Dr. Nelson, do you have a response to that?

SKIP NELSON: As an ICU doc, I can't resist at least offering one consideration, even though age could be considered a continuous variable, one of the things you discuss is the importance of the uniformity of the population that you might enroll in a clinical trial. There's a significant difference between, say, a 4 year old and an 8 year old potentially in terms of airway anatomy. One is when you're 4, your cricoid cartilage is the narrowest part of your airway, when you're 8 it's your vocal cords, so that's why we use a round tube or a tube with a cuff when we intubate them.

So the question would be are there developmental differences that would make natural break points that would suggest that if you enrolled both a 4 year old and a 9 year old in the same trial, are they apples and oranges, independent of whether you consider age a categorical variable. So that's just something that would be worth

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discussing.

RALPH D'AGOSTINO: Earlier when we were saying we could do adults and bring it down to all children, now we're dicing up the children which I think is a right discussion.

MARY TINETTI: Any of the pediatricians want to comment on that point?

Dr. Joad.

JESSE JOAD: Well a natural break point might be 3 years instead of, because 3 years and under is where viruses can cause bronchiolitis and croup and it's not usually considered the cutoff at 2, it's usually considered a cutoff at 3. So there's an argument that it is truly different -- the disease could be truly different in that age group versus others.

DENNIS BIER: You know, it seems to me if you have enough children, then there ought to be enough children to do this study. You know, with enough children in any age group from 2 to 12, then

you determine whether or not there's an age effect, it's a continuous variable. If there's not, well

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there may be differences in anatomy and things, but they don't have any affect on the end point variables. If there are, then you find out, is it an anatomical thing, is it a different, different, you know, different viral, you know, infection or whatever.

MARY TINETTI: Jan.

JAN HEWITT: Yes, yesterday I saw some data related to P 450 metabolic profiles and poor metabolizing and extensive metabolizing in some of the ingredients, but not all, would the FDA along with the pk data consider more data along with the P 450 metabolic profiles of individuals particularly, for example, if Caucasians, 10 percent of them do not metabolize Dextromethorphan appropriately. As a parent I would probably want to know that data before administering the drug.

CHARLIE GANLEY: You know, I couldn't hear your voice, so if you could speak louder.

JAN HEWITT: Sorry, I'll just get closer. So along with the pk data, is the FDA or would the FDA consider more P 450 metabolic, I'm not

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an expert in that area but it seems to me that I saw some of the drugs have data in 2D6 and 3A4 but not all the ingredients had a good profile of what that data was, so would they consider that as well was my question.

CHARLIE GANLEY: Well I think the, you know, the, generally when the, and I think the efficacy studies are done and, you know, other folks can weigh in, that I think there's sparse sampling done also in the efficacy studies.

The point I'm not sure about your question is that to me is you have to determine what is the safety profile related to an individual drug, so if it turns out that a poor metabolizer of Dextromethorphan doesn't tolerate the drug with regard to, you know, gets some dysphoria or something like that, well the, I think it's hard for

an individual to determine whether they're a poor metabolizer other than they get the symptom and generally we'll try to label products if, you know, there's a symptom that may occur because you're sensitive to the drug or you just don't metabolize

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it. We try to characterize it by reporting what symptoms you may get and then the individual would on their own or their care giver on their own would make that determination.

I think it's the same thing that's applicable to the prescription side when a physician writes a prescription and the individual takes it home and they don't tolerate it, that there may be some, you know, there's huge inter-individual variation in drugs and adults so they're going to call you up and say, you know, I took this and, you know, I got terrible pains in my legs and I just don't tolerate it well. It's pretty much the same way for an OTC drug.

You try to characterize what the downside is and if it turns out that a drug is, you know, metabolized in such a way that it leads to such a serious adverse event and there's no way we can identify that population on an OTC label, it's not necessarily going to be an OTC drug.

MARY TINETTI: Okay. I'll move on to question number 2 related to safety. The safety

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discussion in the petition focuses on cases of misuse, unintentional overdose and excessive dosing of over-the-counter drug and cold drug products. The petition does not specifically address the safety of OTC drug products for children under the age of 6 when used in accordance with the labeled instructions and under a physician's care.

Considering the widespread use of over-the-counter drug and cold products, over decades there are reported cases of serious adverse events. We are interested in understanding why these events happened and would like to be able to reduce the occurrence of preventable events.

And so the first part of that question

is really a discussion, aside from issues related to excessive dosing, please comment on any significant safety issues that can be identified when these drugs are used at the currently recommended doses and I presume implied in that question are also steps that can be taken to reduce, reduce those occurrences.

Dr. Calhoun.

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WILLIAM CALHOUN: So this actually goes to the question I asked yesterday afternoon, in looking at the safety database at least in the AERS, it appears that most of the serious adverse effects were largely related to overdose, but the occurrence of seizures was not necessarily associated with overdose and the concern there is that unlike transient tachycardia or unlike transient loss of consciousness, a seizure, even if afebrile seizure may, at least in my understanding, may convey some longer term risk of recurrent seizures.

And so I guess I would like to see that seizure database cleaned up a little bit so that we can perhaps sort out those that are attributable to febrile seizure from those that could, in fact, be related to an adverse interaction between viral infection and the administration of these agents.

MARY TINETTI: I think that's an excellent point, particularly seeing the seizure occurrence happened across all the different products and you wouldn't necessarily expect it. I think that's an excellent idea.

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Dr. Parker.

RUTH PARKER: Just to speak significantly to any safety issues broadly, I would say that I have concern about the multiple ingredients and the average person's ability to understand and decode what these ingredients are and what they're treating. So in my own quick, quick way I'm thinking about the nose, you know, it can be runny, it can be stuffy, it can be congested, it can be itchy and which ingredient targets which one of those. I think most people know that we advertise

and market problems and so those are what are on the labels.

The problem, the symptom, you know, what you have, and so I think as a safety issue it is how these are presented on the shelf and how the average person is able to look at the problem that's marketed or advertised on the label and self-diagnose in order to adequately treat the condition that they, you know, that they go to the store in order to purchase.

So I'm concerned with the combination

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products very specifically and the ability to understand and when you, when you break that down into the details, I use it all the time in teaching residents about over-the-counters where I litter the table with products and ask them to pick which one do you use for what and they can't do it. And those are all licensed physicians.

MARY TINETTI: Dr. Griffin.

MARIE GRIFFIN: Yeah, I think the, the data, I think we have to remember with the data we have on safety are case reports and so there's a little bit of circular reasoning. If a child dies suddenly and they have high blood levels of these components, we attribute it to the components and if they don't, then we don't. So that, therefore, we end up with saying, well, these deaths are because of misuse.

I think we really don't know, like the febrile seizures, we don't really know if these components cause seizures or if they're just temporarily associated with taking these drugs.

So I think the level of data we have on

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safety is really pretty bad and maybe one thing the Committee could do is deliberate on what level we think we need.

Do we want to say 1 in 1,000 children with a serious adverse event is too high or where do we stand so that when we're thinking about efficacy studies, I think we also have to think about what power we need to rule out serious adverse events for

drugs that are used for symptoms and don't save lives or prevent disability.

MARY TINETTI: Dr. Cohen.

MIKE COHEN: Yeah, I'm not sure that this is the right place or the right time that is to talk about this, but it just seems to me that if we're doing the efficacy studies, et cetera, that we were talking about before, perhaps we could also look at comprehension of the labeling, product selection, the dosing devices, et cetera, et cetera, there as part of this question.

It just seems reasonable because we really don't know and we heard lots of testimony yesterday about all the product variation,

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800 products, brand name extensions, et cetera, that does seem to be causing confusion based on reporting to the AERS program.

MARY TINETTI: So you're stating in terms of the safety issue that the, that the labeling and the multiple ingredients is contributing to the confusion which then contributes to the safety?

MIKE COHEN: And misuse, yes.

MARY TINETTI: Misuse, yes, and dosing. So lack of dosing standards and the labeling.

MIKE COHEN: Right, yeah.

MARY TINETTI: Thank you.

Dr. Rosenthal.

JEFF ROSENTHAL: I just have a point regarding item number A having to do with safety issues at least within the current labeling and in my, I just want to make the point that in my pediatric cardiology practice we uniformly recommend that patients avoid this group of medications because of an observation that kids with rhythm, heart rhythm disorders are more likely to have these

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provoked by at least some of the agents within these cocktails and I think, you know, specifically looking at safety in subgroups like cardiac patients would be important.

MARY TINETTI: Thank you.

Dr. Garofalo.

ELIZABETH GAROFALO: Thank you, Betsy Garofalo. I wanted to make two comments, one was to the question about seizures and say of course that I concur that this could be a confounded data set, in other words, the children are ill and potentially have the fever and have the seizure, but I certainly agree it's worth going back and trying to parse that out, but it may essentially be impossible, it's pretty common, of course, in children and that, you know, simple febrile seizures don't, in general, have sequelae.

That said, I also wanted to comment on the combination products because of course there are a lot of them out there and there is some apparent concern that there is a higher safety risk with those, but I think in looking back at the data from

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what we were presented and what was in the briefing information, there's such a high percentage of use that it's sort of comparable to the percentage associated with combination products in the serious events that we saw. I was trying to find the spots where I would see that, but it didn't, it wasn't a disproportionate number of serious events reported from the combination products as far as I could tell.

MARY TINETTI: Dr. Hennessy.

SEAN HENNESSY: Sean Hennessy. Because these products are available over the counter, they're not captured in administrative claims data, so doing a large administrative claims data studies is going to be impossible.

Prior to Ibuprophen being approved for OTC use in kids, there was a large simple trial done to assess the safety primarily and I think that would be a good idea for any of these products as well.

MARY TINETTI: Dr. McMahon.

ANN McMAHON: Ann McMahon. A couple of

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different points that people have been making, one of them about febrile seizures. In the review that

was done in the Office of Safety and Epidemiology, it does parse out to the extent that it was possible how many of these cases were associated with fever.

Now, you know, if they say they were associated with fever, that's noted. If they don't say they were associated with fever, they may or may not have -- fever may or may not have been present, but to the extent that it was possible it was sorted out in the, in the document that was written in support of the, of the comments that were made yesterday.

Now as far as the, a safety study and it, as, as people have alluded to with the passage of surveillance data, there's just so many limitations. It's also very, very unclear exactly how large the safety study would need to be to be really very useful and so I think it would be, it would be helpful to hear peoples' input on, on how such a study would need to be done if it, if it were to be done.

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As, as you had mentioned, it's, these drugs aren't going to be picked up in administrative databases, so, you know, sort of the model of a post marketing type study, safety study, how would that be done.

MARY TINETTI: We have to break for lunch, I'm just going to, so hold your comments to after lunch, we're just going to end up right now with Dr. Rappley.

LAURA MARCIA RAPPLEY: I'd like to just add to the comment about how we consider what rate of adverse events we consider acceptable or we are willing to tolerate, not only is that in balance with the efficacy of the medication, but I think we need some sense of the risk of not treating and I know that that's not an easy thing to examine in a rigorous way, but I think we all have the sense that colds and coughs due -- or coughs and runny noses due to the common cold are innocuous and self-limited and don't lead to other more serious problems, but I'm not sure we have real data about that.

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And so as we look at the risk of treating, we need to balance that also with the risk of not treating.

MARY TINETTI: Thank you, I think we are actually going to reconvene in 45 minutes, a quarter to 1 and the Committee will be eating in the same room.

And remember, no, no discussing the topics during lunch, thank you.

(Lunch recess taken 11:56 a.m.)

0202

A F T E R N O O N S E S S I O N

MARY TINETTI: We're going to, we're going to get started again, so if everybody.

Hi, Dr. Rappley, we're just going to get started again for the afternoon session and welcome back to everyone.

Dr. Ganley has asked us to go back to further clarify an issue related to extrapolation, so I'm going to finish I think with question 2 and then we will go back and re-address some of the extrapolation issues.

So you recall, we were discussing the issue related to safety and were there any significant safety issues that could be identified when these drugs are used at the currently recommended doses. And some of the issues that have already been brought up are trying to disentangled for the high rate of seizures, is there a way to

disentangle drug effect from, for instance, the febrile illnesses.

There was an issue raised that the

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multiple ingredients and the present labeling was confusing, we felt that that could lead to lack of difficulty with safety. Lack of standardization of dosing. And dosing devices, devices are directly addressed.

So, if there's any other issues related to safety that aren't covered there, that's fine, otherwise we can move on to the next part which I think is probably the important part is what actions might we recommend.

Before we do that, are there any other specific safety issues that have not yet been raised that we want to include?

Dr. Cnaan.

AVITAL CNAAN: The single issue, Avital Cnaan, the single issue that was raised several times and that is the dosing by age rather than by weight for children who are small for age, I think this is a risk that should be considered.

MARY TINETTI: So your point is the lack of dosing by weight in --

AVITAL CNAAN: Yes.

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MARY TINETTI: Okay, thank you. Okay, we'll move on to the next part then is obviously, hopefully will lead directly from our previous discussion is what actions do you recommend the Agency consider in order to reduce the occurrence of these adverse events related to factors that might be associated with the drug or the age group such as variations in metabolism, variations in weight.

So, again, what actions might we recommend for the FDA to reduce safety issues again with usual usage in, with indications stated.

Dr. Joad.

JESSE JOAD: Did we skip the additional safety data I think? I mean I was interested in Dr. D'Agostino's 29,000 patients that he can look at in a safety study. We didn't really discuss that.

That's above that one you just read.
MARY TINETTI: Well I don't think we skipped it, I mean I think -- so we mentioned I think one of the actions might be is to review, review the safety data that already exists, is that your point?

