would be based upon

the clinical trials of the appropriate mouth rinse? In other words, the mils per day, the times per day, when --

DR. KATZ: Right. No, that would be appropriate.

CHAIRMAN GENCO: Okay. Yes, Bill and then Stan. With the caveat the 12 and older, that I think we feel strongly about.

DR. KATZ: Okay.

CHAIRMAN GENCO: For use in adults and children age 12 and above.

DR. BOWEN: Max raises an important point that there is good evidence that if you don't rinse after you use a fluoride toothpaste that you probably enhance the clinical effectiveness. So there's a case to be made for not using these immediately after tooth brushing in contradistinction from using the fluoridated mouth rinses immediately after rinsing.

So I would suggest any reference to after tooth brushing be omitted. Simply use it twice daily as the manufacturer suggests.

CHAIRMAN GENCO: Okay, so the manufacturer

may suggest, for example, morning and evening use and you'd like to go further and say, and furthermore, do not use after brushing or rinsing with a fluoride toothpaste. Because you may use it in the morning after brushing your teeth and use it in the evening after brushing your teeth. That's your point.

DR. BOWEN: And you would run the risk of diluting the effect of fluoride. So I would not make any reference to after tooth brushing. Simply say, use it twice daily.

CHAIRMAN GENCO: Okay. Yes.

MR. SAXE: Bob.

CHAIRMAN GENCO: Yes.

MR. SAXE: There is, in the handout that came from Bob Sherman or one of them on labeling, in that are included some examples of submitted directions. And there's a sentence in one of them for rinse that might be considered. And it says, "the rinse is not intended to replace regular brushing and flossing". And I would suggest that perhaps this would be a good addition to directions.

CHAIRMAN GENCO: Okay, anybody have any

comments on that?

DR. LISTGARTEN: Yeah, I agree, I think that's important. Some people may feel that a quick rinse may be equivalent to brushing. I think that's a good statement.

CHAIRMAN GENCO: What about the statement of do not swallow, which is in the fluoride rinses. Again, not used for ingestion, so to re-emphasize that.

MR. SAXE: Particularly with alcohol and young people, sure.

CHAIRMAN GENCO: Okay. So the instructions, the specific instructions with respect to milliliters, how many seconds and times per day comes from the manufacturer based upon the test. The additional are adults and children over age 12, do not swallow and --

MR. SAXE: Rinse is not intended to replace regular brushing and flossing.

CHAIRMAN GENCO: -- rinse not intended to replace regular brushing. Any other? How about the do not eat or drink? That's relevant to the fluoride

and it's not really relevant to these anti-plaque, anti-gingivitis. Any other elements of the directions, Bob, that you think we should be concerned with?

I think we've taken the advice not to mix warnings and directions here, instructions and use.

DR. KATZ: For any of these ingredients again that we've been looking at, products, are there any other age restrictions other than for the Listerine that you might have that we need to consider on any of the products? I mean in terms of the directions.

CHAIRMAN GENCO: So the use was from age 12 and above.

DR. KATZ: That's for Listerine, though.

CHAIRMAN GENCO: Right. For the mouth, both mouth rinses. Listerine and CPC.

DR. KATZ: And CPC. And are there any other restrictions for age that you might want to have for a stannous fluoride?

CHAIRMAN GENCO: That means don't use in children under age 12. You mean be more specific, not

for use or use under --

DR. KATZ: Or for stannous fluoride as well. Would that also be --

CHAIRMAN GENCO: Okay, the stannous fluoride is, excuse me, is a dentifrice. And that was the first discussion and that we were instructed by the anti-caries dentifrice monograph and that has a lot about age. I mean children under age six do not use unless directed by a dentist. Supervise children as necessary. Instruct children under age 12 and make them swallow, all of that. That would not be relevant to the Cepacol mouth rinse or the Listerine mouth rinse.

The only age suggestion there was do not, for use in adults and children over age 12. Unless you feel more strongly and you want to make a do not use in children under age 12 or something like that.

DR. BOWEN: I think the positive is better.

CHAIRMAN GENCO: Okay. So the statement that we discussed was for use in Adults and children over the age of 12. Bill is suggesting that we also

add, in addition to the do not use, not for use or use only as directed by a dentist in children under age 12.

DR. BOWEN: I'd simply say, for use in children above the age of 12.

CHAIRMAN GENCO: Okay. The positive statement.

DR. BOWEN: The positive statement.

CHAIRMAN GENCO: Not the do not use. Okay. Comfortable. Okay, anything else about the labeling or the directions, excuse me.

MR. SHERMAN: I think that should cover it.

CHAIRMAN GENCO: Okay, thank you. Well, I think now we're down to the last item and that's the calendar. I have to say that unfortunately I wasn't planning on that meeting in October and I'm going to have to check home, you know, to see what my calendar is like. I have it here, but I'm not sure it's complete for October. You know, there's certain things happening. So we can do that and I would recommend that everybody get it done Monday or Tuesday

so that we can get this date and there was an overwhelming feeling that we would like to stay or have our meeting at the most elegant hotel in the city of Washington.

(Laughter.)

CHAIRMAN GENCO: And possibly, if you could put us up in the penthouse rooms, we'd appreciate it.

(Laughter.)

DR. BOWEN: With appropriate per diem.

DR. D'AGOSTINO: Is that a motion?

MR. CANCRO: Second.

CHAIRMAN GENCO: And Bill said, it would be nice if we had a Christmas bonus too.

(Laughter.)

CHAIRMAN GENCO: Well, I'd like to thank Bob and Rhonda for organizing. Linda and Fred for their help. I think they showed a lot of restraint and we appreciate that too. And it's been a pleasure, this three days working with all of you, the committee and all. And I think over the years we've seen the interaction with industry to be extremely productive

and also NDMA.

And I'd like to thank everyone for their hard work in preparing for this meeting. So look forward to seeing you in October. Thank you again.

(Whereupon, the foregoing matter was concluded at 11:10 a.m.)