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JESSE JOAD: Maybe I just misunderstood, but I thought they were asking us what we thought, what kind of data we thought we needed other than the data that we already have.
MARY TINETTI: Well I think that would probably come under an action item, so we can --
JESSE JOAD: Okay.
CHARLIE GANLEY: Well, Dr. Tinetti, it would be helpful to have more discussion because the industry had already said that they would be willing to do additional safety studies, so we need to understand a little more what that means.
MARY TINETTI: I think that's what I just said, that's what we're going to discuss though, the safety, the additional safety data.
CHARLIE GANLEY: Oh, okay.
MARY TINETTI: That's what's proposed and I said that's what we were going to be discussing, so if there were additional safety data that we felt were needed that was part of an action item.
Does anybody want to address that point?

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Dr. Griffin.
MARIE GRIFFIN: Well I think, I just want to say again, I think it would be helpful if we specified what level of serious adverse event we want to be able to detect because I think that the current safety data can inform us about that and I don't think re-reviewing case reports are going to tell us anything about drug outcome relationships. So we need denominator based data, so I think I would like to hear other peoples opinion on how, what level of safety we think we need for these products.
MARY TINETTI: I think even before that

is the fact that you'd need the data, that we need actual rates which is presently lacking. We're actual lacking both a numerator and the denominator data, so I think we propose the actual rate data for adverse events are needed.

Does anybody want to comment upon what, if any, rate would be acceptable once we are able to obtain those safety data? It's a little bit hard to do that without knowing, again, I mean it's hard to

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know what safety -- what rate of adverse effects you'll accept until you know what the benefit is.

MARIE GRIFFIN: Yeah, but you know the benefit is not going to be saving lives or, you know, the benefits going to be symptomatic, so there may be some level even if we got good symptomatic relief, we may say that some level of serious adverse events are unacceptable.

I think in this country we made a vaccine policy based on a tolerance for a very teeny level of adverse events in children, so we changed from oral polio vaccine to an activated polio vaccine because of 8 to 12 cases of vaccine are associated with polio. I think the ethical considerations for vaccines are different, but I think that we have to think about whether serious adverse events, things that can kill children or cause permanent harm are acceptable and at what level.

MARY TINETTI: So assuming that these studies that we have just proposed, that they do show some effectiveness for symptoms because

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obviously if there's no effective symptoms, it's a moot point, what rate of adverse effects and that probably depends upon what adverse effects we're talking about, so maybe you, would you like to make a specific proposal, Dr. Griffin, for us to address?

MARIE GRIFFIN: Well, I mean things that we consider serious adverse events, things that would land a child in a hospital or cause death or permanent disability.

To me, 1 in 1,000 would be pretty high,

but I guess I would think it would be nice to have trials that could at least rule out that level of risk.

MARY TINETTI: I think we may want to separate out how the data get obtained I think for trial -- I mean actual clinical trials would have to be enormous to find that, but regardless of how the data are obtained, what, what death rate is, I would think 1 in 1,000 would be absurdly --

MARIE GRIFFIN: I'm saying serious adverse events.

MARY TINETTI: Let's start with death, I

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mean it's -- we heard yesterday that no death is acceptable. Can we put a number on that or is that beyond the scope of what we can -- we know that if there is effectiveness there's nothing that's completely safe, I mean that's, that's a standard that would be wonderful but it's not obtainable. Do we want to put a number on that or?

ANN McMAHON: So I just want to clarify that one of the things that we're talking about here is safety data on appropriately dosed.

MARY TINETTI: Yes, this is all appropriate dosed.

ANN McMAHON: Right.

MARY TINETTI: This is all appropriately dosed.

Dr. Daum.

ROBERT DAUM: So Dr. Griffin's comments inspired me to recall a vaccine safety workshop which was held at FDA, I'm very good -- very bad at remembering retrospectively how many years ago it was, but I'd say about seven where this kind of issue was addressed, is what kind of frequency of

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adverse event did the vaccine community want to pick up and study condition trials where every patient was watched and monitored and enrolled prospectively and then what kind could be, would we tolerate being picked up in much larger enrollee numbers post marketing trials.

And so I would wonder if we shouldn't

think about the analogy and I'm certainly not one of the statisticians at this table, but the analogy of thinking about the studies that are going to look at efficacy when they get powered and designed correctly to also be, have some thought assigned to looking at common major and not so major side effects and then recognize some frequency that the study designers would impune -- impart, excuse me, to the study design that would detect what I would call common side effects.

And then I think that the only way to realistically capture rare, rare side effects is a post marketing trial. I don't think you can do that in study conditions without bankrupting the system.

So I think we have to think about it two

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different ways and I would propose that the common ones be rolled into the study design for the efficacy that we've said this morning is important and that the less common ones be done in a post marketing surveillance kind of fashion.

MARY TINETTI: Okay.

ROBERT DAUM: I can't give you the numbers because I'm not a study design guy, but there's a guy who can.

MARY TINETTI: Dr. Garofalo.

ELIZABETH GAROFALO: Actually I'm just going to echo that exactly, I think in the controlled trials you have a control group so you can get your common adverse events, but you're not going to see the rare adverse events in that setting, that duration, et cetera. And so we have so much data already, perhaps not at the doses that we'll end up with, but we have so much data over many, many years of surveillance that, you know, again trying to do something that's a longer controlled trial for safety doesn't make any sense to me. So I'm just echoing what was just said.

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MARY TINETTI: Okay, thank you.

Anything to add to that? Dr. Goldstein.

GEORGE GOLDSTEIN: In the interests of time, no, but there are 40 years of data presented

by --
MARY TINETTI: I think we've heard that, thank you.
Dr. Rappley.
LAURA MARCIA RAPPLEY: Yes, we looked at this issue around the sudden death associated with stimulant medications and it was very helpful for our panel to look at the, the best estimates we have of sudden unexplained death in young people and just, so just to give a frame of reference, that, we think the best study is probably Lieberson in 1996 and it showed a background rate of 1.3 to 8.5 per 100,000 person years.
So if we think of that as a background rate for an unexplained death in young people, that would be a reference point and if we say that there -- no cases of death associated with these meds are tolerable, then it would be something

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higher than that background rate, I would think.
MARY TINETTI: Okay. Dr. Shrank.
WILL SHRANK: Will Shrank, so Dr. Hennessy appropriately noted before that a lot of this post marketing surveillance work would be especially difficult in this population because over-the-counter medications aren't collected, but many of these drugs are prescribed at times, so there may be, it, I don't know what the proportions are, but probably not an inconsequential proportion, so I don't know if it's impossible to do the post marketing surveillance work.
MARY TINETTI: Dr. Newman.
TOM NEWMAN: Yeah, I just think one of the issues that comes up is that it's going to be very, very hard for any of these deaths to know whether it was due to the medication or not, so in that way it's very different from the Polio vaccine where if you got the Polio from the live virus vaccine, you knew, okay, this is someone who was affected by this, this medication.
All of these kids will, many of them

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will have fevers and URIs and things which can

predispose to other, you know, bad things and so, you know, my, my thought would be something quite a bit less than 1 in a million but it would be with a knowledge that probably the way to answer the question would be some sort of case control study of sudden deaths and try and see whether use of these medications is -- in the absence of overdose, use of these medications is independently associated with the outcome, independent of the symptoms they were designed to treat.

RICHARD NEILL: Richard Neill. It seems like what we're dancing around a bit is the fact that efficacy, which hasn't been shown in these entities, may exist, needs to be studied, hasn't been demonstrated yet, but if it exists it's likely to be measured in terms of things like numbers of sneezes in a day, we get two, and so let's add up whether millions of sneezes is worth a life and if not a life, then are millions of sneezes prevented worth lifetime seizure disorder or some other potential adverse event.

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And I make that comment in the context of what I think is pretty striking and quite frankly, although subject to interpretation, pretty safe data here. These seem relatively safe, not perfectly safe, and I think it's an honest question whether we balance the rare, difficult to measure, extremely untoured, undesirable event or whether we ought to instead design side effect safety trials that allow a parent to ask is it worth cutting down on nasal stuffiness if what I'm doing is exchanging it for headache, constipation, whatever, fill in potential side effects here.

And I'll be honest, I don't know the answer to that but I do think that it adds a second layer of difficulty in answering the safety question which is no less difficult than the more important that you already mentioned, you know, what's the efficacy ratio there, how much effectiveness for safety do you get.

MARY TINETTI: Dr. Joad.

JESSE JOAD: I am arguing -- sorry, I am

arguing for large safety trial -- official ones like
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they did for Almeterol, that sort of thing where people are, because of the reasons we're talking about, the reasons to give the drug are just symptomatic relief and the concerns we have are serious, very serious and I think we can't, shouldn't go by just voluntary reporting.

MARY TINETTI: Dr. McMahon.

ANN McMAHON: Oh, I was, I was just going to make the point that if it's a post, large post marketing trial, it doesn't mean that it has to not have a comparator group and I'm not saying what that should be or whether there should be other study designs, but that's just an observation.

MARY TINETTI: Dr. D'Agostino.

RALPH D'AGOSTINO: We did in this panel actually see a study of phenylpropylamine that was a case control study, basically a case control study but done in a very rigorous manner, one may argue with the small number of events, but that's going to be the case here also.

So there are designs that one can actually do and I think, you know, with the idea of
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the efficacy studies, the efficacy studies just aren't going to be big enough to really get a big database on safety and I just don't think we can design them, we can't keep people on placebos over and over again, so I think the efficacy studies will be limited in terms of their safety data, but if we do enough combinations, I guess we'll be running enough studies so we may end up getting a big database.

I think the things like the case control, the prospective, would practices, bringing in practices and then naturally registering -- not registry as such, but that type of notion that large numbers of individuals come in and I do think also that it's going to be very important to have sort of underlying background rates or control groups in order to be able to figure out what's really going on.

But these things, you know, we did it with PPA or it was done with PPA, I didn't do it, but it was done with PPA and phenylpropylamine and I think there's, there's lots of different ways of

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doing it and if there's a big enough set of, what do you call them, pediatricians and practices that can be brought on board, which it sounds like that's really possible, I think that one could work out some very clever designs.

MARY TINETTI: Let me ask the FDA, could we require and actually request a safety study that was a case controlled design or a large trial?

Is that something, the level of recommendations we can make or is this now you're just wanting to hear from us what are some of the pros and the cons of the different approaches?

JOHN JENKINS: We are always welcome to your recommendations.

It might be useful for you to know how we approach this for new drugs that go through the BPCA PREA process, meaning not these old drugs that have been on the market for a long time. Even in places where we ask for efficacy data in children, the database is not often more than a few hundred people because -- children, because we already have the knowledge we have from the adult data and we are

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generally looking for common adverse events in the pediatric trials, not rare adverse events.

That mirrors how we do drug development in general. We don't expect to be able to detect rare adverse events in the controlled clinical trials. We usually rely on post marketing experience and as people have pointed out, we have a lot of post marketing experience with all of these agents. You can argue whether the reporting is what you would like, but you could also probably take some understanding of what the rare serious adverse reactions of these drugs are from what you have from the post marketing reporting data.

I don't know what our experience has been in, you know, large, many thousands of safety,

patients of a safety trial in pediatrics. There are some examples of that in the adult arena, I'm not sure I'm aware of any, you know, many thousands of patients safety trials in pediatrics.

Even with those large studies, your ability to rule out rare, truly rare adverse events is very limited. If you have a, even a 20,000

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patient study, it isn't going to help you very much if a truly rare event occurs 1 in 100,000 --

RALPH D'AGOSTINO: You're talking about 1 in 1,000 versus a relative risk of 1.5 or something like that with a 20,000 subject study.

What I was suggesting is in terms of the practices is a sort of post marketing, but a more rigorous follow-up on them as, you know, really getting the identification of who's taking the drug and what happened, and if anything happens as opposed to waiting until this is spontaneous reporting.

I agree with you in terms of trying to put a safety study together that has treatment A versus treatment B, it's not going to, it's going to be very hard, if not impossible, to pull a study like that together.

The case control studies are much more possible and then you have to worry about what the controls are, but these designs are out there and it's quite possible to be able to get it. What about like a large, you know, a Kaiser Permanente

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type of setting and things of that nature.

MARY TINETTI: I'm not sure we want to get to that, we're going to be here for the next three weeks otherwise.

RALPH D'AGOSTINO: No, but things are possible.

MARY TINETTI: Things are possible. I think one of the things I'm really hearing about and I think the phenylpropylamine is a very good example, although it wasn't the FDA, I know it was done in the context of some other clinical trials and it came from investigators pushing it, but it

does show that rigorous case control designs can, can be effective and it is something I think the FDA should think about.

I want to get beyond the actual, some of these safety studies to other issues that relate to actions that the Agency can consider, but before I do that, did you have another comment, Dr. Griffin?

MARIE GRIFFIN: I mean there are, Kaiser Permanente did do a 35,000 children study for pneumococcal vaccine, Rotavirus vaccine is being

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studied in 75,000 children and some of those are safety, because of safety and some of them are for efficacy.

I think the question about estrogen in women was resolved because of a very large clinical trial and it may be beyond the scope of the manufacturers to do this, but it may be in the interests of the public and the Government to support these kind of trails for a very, very common condition for drugs that are used by half of the population. You know, I think we ought to think about what, what we would really like to see. I'm not saying that we need to make the manufacturers do this.

MARY TINETTI: Dr. Hennessy.

SEAN HENNESSY: So McNeill sponsored a study out of the Sloan Epidemiology Unit that Sam Letcho was a principal investigator of where they randomized about 27,000 children to receive either Ibuprofen or Acetaminophen and that was a kind of large safety randomized trial that I was thinking of.

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MARY TINETTI: Would you like, well we may come back to that because I want, the question is whether or not at this point you just want some recommendations or you actually want a vote on some of these proposals, but I think we'll, we'll come back to that in a minute.

But see if there's any other, other actions that we think the FDA should take to enhance safety.

Dr. Parker.
RUTH PARKER: I think looking at standardized dosing devices as a means to decrease variability for consumers, patients who choose self-select to take these products is a critical step. So standardization of the dosing devices and also a serious look at an attempt to standardized the dosing regimen because currently it varies by, by product and by manufacturer and I think when you're asking people to understand subtle differences that are a part of labeling, that these, these -- the existence of the variability is a root cause for misunderstanding, misinformation and
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mistakes, so I think taking a very serious look at the best possible, what language should it be, very specifically, and then how to communicate that in a standard way.
Let me also say from a cultural standpoint that the closer you get to standardizing the dosing device and the label, you pay -- you pave the path to being able to provide that information in other languages. Currently if you try to translate subtle differences that appear and do a direct translation into other languages, it's much harder than if you had a standardized language and then you just try to translate it.
So as manufacturers look to whether or not it makes good sense to provide label instructions for over-the-counter medications in another language for increased access to the population, I think having that standardized language across manufacturers and that comes with the Federal oversight is a really important safety issue.
MARY TINETTI: So you're proposing both
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standardized dosing devices and standardizing wording?
RUTH PARKER: Yes.
MARY TINETTI: Thank you. Okay.
Anything else?
MIKE COHEN: Well I agree with

Dr. Parker with the standardized dosing devices and other comments, too. Also standardizing the units of measure. There's confusion sometimes between teaspoons and tablespoonful, for example, probably metric volume would be a good way to do it.

But also, I think, just the labeling of the products, themselves. We need to do a better job at getting the ingredients I think on the front label panel, when you're --

MARY TINETTI: We're going to be addressing label specifically, so if you can hold those comments because they're going to be very important.

MIKE COHEN: Sure.

MARY TINETTI: Thank you.

Dr. Ganley.

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CHARLIE GANLEY: Just to get some clarity from Ruth, are you talking about, for example, concentrations should be standardized and things like that, so it should be if you're going to buy a diphenhydromine in a liquid suspension, we should, because the monograph doesn't include that now, we should state it has to be this concentration, is that what you're saying?

RUTH PARKER: Yes, I think variabilities in the concentration is a root cause of misunderstanding, misconceptions and that is an actionable item that could decrease variability and lead to less misunderstanding and less confusion and medical errors in the outpatient setting. Yes.

MARY TINETTI: That was nice and clear, thank you.

RUTH PARKER: I've said it before.

MARY TINETTI: You said it well.

The next question is a yes/no question for us, so hopefully this will be a little more straightforward.

Should dosing devices be required with

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liquid formulations, yes or no. Do we need any discussion on that before we can vote? Standardized, standardized wording, standardized

dosing, standardized concentration, standardized wording and standardized unit of measure.

Did I miss anything? Okay.

Dr. Hennessy.

SEAN HENNESSY: So this isn't an area that I've given much thought, so I think I'd ask Mike Cohen who probably has given some thought to this to help bring me up to speed.

MIKE COHEN: Yeah, this is Mike Cohen. There is, as I was saying a little bit earlier, there is confusion between the various dosing devices and some things like cups, for example, that you can literally take a cup from one item and place it on a totally different drug without even, you know, without the family even recognizing it and then it might have differing units of measure when they go to measure that specific medication that it was placed upon.

You know, as I said a little bit

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earlier, too, confusion between dosing units, the teaspoon and milliliters, et cetera.

SEAN HENNESSY: Is there any downside to requiring product specific measuring devices?

MIKE COHEN: I can't think of any. You know, if it was by volume, for example, that would even take into account the product concentration, so, I mean the dosing would be different.

MARY TINETTI: Amy Celento.

AMY CELENTO: Amy Celento, in relation to this I feel very strongly that the product name should be tied directly to the device, to the syringe, to the cup, whatever, I think it's linked to Dr. Parker's point about clarity and really making it fool-proof and then you could come up with ways to communicate that multi-culturally, as well.

So it should be tied to the actual medication.

MARY TINETTI: I'm not quite sure what you mean, I mean if we're talking about standardization, it would be across all the different products. I'm not, can you clarify what

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you mean by --
AMY CELENTO: Well you may have a product that has a specific dosage but a different formulation, a different medication has a different dosage and people think oh, I'll just use that little cup, all the cups look the same, so now you standardize our calibrating the cup but it could be different for a completely different medication, am I correct about that.
RUTH PARKER: That's what we've got to get beyond, so that just to be very specific, so that when I open up my medicine cabinet and I realize that, you know, we have bought six different formulations because I've got five kids and, you know, they get sick and different people buy it, I can't have five different cups that mean, you know, that go with different things because I've lost those cups, you know.
We really have to get down to figuring out from the patient perspective, the consumer perspective how we, so this is a clinical trial, let me get specific, looking at which standard dosing

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device we actually want to use and why, with cognitive testing of it to show that people, the people who use it understand it and then we have to use it across products and when you have a concentration, they have to be -- you know, we may end up with needing two different concentrations, I hope not 10, and dosing devices that match the concentration, but we want to keep it to as few as possible to limit the options of variability for a consumer and limit the choices for making a mistake.
MARY TINETTI: So to clarify, right now I probably have five different brands and five different devices and I pick up whichever one I use and so I use a different device from a different product. You're saying it should be that should not happen, regardless of what product I use, regardless of what formulation, the calibrations, the wording should be exactly the same.
Okay. Dr. Cohen.
MIKE COHEN: I was just going to give

another example, Mike Cohen. At one time we had a product issue with the dropper and the dosage was

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expressed in terms of droppers full. And what a dropper full is to different individuals, you know, things can change, some people would draw the liquid all the up to the top, almost to the bulb of the dropper whereas others would, you know, draw it up three-quarters of the way, for example, and if it's a concentrated product, that really could make a difference, so, just changing that to volume and then expressing the dose as volume really would help that situation.

MARY TINETTI: Okay, thank you.

So what I'm hearing then and Dr. Cohen and Dr. Parker, correct me if I'm wrong with the wording of this, should dosing devices that have standardized wording, standardized volumes across products and across formulation be required with liquid formulations? Is that? Okay.

Did you have a comment before we vote?

LEON DURE: Yes, Leon Dure, Birmingham, and I, I just, I mean I agree with you completely in principal, but I just want to get practical because in, say, for example, anticonvulsants, if you're

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treating an infant, a one month old with an anticonvulsant and then have the same, you know, have a child 15 years old on the same anticonvulsant with uniform volume or concentration, et cetera, I'm not sure about the device and how that's going to look because the volume is going to be very different, so is this going to be, I mean that's a prescription drug, I understand, but I'm not quite sure I see that. I agree I would love, I would love to see it, but I don't know if I can envision it right now.

RUTH PARKER: That's because it needs to be developed.

No, this is very serious, these, this needs to be done in clinical research trials. This needs to be done very carefully with cognitive psychology testing of what the words are and it has

to be done in conjunction with the people who are going to use the product, not with those of us who talk about what it's going to look like, but with the people who are actually going to use it, ensuring, back to label comprehension and that kind

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of thing that the people who are going to use it understand it in a way that meets our, our level of, of acceptability.

MARY TINETTI: Two more comments. Dr. Newman and then Dr. Bier.

TOM NEWMAN: Yeah, I just want to clarify what we're voting on, are we voting on what we want all devices, whether they're cups, syringes or droppers, to be labeled in milliliters or are we saying we only want one kind of device, because I think we may need more than one kind of device.

MARY TINETTI: We're not talking about one kind of device, I think we're talking about standard --

TOM NEWMAN: So just they'll all be measured in milliliters and --

MARY TINETTI: Yes -- well we haven't said that it's going to be milliliters, we've just said that it's going to be standardized. We haven't commented upon what type of devices.

TOM NEWMAN: Okay, well I would vote for milliliters, but the other thing that would be

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really nice if they could do it would be to say, you know, if you have a 20-pound kid, then your dose of medicine is going to be 2.5 ml or something regardless of what medicine it is, that would be enormously simplifying.

MARY TINETTI: I think that's the point. Dr. Bier and Dr. Daum and then we will vote.

DENNIS BIER: Yeah, I'm not sure we can get all the way there, but we can probably get 90 percent of the way there compared to what there is today and we have other examples, you know, we have the insulin syringe, for example, which for quite a few years was standardized across people so we didn't have mistakes, I mean it's a similar type

of thing.
The doses, the doses in the vial were standardized, the syringes were standardized, so we have examples of using this.
ROBERT DAUM: Just briefly, Robert Daum, is the context of this question in studies that are to be designed or in existing products that could be sold?

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MARY TINETTI: I think the context of it is what would be required for anything that was on the market.
ROBERT DAUM: Existing products.
MARY TINETTI: Assuming, assuming those existing products continue after today, yes.
One quick comment, we really need to move on.
GEORGE GOLDSTEIN: Quick comment, just to raise a question, what does the rigid and complete standardization do to efforts to innovate, to create better, safer, more useful packaging and labeling and choices? I think that needs to be kept in mind as well.
MARY TINETTI: Good point, thank you. Okay, I think we're ready to vote.
Does everybody remember the question, should dosing devices that are standardized in wording and dosing be required with liquid formulations.
All in favor?
CHARLIE GANLEY: Can I, can we just vote

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on C as it's written first, whether they should be required and then we can take your comments back as to standardization and, because that was --
MARY TINETTI: Why wouldn't you want us to vote on the question as we've already --
CHARLIE GANLEY: Well that's the next one, the next one is the question on calibration and standardization.
MARY TINETTI: That's a, that's a little bit different point.
CHARLIE GANLEY: But it's, the easy one

is does everyone think we should require, you know, dosing devices where there's a need for a, if there's a --

MARY TINETTI: Well we can do this in two points, we can do yes or no, but I think we're going to vote on the wording that we've just come up with. But we can do, first of all we can do the yes/no.

So all in favor of whether dosing devices should be required with liquid formulations, all in favor, yes? Keep your hands up and we'll

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start with Dr. Rappley.

LAURA MARCIA RAPPLEY: This is Marcia Rappley, I'm voting yes.

MARY TINETTI: Okay, and if we can start with Dr. Mike Cohen, are you first? Yes --

WILLIAM CALHOUN: Michael Calhoun?

MARY TINETTI: Calhoun, I'm sorry. Calhoun.

WILLIAM CALHOUN: Bill Calhoun. Yes.

TOM NEWMAN: Tom Newman, yes.

MIKE COHEN: Mike Cohen, yes.

JESSE JOAD: Jesse Joad, yes.

PRESCOTT ATKINSON: Prescott Atkinson, yes.

ROBERT TAYLOR: Robert Taylor, yes.

MARIE GRIFFIN: Marie Griffin, yes.

JAN HEWITT: Jan Hewitt, yes.

WILL SHRANK: Bill Shrank, yes.

RALPH D'AGOSTINO: Ralph D'Agostino, yes.

BEN CLYBURN: Ben Clyburn, yes.

RUTH PARKER: Ruth Parker, yes.

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MARY TINETTI: Mary Tinetti, yes.

DENNIS BIER: Dennis Bier, yes.

AVITAL CNAAN: Avital Cnaan, yes.

RICHARD NEILL: Richard Neill, yes.

AMY CELENTO: Amy Celento, yes.

ROBERT DAUM: Robert Daum, yes.

LEON DURE: Leon Dure, yes.

JEFF ROSENTHAL: Jeff Rosenthal, yes.

SEAN HENNESSY: Sean Hennessy, yes.
MARY TINETTI: Okay, any nos?
Any abstentions? Okay.
Do you want to -- go ahead.
DARREL LYONS: So question 2C, for the record, 22 yes, zero no, zero abstain.
MARY TINETTI: Okay, so then we are going to vote on the wording that Dr. Cohen and Parker have suggested with, that is requiring standardization.
All in favor?
LAURA MARCIA RAPPLEY: This is Marcia Rappley, I vote yes.
MARY TINETTI: Okay. We'll start over

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on this side this time.
SEAN HENNESSY: Sean Hennessy, yes.
JEFF ROSENTHAL: Jeff Rosenthal, yes.
LEON DURE: Leon Dure, yes.
ROBERT DAUM: Robert Daum, yes.
AMY CELENTO: Amy Celento, yes.
RICHARD NEILL: Richard Neill, yes.
AVITAL CNAAN: Avital Cnaan, yes.
DENNIS BIER: Dennis Bier, yes.
MARY TINETTI: Mary Tinetti, yes.
RUTH PARKER: Ruth Parker, yes.
BEN CLYBURN: Ben Clyburn, yes.
RALPH D'AGOSTINO: Ralph D'Agostino, yes.
WILL SHRANK: Will Shrank, yes.
JAN HEWITT: Jan Hewitt, yes.
MARIE GRIFFIN: Marie Griffin, yes.
ROBERT TAYLOR: Robert Taylor, yes.
JESSE JOAD: Jesse Joad, yes.
PRESCOTT ATKINSON: Prescott Atkinson, yes.
MIKE COHEN: Michael Cohen, yes.

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TOM NEWMAN: Tom Newman, yes.
WILLIAM CALHOUN: Bill Calhoun, yes.
MARY TINETTI: Any nos? Any abstentions?
DARREL LYONS: For the record, it's 22

yes, zero no, zero abstain.

MARY TINETTI: So next question does have to do with the devices, is should all dosing devices, and perhaps we've already addressed this, cups, spoons, syringes, bear only the calibrations corresponding to and identified with the same unit of measure for the specifics doses described on the package labeling.

So I think we've pretty much already addressed that. Do we need to vote on that to --

RUTH PARKER: Just from the standpoint of the standardization allows for an educational campaign with really teaching to the test.

If, if what's on the test, taking your medicine correctly, then what you're able to do is by having one thing that you're trying to use and learn how to use correctly, you're more likely to

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get the answer correctly on the test.

So this thing of the subtle variabilities just to re-enforce as we now know a source of error.

MARY TINETTI: Okay, thank you, the last part of this question is comment on whether there are other formulations that will assist caregivers in providing the correct dose. Again, other than what we've already discussed, an example was given, pre-measured drugs.

Any other formulations or ideas? Dr. Cohen.

MIKE COHEN: Yeah, I'm assuming they mean, for example, a unit dose package or a unit of use package that's pre-measured, say 5 milliliters or something like that. I guess I would have somewhat of a problem with that because people might use a full dose instead of a half dose or even in a hospital situation we sometimes see medication errors where, you know, that type of mistake is made or one of the containers of two that are supposed to be administered are returned to pharmacy, for

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example, and unadministered, so I don't, I don't understand why that would be necessary.

MARY TINETTI: Any other comments? Okay. Yes.

SKIP NELSON: I guess I don't want to presume that the standardization vote necessarily answers the question about the linkage between calibrations on the dosing device and the package labeling as an interim step because what that would also -- what that would mean is that you could not, in fact, exchange a device from bottle to bottle if the unit was different.

So I, it's, it's not clear which way people could go on the answer -- on to this question, sort of C question 2.

MARY TINETTI: So you want us to vote on that? We can certainly do that.

SKIP NELSON: Well it's just not clear to me what the implications would be because if this device is only linked with that product in that package which would eliminate one of the mistakes I think it was brought out in the presentation

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yesterday about, you know, having 15 different measures on the one device, you could not in fact take it to another bottle so would people then use it anyway or would they realize they can't use it and then discard it, which would be the good action instead of the bad action.

So it's not clear how that would work out.

RUTH PARKER: I think the intent would be to look at how many different concentrations are required from a dose standpoint for the various products that were proved to be effective, okay.

And so, you know, it's kind of hard to put this out there, but let's assume that there's a suspension that's more concentrated, I don't really know without sort of looking at pieces that we don't really have right now, but let's assume you might need two different concentrations, then there would be, and I'd hope there wouldn't be five, I don't know, but I'm saying let's hope there would be two, for everything that's the more concentrated you might need a measuring device that always works with

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that one because of the units that you would need to calibrate doses on it.

If you were able to get by with one and through cognitive testing found out that one will serve the purpose of all, I think on the end of that you would probably have less errors, but you might find that you have to have two. What we don't want is 10 and what the device actually looks like for an older age, it may be a cup, for a younger age it might be a syringe. That would be developed in a clinical trial.

MARY TINETTI: Dr. Hennessy.

SEAN HENNESSY: Sean Hennessy, so question that subsection C, or the sub question under C says should all dosing devices bear only calibrations corresponding to and identified with the same unit of measure, I would say yes and that should probably be milliliters, but the second part of that says for the specified dosages described on the package labeling, for that I would say no.

So, for example, if the doses in the package are 2.5 milliliters, 5 milliliters or 10

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milliliters, I would think that it should still have increments at 3 milliliters and 4 milliliters because another medicine may require a dosage of three and four.

So this is a two-part question to which I think the first part I would vote yes and the second part I would vote no.

MARY TINETTI: All right, sounds like we have to go back and clarify that.

I guess I'm not quite sure what, what point for the specific doses described on the packaging label, I guess I'm not sure what point you're making here, Dr. Hennessy, what --

SEAN HENNESSY: So if it was, you know, an oral syringe that was graduated in milliliters, I think that's fine but I think that the second part of this question says, for the specific dosages described in the package labeling, so to me that means that if there's no 4 milliliter dose described

in the package labeling, then the oral syringe that comes with it should not be, have a mark at 4 milliliters

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MARY TINETTI: I see, okay, fair enough. That's clear, okay.

That's probably worth actually voting on to get on the, the record because it actually does tie in to what we have already voted on.

Yeah.

AMY CELENTO: Amy Celento. This goes back to my point about potentially having some sort of link to the actual product name and the device, you know, because it's not Tupperware where one lid fits everything that's square. So, you know, that's where I think you give the opportunity for consumers to not get it wrong.

MARY TINETTI: Well, again, under our recommendation that wouldn't happen because it would -- wouldn't matter what with the product formulation, but I understand presently that would be an issue.

Dr. Joad and Dr. Cohen.

JESSE JOAD: Jesse Joad. I would argue that we should standardize everything in milliliters and say no more teaspoonful or tablespoonful at all

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and that there should be a standard syringe that's 10 ml and then maybe some other standard, and everything marked so that it totally can go back and forth between products and --

MARY TINETTI: I think we already voted on that. Yes, we've already voted on that.

JESSE JOAD: But that takes care of Dr. Hennessy's concern.

MARY TINETTI: Right. Right. Right. Okay. Okay.

So I think we're probably, right, if we, if we really do take what we've already voted on, then this question becomes a moot point.

That being said, do you want us to vote on this? Okay, thank you.

I think we will, did we have anything

else. Anybody else?
JOEL SCHIFFERBAUER: Dr. Tinetti, could you discuss 2B further? I don't think we heard enough discussion or any discussion on that, the misdosing and availability of OTC.
MARY TINETTI: I think that's what

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raised the question about the, the standardization issue, but does anybody else have any other comments on the contribution of misdosing to the overall safety profile and how should this affect their availability as over-the-counter products?
I mean I think there's pretty compelling evidence that there's been a lot of misdosing, that's part of what the discussion has been so I guess it addresses the question of availability.
CHARLIE GANLEY: Yeah, let me just, yeah, let me just, it's just not a dosing device type issue, it goes back to the original petition where there are misdosing occurring and overdosing occurring with these products and because that is happening, that's not sufficient to allow them to continue marketing if we don't have sufficient efficacy, okay.
And so given that, if that's the standard and, you know, there's misdosing with prescription drugs and OTC drugs and other areas, too, that it, it's a conceptual thing is well how does that effect availability because we're

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essentially going to say that some products may not be available simply because there's misdosing.
Now if we're moving a drug from prescription to over-the-counter, we'll often do consumer behavior studies because we do care about misdosing and people need to understand the label and, you know, the consequences of getting it wrong can be problematic, but here in this situation we're trying to understand what is the relationship between the petitioner's argument and the requests regarding availability.
MARY TINETTI: Any comments?
Dr. Gorman.

RICHARD GORMAN: The presentation by industry and again echoed by Dr. Temple this morning seem to indicate that the highest chance for misdosing was when there was no dosing information available on a label, so it would seem to me that if we were going to talk about reducing misdosing, that anything that the product is marketed for should have dosing information on the label.

MARY TINETTI: Okay. Thank you.

I think, I think what I'm hearing that the FDA would like some discussion on is the fact if there is any, does misdosing and the possibility of misdosing preclude availability over the counter and your point's well taken that, that all drugs are going to have some element of misdosing, and is that a big enough issue here apart from everything else that it should preclude their availability, is that, is that your point?

CHARLIE GANLEY: Right, and also it gets back to how do you fix situations where serious events are occurring and you know there's, there's 40,000 or more deaths a year in automobile accidents and on face value that's a terrible number, but you have to actually look at well why did that occur, half the cases are because they don't wear seat belts or, you know, seat belts weren't worn in half the cases, there's alcohol involved and text messages, so it's not the question of changing the availability of automobiles, it's the changing of how do we, you know, what you do to prevent those and, you know, in Maryland now there's a, you have to wear a seat belt, otherwise you can get a ticket, okay, so there's measures that were taken to try to adjust that.

And so that, that's what it's sort of getting at here is from a, from that type of approach, you know, to me it's well how do you fix the problem rather than just identifying the problem.

MARY TINETTI: I think that's the sentiment I'm hearing around the table here, I'm not

hearing any sentiment that the misuse is sufficient, that that in and of itself should be a reason for them being off, not over the counter, but rather are there things that we can do to make the use safer I think is the sentiment that I'm getting.

And does anybody else want to speak to that or have any other sentiment? If it's the same sentiment, we don't have to repeat it but if you have anything else you want to say.

LEON DURE: Well, no, Leon Dure, I mean I guess is this, I understand your question but I mean this is perhaps not the venue because the

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problem with misdosing in the under 2 is is that for most people there is no dose, so it isn't the same thing as other types of drugs where there may be an accepted dose.

MARY TINETTI: Okay. Dr. Bier.

DENNIS BIER: Dennis Bier, you know, we've talked about a variety of things, standardizing the dosing instrument and stuff but there are all -- and we have heard about many others, I mean the things that deal with the extended labeling, you know, multiple drug products and all of these things, reducing every one of those is going to contribute to safety and I think that should be the goal here.

MARY TINETTI: And I think we'll be extensively discussing labeling and multiple ingredients and I think those will both be very big issues.

Okay, let's go back to the question of extrapolation that the FDA asked us to clarify a bit further and I think the issue there had to do with extrapolation and so we've already voted that it's

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not appropriate to extrapolate from adults to children.

I think the question now that we're asked to comment on further, is it appropriate to extrapolate within children from, we've now said from the, let's say, for instance, the 2 to 12 year old down to the 2 year old or vice versa.

I think to address that we probably need to clarify the ages again and I hate to bring that up again because it's a, there are, there really are no designations that anybody and everybody's going to agree upon, but the designation -- the ages we have now are less than 2 and 2 to less than 12, so I propose that we, we keep those and the question is is it appropriate to, I guess it's nap time, to extrapolate, let's begin, from the 2 to less than 12 year old to the -- is this, is that appropriate.

Will that help you, Dr. Ganley, is that sufficient?

CHARLIE GANLEY: I think it could be a more, a general question in that there may be, you know, if, if they come back with a study that shows

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that there's efficacy in 6 to 11, is there a situation where you would extrapolate down to 2 to 5 or vice versa? If they did a study in 2 to 5 year olds and showed that there was efficacious, are you going to automatically assume then through pharmacokinetics that 6 to 11 would be fine because you already have data on adults, okay.

So it's more to help us.

MARY TINETTI: Could you be clearer what question you'd like us to address, because I mean this could be worded in a lot of different ways and there's a lot of different age ranges, so.

CHARLIE GANLEY: Well I think a general question would be is, is the question that we had, is there ever a situation in people where you would extrapolate within the childhood population being less than 12, okay, and then if there's a yes, for them to just say this is where I think it may be, may be possible, okay.

MARY TINETTI: Could I propose that perhaps, because I think I've heard a lot of sentiment the under 2 is very different. Is it,

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would it be reasonable to say is it appropriate to extrapolate within children other than the less than 2?

CHARLIE GANLEY: That's fine.

MARY TINETTI: Would that be appropriate. Okay. Can we vote on that, then, all in favor, okay.

LEON DURE: Are we just talking about cold medicine?

MARY TINETTI: Yes, yes. Where have you been the last two days?

LEON DURE: No, no, you said is there ever a situation.

MARY TINETTI: No, no, we're only talking cold. We're only talking cold.

Yes, Dr. Cnaan.

AVITAL CNAAN: Within the context, and thank you for that comment, within the -- within the context of cold and cough related to cold, I don't see the need for extrapolation from any age group to any age group because it is the common cold and we can answer the question well and directly.

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MARY TINETTI: Dr. Calhoun.

WILLIAM CALHOUN: Bill Calhoun. So you actually asked two different questions, one was an interpolation question, actually, if you have data in 2 to 6 and data in adults, that's actually an interpolation which probably scientifically is a little more justifiable than an extrapolation, so were you --

CHARLIE GANLEY: Yeah, I, so there would be situations where you're, you know, we call it interpolation but it is an extrapolation, also. It's -- interpolation in my view still falls under extrapolation -- you know, it's a subset of extrapolation.

You may not agree with that, but I still, you're extrapolating data from one population to another. Your data may be better in that you feel more comfortable because you're covering both ends of the spectrum and whatever variable -- well in this case it's age.

MARY TINETTI: Okay. So I think the -- yes, Dr. D'Agostino.

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RALPH D'AGOSTINO: Ralph D'Agostino, but

are we saying that, is the contrast to that these companies should always in children do studies from 2 to 12, including 2 to 12? I mean what's the alternative. If we say no, then is that what we're saying they should do, they should always have 2 to 12?

CHARLIE GANLEY: Well if your answer is that there should never be extrapolation, then it's essentially saying that the population enrolled in the clinical efficacy study is 2 to 12.

If you say yes, I think in certain circumstances it could be -- well what is that circumstance.

MARY TINETTI: Okay, so the question under discussion or under vote hopefully is is it ever appropriate to extrapolate in the children over the age of 2 data I guess within -- from one group of children to another group of children?

Is that, because we've already said it was not appropriate to extrapolate from adults, so it's really within children, right? Is it ever

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appropriate to extrapolate, so --

TOM NEWMAN: For colds, for colds.

MARY TINETTI: For colds, for people over the age of 2. Okay.

So I guess the question is is it ever appropriate, those who think it is ever appropriate to extrapolate data within children for those over the age of 2 for colds.

ROBERT TAYLOR: Clarification, what kind of data, efficacy, safety?

MARY TINETTI: Efficacy, we've already decided that they need to have efficacy data.

Is anybody in favor of extrapolation within children? Okay, all in favor, raise your hand.

Okay. Dr. Calhoun, do you want to --

WILLIAM CALHOUN: Yeah, Bill Calhoun, yes.

MARY TINETTI: Mary Tinetti. Yes.

All those say no?

RUTH PARKER: Ruth Parker, yes.

LAURA MARCIA RAPPLEY: This is Marcia Rappley, I'm voting yes.
MARY TINETTI: Okay.
Nos? Dr. Newman.
TOM NEWMAN: Tom Newman, no.
MIKE COHEN: Mike Cohen, no.
PRESCOTT ATKINSON: Prescott Atkinson, no.
JESSE JOAD: Jesse Joad, no.
ROBERT TAYLOR: Robert Taylor, no.
MARIE GRIFFIN: Marie Griffin, no.
JAN HEWITT: Jan Hewitt, no.
WILL SHRANK: Will Shrank, no.
RALPH D'AGOSTINO: Ralph D'Agostino, no.
BEN CLYBURN: Ben Clyburn, no.
DENNIS BIER: Dennis Bier, no.
AVITAL CNAAN: Avital Cnaan, no.
RICHARD NEILL: Richard Neill, no.
AMY CELENTO: Amy Celento, no.
ROBERT DAUM: Robert Daum, no.
LEON DURE: Leon Dure, no.
JEFF ROSENTHAL: Jeff Rosenthal, no.
SEAN HENNESSY: Sean Hennessy, no.

MARY TINETTI: Any abstentions?
DARREL LYONS: For the record, the vote was 4 yes, 13 no and zero abstentions.
MARY TINETTI: We're missing some people.
DARREL LYONS: 4 yes, I'm sorry, 15 -- 18 no.
MARY TINETTI: Oh, you said --
DARREL LYONS: I said 18 no.
MARY TINETTI: All right. Thank you.
Could you move on?
DARREL LYONS: For the record, Darrel Lyons, for the record again, there was 4 yes, 18 no and zero abstains.
MARY TINETTI: Thank you, okay.
I believe we are finished with question 2 and we can move on to question 3, which is based on the discussions regarding efficacy and safety,

are there age groups for which ingredients should not be used right now, i.e., should they be disallowed for any particular age group, if so, which age groups and which ingredients.

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Any discussion? Dr. Hennessy.

SEAN HENNESSY: Sure, so which age groups, I would say everyone under the ages of 12, and which ingredients, I would say all the ingredients being discussed today.

MARY TINETTI: So you're saying as of today, those drugs should no longer be allowed for anyone under the age of 12.

SEAN HENNESSY: Given that there's no evidence of efficacy of the drugs and there's evidence of harm of the drugs, yes.

MARY TINETTI: Any other discussion?

RUTH PARKER: I think this was the one where I had written down to here ask what are the options, because it seemed like under this you referred to this as being a question where there was going back to a rule-making or are there other options and I'm just trying to understand what --

CHARLIE GANLEY: Well I think this gets back to one of the requests from the petitioner to make some immediate statement as to, you know, to the public regarding that and so I think that's what

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it's trying to capture, you know, whether we can do some -- you know, what you recommend under an administrative procedure is a different issue, I can't answer that today. You may all vote that they should go away today, but under administrative procedures that may not be sufficient.

And so, but it, it may be that you say, well, for two years and less we just don't think that anyone should be recommending the use of these, yet but from 2 to 12, you know, we are, you know, going to have to, you know, because of either the benefit/risk assessment for those, you know, various children older than 2, that it's sort of nebulous whether it's, you know, going to cause, it's an imminent hazard type of thing where, you know, we

just, these are just so bad we need to take them off the market.

It's interesting where, you know, where everyone acknowledges that these events are really rare, a lot of it's related to misdosing and that, but they need to have some statement or some, something from the FDA that we have to immediately

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do something right now.

And again, it's just to give us a sense, I don't know from the Administrative Procedures Act whether we, what we can do and how fast we can do things, but I would like to get a sense from the Committee of what they think because you know the possibilities is if you say these shouldn't be available tomorrow and there's a way that we can do it and we decide that that's a reasonable way to go, you're not going to have any, potentially, cough, cold allergy products for children recommended under 12 years of age and you have to know that's what the consequences is.

And, you know, the question also here is there's been a lot of extrapolation carried on on the OTC products and also on some of the prescription products because, for example, Pseudoephedrine, you know, has not been studied in children, whether it's prescription product or not, there is a determination that we already know what Pseudoephedrine doses is in youngsters and it was based on extrapolation, so this will have a greater

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impact on prescription drugs and OTC drugs. So you need to understand the consequence of your vote here.

MARY TINETTI: Dr. Daum.

ROBERT DAUM: So, unless I misremembered something I heard this morning, this is Robert Daum from the University of Chicago, I think we said this morning that we don't believe there is demonstrated efficacy for these drugs and I hope we all are talking about these drugs correctly, it might be useful to look at the list at some point during this discussion, under 12 years of age and if that's

true, then it seems to me it would be internally consistent -- inconsistent, internally inconsistent, we shouldn't do it to use these drugs any longer in children under 12. If there is no demonstrated efficacy, why would we say we should use them.

MARY TINETTI: Well I think the point is there's a couple of different things is usually when immediate action happens it's because of more concern about harm than lack of efficacy, if I'm paraphrasing, number one, and number two is the

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discussion was, was not 100 percent that they were, that we had evidence that they weren't effective, is that we lacked the evidence of the effectiveness which is why we're recommending clinical trials.

The question is is while these trials are taking place, should they be available or should they not be available and for different age groups I think is the practical issue at hand.

ROBERT DAUM: So if I could respond to that, the question is worded, it says based on the discussions regarding efficacy, and the discussions I've heard regarding efficacy is that there's none demonstrated and if that is true, then I can't support using these agents --

MARY TINETTI: Lack of evidence of efficacy is not evidence of lack of efficacy.

ROBERT DAUM: I understand that, but I think that someone pointed out on the other side of the table this morning, people sitting around who have a scientific background and scientific integrity and you have to demonstrate the efficacy.

MARY TINETTI: Fair enough, so I think

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as we do the vote, I think we'll be talking about the ingredients and the age groups and that could certainly be, be a basis for that.

ROBERT DAUM: Could you clarify before you move on, I'm sorry, what, what the words these ingredients means.

MARY TINETTI: I think we're referring to the ingredients that we're working, we're addressing, which are the decongestants, the first

generation antihistamines, the, and the antitussives, is that -- and the expectorants are the four classes.

RUTH PARKER: The other concern I have is the same point that comes up, this is for use of cough and cold symptoms associated with the common cold, so you get back to the consumer and their self-selection about the, you know, what they're choosing the drugs for and we did not look at the data or talk about the implications of this for lack of access, for allergic rhinitis in that same age group.

So, you know, when I hear, you know, not

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available for 12 and under for cough and cold, I'm assuming that's for cough and cold, that someone's self-diagnosis is related to the common cold as it's described to them as they approach a shelf, I'm just trying to --

MARY TINETTI: Well I mean practically speaking it would be hard to have them on the market for one and not the other. I mean I think when we vote, that's a consequence we need to sort of think about.

CHARLIE GANLEY: And I think Darrel has some slides that shows you what specific uses or indications are for each category if you want to just pull those slides up, Darrel.

MARY TINETTI: So essentially we would be discussing the, these, these particular drugs for these particular indications.

CHARLIE GANLEY: Yeah, I think to try to get some clarity is, you know, again, this is the burden that we're going to have to share internally because a lot of these other claims were extrapolated, but for an antihistamine, for example,

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the first one really just refers to allergy. The second claim refers to a common cold, okay.

If we can go, is there a slide before this? Okay, the antitussive, you see there's a temporary reduces cough due to minor throat and bronchial irritation associated with a cold, there's

a cold claim. The next one or that also has a cold claim but you see it may also state cough suppressant which temporary reduces the impulses to cough. Temporary helps to cough less and things like that.

So if you're just talking about claims related to a common cold, the first two ones would, you know, disappear but can they still make all the others and do you have the next slide.

Expectorant really doesn't have anything associated with a cold, so the question is well should that exist even since it's extrapolation, but again that, there's no cold claim there.

And is there a decongestant, and there, as you see the, there's a claim for, you can write it as temporarily relieves nasal congestion due to a

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cold and hayfever and other respiratory allergins or you could kick out cold. Okay.

You see, we, we need to get some clarity what you're talking about and also what age groups, if people are just saying we just don't want it marketed for colds and things like that, but we're okay with the hayfever and upper respiratory allergies and things.

MARY TINETTI: Well we haven't, we have not addressed hayfever or allergies and so I propose that we, that we focus our discussion today on the cold.

Let's see, Celento I think was, Amy Celento I think was next.

AMY CELENTO: Hi, Amy Celento, I think it's a little bit hard to answer this question without looking at the labeling question next, but I do not believe that these products should be removed for under 12.

I do not administer these products to my child, but there are many, many adults who will and they will administer adult products to their

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children because they know they work for them or they feel they work for them and I have some significant concerns about the fact that they're

completely gone and people have no alternative and practitioners have no other options but to say stay hydrated, use saline, sleep.

MARY TINETTI: Unintended consequences, that's a good point.

AMY CELENTO: Absolutely.

MARY TINETTI: Other. Dr. Rappley.

LAURA MARCIA RAPPLEY: I think that's a very good point and it hasn't been raised in the last two days but I think it's worth thinking about.

I also want to suggest that maybe we should first take a vote on age less than 2, because I felt that there was more agreement and consensus and then we could move, we could at least have that piece done and move on to the discussion of 2 to the less than 12.

MARY TINETTI: That's actually a good proposal, so unless anybody had any discussion that's not relevant to that, maybe that will help

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focus our discussion. Is that, okay.

So the proposal here then is based on discussions regarding efficacy and safety, should the, should these ingredients, and here I think we're talking about again the antihistamines, the decongestants, I guess actually not the expectorants if we're limiting it to cold and the antitussives, should they not be used right now in people -- in people under the age of 2.

Those in favor of, of that, raise your hand.

LAURA MARCIA RAPPLEY: This is Dr. Rappley and I vote yes, they should not be used in the age of less than 2.

MARY TINETTI: Thank you. Okay.

Dr. Newman, do you want to start?

TOM NEWMAN: Tom Newman, yes.

MIKE COHEN: Mike Cohen, yes.

PRESCOTT ATKINSON: Prescott Atkinson, yes.

JESSE JOAD: Jesse Joad, yes.

ROBERT TAYLOR: Robert Taylor, yes.

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MARIE GRIFFIN: Marie Griffin, yes.
JAN HEWITT: Jan Hewitt, yes.
WILL SHRANK: Will Shrank, yes.
RALPH D'AGOSTINO: Ralph D'Agostino, yes.
BEN CLYBURN: Ben Clyburn, yes.
RUTH PARKER: Ruth Parker, yes.
MARY TINETTI: Mary Tinetti, yes.
DENNIS BIER: Dennis Bier, yes.
AVITAL CNAAN: Avital Cnaan, yes.
RICHARD NEILL: Richard Neill, yes.
AMY CELENTO: Amy Celento, yes.
ROBERT DAUM: Robert Daum, yes.
LEON DURE: Leon Dure, yes.
JEFF ROSENTHAL: Jeff Rosenthal, yes.
SEAN HENNESSY: Sean Hennessy, yes.
MARY TINETTI: Any nos? Any abstentions -- oh, no.
WILLIAM CALHOUN: Calhoun, no for exactly the reason that Ms. Celento mentioned, the alternative indications.
MARY TINETTI: Thank you.

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Any abstentions?
DARREL LYONS: For the record, 21 yes, 1 no and zero abstentions.
MARY TINETTI: Thank you. That was helpful.
So now the discussion is for cold indications for children between 2 and less than 12. Let's see, we can go back to some of the people who had some discussion, questions before. Dr. Neill I think was next.
RICHARD NEILL: This is the first meeting that I've been at where we've been asked to consider the efficacy of eight separate chemical entities and given so little data because so little exists in published form regarding the individual entities as opposed to combinations, however FDA staff, you guys did a very nice job putting together a summary and having gone through that, looking at Brompheniramine, Chlorpheniramine, Diphenhydromine, Doxylamine, Phenylephrine, Pseudoephedrine,

Dextromethorphan and Guiffasen, amongst all of those the only that I, only entity that I could even come

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close to making a case for would be Pseudoephedrine based on the '94 study by Gallardo which demonstrated an effect, although the data that I reviewed didn't allow me to see whether that effect was uniform across the ages from 2 to 12.

It's also I think worth considering that Sudafed has a different status now than it did when the study was done and that that study included Pseudoephedrine in combination with Naprosin and the clinical end points that were measured did include end points that may have combined fever reduction and pain with things like decongestant effect.

And so that's really as close as I can get from any of these individually.

Having said that, the question that you asked earlier, Dr. Ganley, which I heard as do you really want to be responsible for the outcry that will arise when these things become unavailable in my mind has to be balanced with the outcry that we haven't heard for 30 years, which is why aren't people complaining that they're spending money for things that don't work.

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And that I think is a reasonable question and I think we've, we've asked it and it's been answered a little bit, it's because these things are marketed and they're marketed very well and when that question gets asked and answered, gosh, it doesn't work, then the ingredients change but the name stays the same. And while I think it's rational for any parent to want relief for a child with these kind of symptoms, you know, my response to Amy, your question, would be consider one of the other potentially safer, equally effective or ineffective fill in the blank here entities that are available over the counter, whether that be Vitamin C in the form of orange juice or I could imagine many others.

And so it's a real question, I don't want to, a Committee 30 years from now to be

laboring about public relations, in effect, when I think our job ought to be more focused on the science of the issue and the science is pretty clear.

MARY TINETTI: Dr. Nelson was next. Did

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you still have --

SKIP NELSON: Well I was just going to point out that if, that the safety profile needs, is part of this question, the overall risk/benefit and if that is felt to rise to the level where withdrawal would be an appropriate action, I'm curious as to why then there wasn't much discussion about the misdosing leading to it being taken off over-the-counter status because much of the safety issues are related to misdosing.

MARY TINETTI: Okay, thank you.

Dr. D'Agostino, did you still have a question?

RALPH D'AGOSTINO: Yeah, I think the, from 2 to 12 they should stay on the market. I think the, what we've, there is a safety issue but I, I come down to, I'm going to keep writing it down, overdose, chronic prolonged medication, deliberate misuse, accidental interactions.

I think that we, we do have to be very concerned about the safety issue. Hopefully this, this press that this meeting will get will raise

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awareness of that, if it hasn't already done so, and I do think that the, it's time to forget this pk to the young, put clinical trials together, we've said all of that, so I think in sort of the spirit of what we've done with OTC products that have been on for many years in the past is that we make a, make ourselves aware of the safety issues and put out a meaningful agenda that can get to the efficacy and also more safety issues and resolve them and while that's happening, I think we should be keeping these products on the market.

MARY TINETTI: Thank you. Dr. Newman.

TOM NEWMAN: Just a question for clarification from the FDA staff and my question is

is what is the alternative to should not be used right now, because I think the regulation states that they can be marketed if they're generally recognized as safe and effective. We've established that they're not generally recognized as safe and effective and so the question is if we don't vote yes on this, is there some time line during which if they get re-classified as category 3, what is the

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time line by which the sponsors would need to produce evidence of safety and efficacy?

CHARLIE GANLEY: Well the regulation process is a long and arduous process, but I think that doesn't prevent us having a meeting with industry and say, look, you need to go down this path because this is where we're heading and, you know, develop a sense of urgency for them.

And again, the, you know, the, your recommendation is something that we'll take into consideration and even if we wrote a proposed rule that, you know, to, to take some action, that's how, that's the process here. The Administrative Procedures Act allowed Dr. Sharfstein to submit his petition and challenge this, just as if we come out with a proposed rule, it allows other people to challenge our decision and, you know, if we agree with your decision, you know, your comments, so.

But again, I think there's mechanisms where, you know, there can be interactions that say this is where we're going to be heading, you know, through feedback meetings and things like that and

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they should have a sense of urgency and understanding that they need to collect some information.

TOM NEWMAN: But you're not able to give any kind of a time line about when it would be or how long it would be able to continue to --

CHARLIE GANLEY: Well, you're welcome to say we want it done within so many, within two or three years we want to see something back.

TOM NEWMAN: Well, what, we as an Advisory Committee?

CHARLIE GANLEY: As an Advisory Committee. We can't -- we may not be able to do it from a regulatory point of view other than to get the rule-making process moved a little quicker, okay, but it, if you think that's important, then say we want to allow these to continue marketing but within three years we want this, this, this or we want the things done.

RALPH D'AGOSTINO: Charlie, what I was just saying is I would be very happy to put a motion up that, in following what I was saying that we give

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the three-year time limit, that -- I was trying to say what you're saying, that there is an urgency and to put a time on it I think is very appropriate.

CHARLIE GANLEY: And we're talking about the 2 to 12 year age, is that --

RALPH D'AGOSTINO: The 2 to 12, yes.

CHARLIE GANLEY: All right.

MARY TINETTI: Okay. Perhaps just a few more questions, I think Dr. Daum was next.

ROBERT DAUM: So, the question as I understand it was not about pulling things on and off the market because I'm not sure we have that jurisdiction or capability, it was a question about should they be used right now. And I'm mindful of one of the advertisements we were shown yesterday with the cute little infants on top and checkmarks as to which symptoms you have or don't have, your baby, and therefore which ingredient you should or should not be using.

The American Academy of Pediatrics, the National Association of Nurse Practitioners and as I understand what we just voted on a few minutes ago,

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this FDA Advisory Committee have all said that there's no benefit, no evidence of efficacy in these children for these products, so I don't know how we could possibly vote no on this question and be internally consistent and I, I'm just thinking --

MARY TINETTI: Doctor, you've made that point, thank you.

ROBERT DAUM: Well I'm emphasizing it.

MARY TINETTI: Thank you.
Is there any new points? We really do need to move along so I really ask you to confine your, to telling points that you think are new and relevant at this point.
DENNIS BIER: I'm not sure it's entirely new but it's addressing your issue as to how you could vote no. If these products were not on the market, I think the absence of any demonstrated efficacy would keep us from putting them on the market. Because they've been on the market for 40, 50 years --
(Please pardon the interruption, your conference contains less than three participants at this time, if you would like to continue press star 1 now.)
DENNIS BIER: Because there have been millions of person years of use and the absolute, you know, safety risk has to be very low, I believe it's very low.
What I'm, my, my, you know, my position here is we haven't demonstrated one way or the other whether or not they are efficacious and we should have the opportunity to do that, so I think that allowing a period of time to get those data with a real, with a, you know, a hard end point is what I would be interested in seeing.
MARY TINETTI: Dr. Calhoun was next.
WILLIAM CALHOUN: Thank you, Bill Calhoun. So the question is that I, we understand I think collectively that there has not been efficacy demonstrated for cough and cold.
The question really has to do with other indications for using these agents, in particular atopic disease, rhinitis and congestive rhinopathies, so is the implication of voting yes here that they would be removed for all indications or would products that are specifically marketed for allergy, even though they contain the same molecules, still be permitted?
CHARLIE GANLEY: Well that's not the

easiest question to answer because, for example, with cough, as you saw, there would be multiple, there's multiple claims in there aside from the common cold. The data to support those claims is pretty much the same, it's carried forward and so the, you know, again, we would have to propose a rule that lays out specific new types of claims where we're saying certain claims are not acceptable and others may be, okay.

WILLIAM CALHOUN: See, I would be concerned about removing these products from the market when there are legitimate reasons for using nasal decongestants and antihistamines for the treatment of atopic diseases.

CHARLIE GANLEY: Again, it's, it's hard to say how this is going to work itself out in that situation and so we, we do have to get some sense

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of, you know, what the position of the Committee is and again it goes back to what the petitioner has asked us to do. They want some immediate action, okay, and the administrative procedures don't necessarily allow me to make, take an immediate action unless there's, you know, compelling safety that, you know, we can't have this, these products available, okay, so, again, it's just not an easy question to answer in that regard and this question was generated a lot in what the petitioner had asked us to do.

Now again, the, whether things should be, you know, there, you know, the prominence of the marketing and things like that which we don't control, that's something that industry's going to have to decide. I think they've heard a little bit about, you know, the advertising of that, of these products and presenting fair balance in that and so, but -- I can't explain it any better than that. I wish I could. It's --

MARY TINETTI: I think the answer is we're not sure what will happen based on our vote.

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CHARLIE GANLEY: Right, again, and again, yours is a recommendation, okay. There was

another panel that recommended these were fine, so right now they're, you know, in the regulatory history they're considered safe and effective and there's a process we have to go through to change that. And that --

MARY TINETTI: Thank you, I think we'll move on, just do perhaps a couple more.

Dr. Atkinson was next.

PRESCOTT ATKINSON: Yeah, I just wanted to point out that even though the Dr. Levy and the petitioners, you know, have, have called for a withdrawal of these products for use in patients under 6 years of age, if you look at the American Academy of Pediatrics, the Academic Association of Pediatricians, they sort of fall short of actually calling for that drastic a measure and if, I think data was presented yesterday to show that the majority of pediatricians use these drugs and at least in older children for cough and cold remedies and my experience, and I've done a lot of outpatient

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pediatrics, is that a lot of, a lot of doctors use these, the majority of the pediatricians that I know and they're going to be left with really very little recourse when patients come to them.

Many patients don't come with an acute upper respiratory infection, they come with a chronic litany of upper respiratory symptoms that are mixed in with allergy and recurrent viral infections from day care and so forth.

MARY TINETTI: Thank you. Again, just if there's just really any, did you get, Amy, get your additional point?

AMY CELENTO: No, thank you, Amy Celento.

I think what we've acknowledged over the past day and a half is that parents are using these medications to relieve what they consider symptoms which in reality in some cases means their child is sedated and they're able to sleep. They may not care that they're not coughing more, even though that they're coughing less, they know that they can sleep and my concern is that by taking these

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medications off the market, parents have limited alternatives and I will say that I'm not going to name names among my friends, but people do use these medications to induce sleep when their children are sick and I think that if we just completely ignore the fact that that happens and that they will find another way to be able to get their kids to sleep and for them to get sleep, we're doing a real disservice to consumers.

MARY TINETTI: Thank you, that's a good point.

Dr. Joad was next.

No, okay. Dr. Hennessy, did you still have your point?

SEAN HENNESSY: Sure, and I'll be brief, so the products were already taken off the market for children under 2 and the world did not come to a screeching halt. The drugs have been marketed for decades with little effort to demonstrate efficacy, they're used for a mild, a self-limited illness.

I think this Committee saying that the drugs should not be used unless and until evidence

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of efficacy is presented will provide the incentive needed to develop those data and that in giving the manufacturers a bye, allowing them to, or us saying that they should still be used in the absence of such efficacy data knowing that they cause risks would be irresponsible.

MARY TINETTI: Okay, thank you.

Dr. Nelson, did you still have your point? Dr. Griffin.

MARIE GRIFFIN: Yeah, I want to know what would happen at the end of three years because I don't think we're going to, we didn't recommend testing combination products, so I'm wondering if --

MARY TINETTI: We'll be getting to that actually, if, maybe sometime on Thursday.

MARIE GRIFFIN: But if we could separate the combinations from the single, you know, if we're talking about removing things from the market, there may be a way to separate out --

MARY TINETTI: Did you want to make a specific proposal?

MARIE GRIFFIN: Well I don't see that

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anybody suggested testing combination products and so if we're not going to test them, then I don't see why we want to keep them on the market, so I -- we did.

So I, I think we could separately consider whether we think that combinations should not be available.

MARY TINETTI: Okay. I'm going to try to -- very brief, very brief.

JOHN JENKINS: Well that is question 5A. But I think it would help to have some clarification from, but I think the way we handle combinations, someone I think put it up there yesterday, we expect each ingredient in the combination to contribute to the effect, so we've had a long history of saying if you've got an antihistamine that you want to combine with a decongestant, you don't have to study that specific combination if, in fact, you're confident that the antihistamine addresses, say, runny nose and the decongestant addresses nasal congestion. We've allowed for those combinations.

We often require pharmacokinetic data to

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make sure there's no drug, drug interactions, but we don't normally ask people to study combinations, per se, because in this class of drugs they're targeting different symptoms and if we're confident that the individual ingredients affect those different symptoms, we've allowed rational combination.

So, we're not really talking about studying every possible combination, that's an impossible task. You really, the approach we take is to establish the efficacy and safety of the individual ingredients and then decide if it's rational to combine them and whether we need any further studies to show that they contribute to the effect claimed, but for this group of drugs, we have, on the prescription end and nonprescription side have a long history of allowing these

combinations without additional efficacy studies if they're targeting different symptoms.

MARY TINETTI: Thank you and we'll be discussing that more coming up, so I'm going to try and we'll probably have to work a little bit on the wording of the question now, I think what we're

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saying is now for children 2 to less than 12, for the ingredients for the common cold, I guess -- should, I guess there's really two proposals, should we not allow them as of now or should we allow them for three years giving the, giving time for studies for efficacy.

So I think if that's all right, we'll propose that people could vote for one or the other of those two. Is that --

JOHN JENKINS: Well if I could just make one more comment about this issue, I think throughout the discussion in the last couple days there's been questions about extrapolation of efficacy, there's also the questions about benefit/risk and whether it's an acceptable benefit/risk balance.

So for those people around the table who are asking for new studies to demonstrate efficacy in these pediatric populations, I think we also need to understand if the studies are done and they show the same level of efficacy that we've seen in adults, which we've all agreed going around the

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table is not dramatic, it's small, but it's been demonstrated in adults, does that present you with a favorable risk/benefit profile? People have been commenting as if that will magically change your thinking that if they show the same effect in children that we think they have in adults, that suddenly changes the risk/benefit profile to being favorable.

Is that a correct assumption or is that not a correct assumption?

MARY TINETTI: My guess is that people have come on differently in terms of the safety versus effectiveness and I think we've had a robust

discussion, my guess is there's not, people are going to look around the table and look upon that differently, but I think we'll address the question as, that's dealing with efficacy and dealing with safety.

We may come down differently upon that, but I think we have to, I would suggest that we just vote with the question as it's worded. I think we've already addressed the need for efficacy

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studies and we recognize the data that are available in adults and recognize that those were a sufficient standard to warrant their availability and I think beyond that I'm not sure we can say anything more specific than that.

Dr. Daum has a quick comment.

ROBERT DAUM: When you formulated the wording right now, and I know it's hard to do wording on your feet, so to speak, you said that the use of these ingredients should not be allowed and the language --

MARY TINETTI: Should not be used, should not be used.

ROBERT DAUM: Yeah, should not be used is better. That we recommend that they should not be used.

MARY TINETTI: Okay, maybe that's a little bit better.

We recommend that for children between 2 and less than 12, these ingredients should not be used right now. Would anyone be in favor of that? Do you have --

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JEFF ROSENTHAL: I was just going to ask a clarifying point.

MARY TINETTI: Go ahead.

JEFF ROSENTHAL: The safety data that was presented actually showed some, or suggested some differences in the younger half of that spectrum, so I wonder whether this question of 2 to 6 versus 6 to 12 is relevant in regard to this question.

MARY TINETTI: Are you proposing that

we, that we make it 2 to 6 and ask separately for the 2 to 6 and --

JEFF ROSENTHAL: Yeah, I'd be interested in that.

MARY TINETTI: Okay, okay.

So the question now is should we recommend that children between 2 and less than 6 not use these ingredients right now.

All in favor of that? Okay. Yeses, starting with Dr. Newman.

TOM NEWMAN: Tom Newman, yes.

JESSE JOAD: Jesse Joad, yes.

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MARIE GRIFFIN: Marie Griffin, yes.

JAN HEWITT: Jan Hewitt, yes.

WILL SHRANK: Will Shrank, yes.

BEN CLYBURN: Ben Clyburn, yes.

AVITAL CNAAN: Avital Cnaan, yes.

RICHARD NEILL: Richard Neill. Yes.

ROBERT DAUM: Robert Daum, yes.

LEON DURE: Leon Dure, yes.

JEFF ROSENTHAL: Jeff Rosenthal, yes.

SEAN HENNESSY: Sean Hennessy, yes.

MARY TINETTI: Dr. Rappley, did you want to vote?

LAURA MARCIA RAPPLEY: Yes, Marcia Rappley, yes.

MARY TINETTI: Okay. The nos, raise your hand. Okay, Dr. Calhoun, do you want to start.

WILLIAM CALHOUN: Because I'm not impressed of the safety data comprising an urgent public health hazard and because of the need for alternative indication for these drugs, I vote no.

MIKE COHEN: Mike Cohen, I vote no.

PRESCOTT ATKINSON: Prescott Atkinson,

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no.

ROBERT TAYLOR: Robert Taylor, no.

RALPH D'AGOSTINO: Ralph D'Agostino, no.

RUTH PARKER: Ruth Parker, no.

MARY TINETTI: Mary Tinetti, no.

DENNIS BIER: Dennis Bier, no.

AMY CELENTO: Amy Celento, no.

MARY TINETTI: Okay. Any abstentions? Okay.

So to reiterate, the question is should, should we recommend that these ingredients not be used for the common cold right now for children between the ages of 2 and less than 6.

DARREL LYONS: We have 13 yes and 9 no, zero abstentions.

MARY TINETTI: Thank you.

And so now the vote will be should we recommend that these ingredients not be used for the common cold right now for children between 6 and less than 12. All those say yes, raise your hand.

Okay, starting with Dr. Newman.

TOM NEWMAN: Tom Newman, yes.

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JESSE JOAD: Jesse Joad, yes.

BEN CLYBURN: Ben Clyburn, yes.

RICHARD NEILL: Richard Neill, yes.

ROBERT DAUM: Robert Daum, yes.

LEON DURE: Leon Dure, yes.

SEAN HENNESSY: Sean Hennessy, yes.

MARY TINETTI: Dr. Rappley, did you want to vote?

LAURA MARCIA RAPPLEY: I'm voting no, Marcia Rappley, no.

MARY TINETTI: Okay, Dr. Rappley, okay. All nos. Okay, starting with Dr. Calhoun.

WILLIAM CALHOUN: For the same reasons, Calhoun, no.

MIKE COHEN: Mike Cohen, no.

PRESCOTT ATKINSON: Prescott Atkinson, no.

ROBERT TAYLOR: Robert Taylor, no.

MARIE GRIFFIN: Marie Griffin, no.

JAN HEWITT: Jan Hewitt, no.

WILL SHRANK: Will Shrank, no.

RALPH D'AGOSTINO: Ralph D'Agostino, no.

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RUTH PARKER: Ruth Parker, no.

MARY TINETTI: Mary Tinetti, no.

DENNIS BIER: Dennis Bier, no.

AVITAL CNAAN: Avital Cnaan, no.

AMY CELENTO: Amy Celento, no.
JEFF ROSENTHAL: Jeff Rosenthal, no.
MARY TINETTI: Okay, any abstentions? Okay.
So the question is should we recommend that these agents should not be used for the common cold right now for children between 6 and less than 12. The vote --
DARREL LYONS: The vote was, the vote is 7 yes, 15 no, zero abstentions.
MARY TINETTI: Okay, thank you.
Move on to the labeling question and what's proposed to us is currently the directions for some of the over-the-counter cold and cough products such as a decongestants and antitussives instruct a parent to, quote, consult a doctor for children under 2 years of age. The directions for antihistamines instruct a parent to consult a doctor

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for children under 6 years of age. There's also professional labeling available for antihistamines for children between the ages of 2 to 6.
The consult a doctor or ask a doctor directions have permitted physicians to make clinical judgments about whether an OTC product was right for a child under their care. The labeling proposed in the petition would potentially limit the ability of physicians to prescribe over-the-counter cough and cold products in children less than 6 and may also impact the labeling for children less than 12 years of age.
If there are groups that should not use these products, discuss the language that should be used to convey this and to say what the petitioner has recommended and we could certainly begin by if we accept that wording, then our job is done, but if not, we'll need to talk further, these products have not been found to be safe and effective for children under 6 and we can discuss what age, under 6 years of age for treatment of cough and cold. These products should not be used for treatment of cold

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and cough in children under 6 years of age and we're

asked to agree with this, with this wording.
Any discussion? Dr. Ganley.
CHARLIE GANLEY: Yeah, if I could just have Dr. Parker and Dr. Shrank be put on the spot here of what they think how complicated this language is and how consumers are going to understand it, so I'd be interested in your comments on it since you've done a lot of work on the prescription side, understanding prescription labels, so.
WILL SHRANK: Yeah, it's too complicated. I think that certainly there's a way to simplify this message and make it easier to read and understand.
Also I'm not sure that we'd all feel comfortable saying it's not been found to be safe, maybe we should say it may not be safe. I don't know that -- the safety data I guess is an issue that we don't all feel entirely comfortable with, but certainly I think this message would need to be re-structured so that it's, I would imagine, I don't

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have a lexile with me, but I'm sure that this is a much higher reading level than we would want to have as a critical warning on an over-the-counter medication.
RUTH PARKER: I think I know a couple people who would know what it means, that would be my bottom line.
And if, if what it means is do not take this if you are 6 years old or younger, it's got to be really clear, it's got to be said one way, only one way and the language of that would need to be tested officially to find out with people who are going to be using it, like you do in a label comprehension, what language works and then that's got to be it on all of them across the board.
Also you would want to know if there is a standard warning or icon that draws attention to it that people see and they see it and I'm going to tell you, people will not stop at stop signs if there are 20 different looking stop signs out there -- or stop lights. We need one and it's a

great opportunity if there's one message to say it
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and it's got to be developed with people, it actually has to be tested.

We have good, we have good data now on peoples ability to re-decode and use warning labels and it's not good and so if this is an important message, we need to treat it like it's important and we're going to figure out the best way to say it.

And in its current format, it's not very useful.

MARY TINETTI: So are you saying, I hear from both of you that this wording is not appropriate but it is probably not something that we can sit around the table today and come up with the correct wording, so we'd be proposing that the wording --

WILL SHRANK: I think it's plausible to say that we do or do not agree with the message, but I think we probably really want to develop and test and --

MARY TINETTI: Okay, fair enough.

Any other discussion?

RUTH PARKER: The only other thought I
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have is as you test it with consumers, patients who would be taking it, you need to also query and ask them how they feel about their doctor who asked them to go take it when it says right there on the label not to. If you're asking people to take the label, read it and use it and you've got practitioners who are recommending it, so this actually needs to be thought out, well done so that you get useful information on the other side of it.

MARY TINETTI: So with that discussion, I guess the question to the FDA is it sufficient for us just to yea, nay to this particular wording? Or do you want, or should we, should we actually propose what's being recommended here that attention be paid to the wording because it sounds like we're in support of the sentiment but not the wording.

CHARLIE GANLEY: Well I guess the, the, I think I understand with Will's one exception where

he's a little uncomfortable with it, it's not safe, it may not be safe and there's a lot of nuances and, you know, there's a lot of different things about labeling here. And I think Ruth is essentially

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saying is that I don't what to tell you what to do, but I'd like you to test something and that's what we're going to put on the label with these concepts and that may help eliminate some of the yes and nos for the subsequent questions.

Because these are three things in a row here and if there's a consensus on that where we, you know, it has to be, you know, clear, it has to convey a direct message, we have to understand what it's going to mean, if a health provider is going to recommend that they go use this product in things and if there's a consensus on that that's helpful, and I'm not sure we need to vote on everything else.

MARY TINETTI: Do you want to propose something for us then, Dr. Parker?

RUTH PARKER: Well we spoke about standardized devices, dosing devices, we spoke about standardizing dosing earlier and I think here we could talk about standardized warning and the language of warning and perhaps this would have to be developed alongside the language of the warning, a symbol that is universally used to draw attention

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to it, there again, in something like a label comprehension that would then become a roadmap for how we do this on over-the-counter products in a standardized way, important message, draw attention to it, work with the people who are going to be taking it and then eventually use this in your educational campaign, be you a manufacturer, be you an educator, be you a practitioner to help patients understand, consumers, how to find the information that they need to safely and effectively take their medications.

CHARLIE GANLEY: And I would also be presumptious to think that a lot of you don't like the consult a doctor or ask a doctor language; is that, would that be an incorrect --

MARY TINETTI: I think that would be a correct assumption.

Dr. Neill.

RICHARD NEILL: Richard Neill. I am absolutely in sympathy with the comments that Dr. Parker just made, but want to remind the group and I'd be anxious to hear if I'm wrong about this,

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that the ability of the FDA to influence the language label for the consumer space is limited and so a universal stop or a universal sign I think is a phenomenal direction to go in, but I'm, I'm not confident that any recommendation that we make could be applicable to the consumer space given that it's, you know, kind of wide open wild west out there outside of the monograph and NDA process.

CHARLIE GANLEY: Again, we can write regulations as to what's required in drug facts or on a principal display panel. So if, if the symbol is something that goes on a principal display panel, we do have the authority to write a regulation that proposes that be on it.

RICHARD NEILL: For herbals and supplements and homeopathic as well?

CHARLIE GANLEY: Well we're not talking about homeopathic, no, no, we're talking about OTC drug products now.

RICHARD NEILL: I understand, I'm talking about the consumer space, that's all.

CHARLIE GANLEY: Well are you talking

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about on drug products or on dietary supplements?

RICHARD NEILL: In the consumer space I would defy you to take 10 consumers and ask them what is what and which one is regulated by whom. In fact, we could take the 22 of us and we wouldn't be able to tell.

CHARLIE GANLEY: Well you should write your Congressman, I think.

RICHARD NEILL: Noted.

MARY TINETTI: All right, so getting back to what we can do today, so, so hearing our general sentiments, do you need us to vote on

anything or have you got enough guidance from us?
CHARLIE GANLEY: I think it's a consensus that it's a little too much, we need to come with something that's really straightforward, gets the message across, they understand what that means with regard to whether a physician tells them to take it or not and that they're going to not, you know, I think we get the gestalt and if everyone's in agreement that that's the best way, we can eliminate the rest of the --

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MARY TINETTI: Fair enough. Is there anyone else that disagrees with that?
Dr. Atkinson.
PRESCOTT ATKINSON: I just want to point out that putting the word should not in there has medical, legal implications for the prescribing habits of tens of thousands of pediatricians and I think that the data, you know, that's been gone over in the last couple days are unclear and everybody agrees that more studies need to be done, but this does seem like a little bit of a strong measures considering the lack of, lack of --
MARY TINETTI: So that should get incorporated into the wording is addressing that medical, legal issue of the actual wording, because I think we're saying that this is not the wording we necessarily want to support, the sentiments are appropriate and I think that's another good point that needs to get incorporated.
RUTH PARKER: I would just state that, you know, this progress in standardizing a warning and presenting it in a uniform way is building on

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the progress that FDA made with drug facts on the label and, you know, I think a piece of continuing to take the good work that was done in the standardization of that format and building on it to improve the consumer's ability to self-select for an over-the-counter product.
MARY TINETTI: Okay. Thank you.
I think we can move on and I think actually some of these we have resolved, but part B

of that is reminder that efficacy has been extrapolated for children less than 12 years of age, should FDA consider similar labeling as suggested by the petitioner for children less than 6 years of age. I believe we've already answered that question.

The next is, again, I think we've already answered number C, letter C, you decide that the use of some products in children less than 2 years is not prohibited, please discuss how these products for children less than 2 should be labeled. And again, we have I think voted pretty unanimously against that, so I think that's probably not

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something we need to address further.

D, please discuss additional information that should be on the principal display panel to better inform consumers about the product. Some discussion on the principal -- does everybody know what the principal display panel is?

Okay. Dr. Ganley, do you want to clarify for all of us what the principal display panel is.

CHARLIE GANLEY: Well the principal -- Mike Cohen can probably do it better than I. Yeah, that's the principal display panel, he has an example, it's the front panel that you usually see sitting on the shelf.

TOM NEWNAM: The front or the back?

CHARLIE GANLEY: It's the front. Right, I think some of the discussion yesterday involved you going to a medicine counter and your seeing, your seeing the principal display panel and the amount of information is overwhelming on that and they, the way that the products are selected, it's putting the symptoms on and, you know, not

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necessarily the active ingredient, so if, if you, you know, for example, the active ingredient is not required on the principal display panel for a combination product and your advice may be that it should be on there and that's what we're talking about here.

MARY TINETTI: Okay. Dr. Cohen.
MIKE COHEN: Yeah, I was going to make a push for more prominent use of the ingredients, the actual ingredients on the front label panel. I know with prescription drugs the non-proprietary name has to be about half the height of the brand name and it appears immediately following the brand name, even in advertising, et cetera. And that's not the case for these. As you just pointed out, it doesn't even have to be listed, nor does the strength that I know of have to be listed and so what you have is a primary display panel that's mixed in with a lot of color, large names for the brand name so that people see that and unfortunately I, I really think consumers are at the point where they are beginning to learn the name, for example, Acetamitophen, and

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yet we see advertisements all the time with the word Tylenol, it's not associated with Acetaminophen in ads, on television, elsewhere I've seen the same thing and unfortunately people miss the fact that that is the same --
MARY TINETTI: So are you proposing the ingredients should be on, anything else other than the ingredients that you want to --
MIKE COHEN: The ingredients and the strength.
MARY TINETTI: And the strength. Okay.
Dr. Parker.
RUTH PARKER: You asked what should be on there and I agree with you completely about the ingredients and I'm sort of thinking of someone walking up to the shelf in trying to figure out what to do and, you know, you didn't ask for what should not be there, but I would like to have us ponder this thing about number one doctor recommend being on the front panel.
MARY TINETTI: Are you proposing that it should not be?

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RUTH PARKER: Yes.
MARY TINETTI: Is there general sentiment on that, I don't think we have to vote on

all of these, but I think Dr. Cnaan was next.

AVITAL CNAAN: Yes, one of several of the overdose anecdotes that we've heard from the various databases were when children were taking two products that shared an ingredient and I'm not sure if that is for the display or the back, I'm not that experienced in that, but somewhere to say in a prominent way not to take two products that share ingredients.

I think asking consumers not to take two products that have two different ingredients from the same family is asking too much, but if it's the same exact word, don't take two products with the same exact word.

AMY CELENTO: Amy Celento, I'm not sure this can go on the primary display label, but the instruction not to use this to sedate your children or your child, whatever appropriate wording I think needs to be incorporated.

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MARY TINETTI: And that would be just for the, that would be the for the antihistamines and, I don't know if Dextramethorphan gets used for that or not. Okay. Probably a good point.

Dr. Cohen and then Dr. Newman.

MIKE COHEN: Can I just ask a question about how this would be regulated or how oversight would be applied, I'm not really sure about that, would you change the monograph and then it would be misbranding if you made certain statements in that monograph that would have to be followed and that's how you would do it?

CHARLIE GANLEY: Right, if there's certain required statements and there's folks on compliance here, they probably could answer it better than I could, I don't know where they're at, but if there's certain statements that are required and they're not included in there, then it could become a misbranding issue which would require potentially a recall of that individual product, okay.

Now it gets a little more difficult with

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the number one doctor recommended, okay, because it gets into some First Amendment issues which I'm not qualified to talk about because they are allowed to put what is considered truthful information on their packages. And so that is, becomes a very gray area, but if, if the Committee does want to opine on that, we certainly would be interested in, and I think industry can hear that, too.

MARY TINETTI: Dr. Newman.

TOM NEWMAN: I just want to say not only do we need to make sure that we have the generic names and the number of milligrams per 5 ml or some standard concentration, but that the generic names be, I would vote for at least as big as the brand name but certainly right here you can, they're much, much smaller, so I'd vote for at least as big on the brand name and on the back, I can't even read this, it's really tiny.

MARY TINETTI: Any other comments?

So I think we've heard so far is that we're recommending on the principal display panel that all the ingredients should be listed as their

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generic at least as large as the brand name, including the strength and concentration, and to clarify that you should not take two products with the same ingredients and that they should not be used for sedation and should not include the term doctor recommended.

WILL SHRANK: And we also said something about who shouldn't be taking the medicine or at least Ruth suggested that there be some sort of a stop light for a type of person that shouldn't be taking.

MARY TINETTI: And who should not take the, okay.

RUTH PARKER: Just one, one thing, I worry about with these combination products if you say not, you know, if you warn people, this is why you've got to test it, if you warn people not to take two products with the same ingredients, does that mean if one product contains three ingredients and the other one contains two, that they contain

the same ingredients? So you've got to be really careful about how you do this. If one contains one,

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one contains two, one contains three, so, there again, the wording being incredibly careful to make sure that we're able to communicate the meaning that we want the consumers to have and we come to some common language that our educational campaign around it, in the office, in the public sector, on television, in the magazines is all about the essence of the true meaning that helps people have safe and effective use.

MARY TINETTI: Dr. Calhoun was next and then Dr. Daum.

WILLIAM CALHOUN: So the proposal includes a ban on the use of number one doctor recommended? Is that, did I hear that correctly?

MARY TINETTI: I think it was talking about on the principal display panel.

WILLIAM CALHOUN: Yeah, so just kind of segwaying from what Dr. Ganley was talking about, you might ban a particular phrase, but maybe they put doctor recommended or maybe number one seller or whatever, so there's a whole host of marketing terms that could be applied and I'm not sure that it's

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either useful nor necessarily scientifically justifiable for us to try to exclude specific, what are essentially marketing terms from packaging.

If they're misleading, if they're untrue, then they come under FTC or FDA, depending, I guess, but I'm not sure that it's within the scientific purview to ban specific phrases and if you do, then something else will just crop up.

CHARLIE GANLEY: What would be helpful, though, is for them, for us to get an understanding of what impact that has on a consumer, because it really gets back to, in my view, if you're having number one doctor recommended, well this must be pretty safe and effective and, you know, I can take it and there's no real fair balance in that.

And so we, we have no data and no understanding of how that impacts on the marketing

or the perception of the consumer, so if you're interested in them providing us some information on that so we really understand it, that would be a helpful.

WILLIAM CALHOUN: Yeah, I guess the flip

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side of that is you could say on the market for 30 years or largest seller or used by billions of babies.

CHARLIE GANLEY: You know, it can go on and on.

WILLIAM CALHOUN: You can make all these things up.

CHARLIE GANLEY: No, I understand.

WILLIAM CALHOUN: It's like chasing a --

MARY TINETTI: I think the question is are there one or two of those that are particularly misleading and I guess that's really the question, and if those would be something that we would recommend be tested, yeah, I agree, something else will pop up, but if there's something that's particularly concerning to us, this would be the opportunity to address that.

Dr. Daum.

ROBERT DAUM: Yeah, I'd like to at least raise for consideration the removal of pictures of infants from these boxes because at the least, whether it comes off the shelf or not is a question,

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but at least we're not going to be recommending it for people under 6 and so I don't see any point in putting babies, happy or otherwise, on the box.

MARY TINETTI: That's a very good point. Okay.

Ms. Hewitt.

JAN HEWITT: Along the same lines I'd also be concerned of having an image of a child for which a parent quickly scanning the shelf would pick it for her 7 year old but also would think a 5 year old could appropriately take it without necessarily going directly to the do not use or whatever language we decided upon, the image of a child may still represent a problem.

MARY TINETTI: So you're suggesting there should not be pictures of children?
JAN HEWITT: Right.
MARY TINETTI: Okay. So I think that was just a discussion, I don't think there's anything we can vote on with that. Okay.
Yes.
CHARLIE GANLEY: It's just I hate to

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have you go back, I just want one clarification, I think Dr. Atkinson brought it up about potential language that would impact on a pediatrician or other health practitioner to prescribe or to tell someone to go take a product where, and the language becomes exact and it is at an absolute if a health provider would say even though the label says do not use in your child under 6 years of age or whatever, could a prescriber then, you know, feel confident that they would be able to do that, to tell someone to go use that product for whatever reason.
Now we did see some information that, you know, pediatricians and family practitioners and nurse practitioners are using this, so we heard his opinion, were you the one, Dr. Atkinson.
So it would be interesting to hear if other people think there's, you know, if it got to the point where we had language on there about do not use under a certain age group, could a prescriber then have the freedom to say yeah, you can, because for whatever reason they want.
MARY TINETTI: Any comments or

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discussion? Dr. Goldstein.
GEORGE GOLDSTEIN: Two things, first of all apart from the First Amendment and commercial speech being a protected form of that, there are substantial advertising substantiation operations as we speak both in companies with legal staffs and the networks and other forms of the media, so that this has to go through, a lot of this has to go through a process that, not all the time successful, but tends to filter out, if you will, the more egregious versions of that and I think the panel has to keep

that in mind.
MARY TINETTI: Dr. Atkinson.
PRESCOTT ATKINSON: Yeah, if I could just add on that, I think that if we put language like that in to the OTC products it's going to spill over into the use of prescription products of the same character without a doubt and this will have to have an effect on the prescribing habits or, and so forth and I think it's reasonable if the Committee wants to, wants to decide that parents shouldn't go out and decide for themselves at a certain, you
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know, for young children to use these, but I think considering the thousands of practitioners, family practitioners and pediatricians have used these products and feel that they're safe and effective, I don't think it's reasonable in view of the lack of data for us to sort of dictatorially not put this language in.
MARY TINETTI: Conversely, if we add something like unless directed by a doctor, we've defeated the whole rest of the message.
I would favor, as you said, this is going to go through a lot of legal hoops and my guess is that's where a lot of this will play out, but I think the sentiment is, the sentiment is what the sentiment is here, that they shouldn't be used, that there's no evidence of it, so I'm not sure we want to water that down by, by saying unless directed by a physician. That just goes right back, I mean it just voids all over -- so that would be my feeling, I'm not sure there's any wording that we can come up with right now that would deal with the medical -- the legal issues of it unless anybody
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else has any other feeling about it.
Okay, I believe, Dr. Rappley, you had a question or a comment.
LAURA MARCIA RAPPLEY: Yes, I find the use of doctor recommended particularly egregious and I think from this day forward it has no credibility and if it continues to be used it's used to mislead people, so I would like to go on record and I would

like to take a vote saying that we would strongly recommend that that language not be used.

MARY TINETTI: Okay, so Dr. Rappley has proposed that we actually vote specifically on the term doctor recommended for on the display panel and I presume any, any variations on that theme of doctor recommended?

LAURA MARCIA RAPPLEY: Yes.

MARY TINETTI: The marketers are pretty clever, they get paid a lot more than we do to circumvent, but I think the sentiment is anything related to doctor recommended.

Okay. The proposal is to vote, so the proposal is that we recommend that terms similar to

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or related to doctor recommended not be allowed on the display, on the primary display panel.

All in favor raise your hand.

LAURA MARCIA RAPPLEY: This is Dr. Rappley, I vote yes.

MARY TINETTI: Okay. Start with --

SEAN HENNESSY: Sean Hennessy, yes.

JEFF ROSENTHAL: Jeff Rosenthal, yes.

ROBERT DAUM: Robert Daum, yes.

AMY CELENTO: Amy Celento, yes.

RICHARD NEILL: Richard Neill, yes.

AVITAL CNAAN: Avital Cnaan, yes.

DENNIS BIER: Dennis Bier, yes.

MARY TINETTI: Mary Tinetti, yes.

RUTH PARKER: Ruth Parker, yes.

BEN CLYBURN: Ben Clyburn, yes.

RALPH D'AGOSTINO: Ralph D'Agostino, yes.

WILL SHRANK: Will Shrank, yes.

JAN HEWITT: Jan Hewitt, yes.

MARIE GRIFFIN: Marie Griffin, yes.

ROBERT TAYLOR: Robert Taylor, yes.

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JESSE JOAD: Jesse Joad, yes.

PRESCOTT ATKINSON: Prescott Atkinson, yes.

MIKE COHEN: Mike Cohen, yes.

TOM NEWMAN: Tom Newman, yes.

MARY TINETTI: Nos? Dr. Calhoun.
WILLIAM CALHOUN: I guess on the basis of First Amendment considerations, I'm going to have to vote no.
MARY TINETTI: Fair enough. Any abstentions, okay.
So the question was should mention of related terms such as doctor recommended be removed or not allowed on the principal display panel.
DARREL LYONS: The vote was 20 yes, 1 no.
MARY TINETTI: Is that --
DARREL LYONS: Zero abstentions.
MARY TINETTI: Dr. Leon Dure had left at the time of this vote.
We're on our final question here related to combination products. Most cough and cold

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products are available as combination products, combination products may be considered a problem because, for example, parents and caregivers may use several products not realizing that they are duplicating ingredients and overdosing their children.
Currently the monograph allows for combinations of several ingredients. Should marketing of combination products be allowed for children, yes, no. If no, for which age groups. In addressing this, please consider the following points, there may be advantages of combination products assuming correct use. There may be unintended consequences of prohibiting combination products in that parents will use multiple single ingredient products and there may be disadvantages if overdosing occurs with multiple ingredients.
If yes, should the number of active ingredients in combination products be limited in order to reduce the use of overlapping ingredients in different products, yes or no.
So we're asked to, to address the

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question of combination products and whether they should be allowed and when you answer this, if you

could, at this point we don't necessarily need a yes or no, but if you have a sentiment one or the other, what, what rationale supports your decision.

MIKE COHEN: Excuse me, Dr. Tinetti, you missed the final question about the name in 4E I think it was.

MARY TINETTI: I'm sorry, what did I -- oh, I'm sorry.

MIKE COHEN: We can bring that up after.

MARY TINETTI: Okay, why don't we finish this one, we'll go back, thank you for, it's getting late in the day, thank you, thank you for noticing that. Let's finish on this question and then we'll go back.

Discussion on combination products.

Okay. Dr. Daum and then Ralph D'Agostino.

ROBERT DAUM: I'm going to at least advance the idea that it's fundamentally the same question we considered before, the one we did the less than 2s and the 2s, 2 to less than 6 and the 6

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to 12 -- or 6 to less than 12, so I think that we could, perhaps, if the Committee is willing to cut to the chase and take the same tact or if people think that combinations are different than the singles we should discuss them.

MARY TINETTI: Well I think we've already said nay to under 2 so I don't think we need to discuss that age group, so the question is whether or not, so the --

ROBERT DAUM: Well we've already said nay to under 6, so the question is between the 6 and, 6 and 12.

MARY TINETTI: So we should just focus on the 6 to less than 12.

ROBERT DAUM: That's my proposal.

MARY TINETTI: Any objection to that?

LAURA MARCIA RAPPLEY: I agree.

CHARLIE GANLEY: Well it was a mixed vote on the 2 to 6, I think.

MARY TINETTI: Right, that was my feeling, right.

Okay. Is it a question related to this

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point? No, we're just talking, I just want to just make some decision based on Dr. Daum's recommendation that we focus just on the 6 to, this 6 to 12 because we're, the vote was mixed -- what was the vote again, do you remember, for the 6 -- less -- 2 to 6.

ROBERT DAUM: My proposal was a little different than that, it was just that we take the same tact that we took with the other three age groups and, in other words, the combinations are different than the singles, so it would be --

MARY TINETTI: So allow combinations for the underage groups?

ROBERT DAUM: So no to under 2, mixed votes, but no to under 6 and mixed vote but yes to 6 to 12.

MARY TINETTI: Okay.

ROBERT DAUM: I don't see this as a different issue is what I'm trying to say.

MARY TINETTI: Okay. I think there are some different issues, but that we can certainly start, we can certainly start there.

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Can we just have comments on this recommendation first, Dr. Calhoun.

WILLIAM CALHOUN: So I see the combinations as being just subtly different, I don't disagree with you fundamentally, but I see them as subtly different in that because the combinations enhance the likelihood for misuse and overdosage, I think the risk of combinations is actually greater than the risk of single agents and so that might potentially color some peoples votes.

So it wouldn't necessarily be the same vote for single agents as it might be for combinations because of the enhanced potential for toxicity.

MARY TINETTI: Dr. Parker.

RUTH PARKER: I agree with you theoretically but I don't know if we have evidence on that. It sure would be nice if we did, but I sure agree with you on it theoretically. My

question was what percent of market share are, is represented by combination of these products versus single ingredient?

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MS. SUYDAM: Combinations are 75 percent of the market share and I believe if you will look at the data that was presented both by the FDA and by the industry, that the events actually are about actually -- which means that combinations are safer.

MARY TINETTI: Thank you, I wish we all could be so sure.

I think, I'm still not quite sure that I think, I understand the point of your question but I think perhaps, your point, Dr. Daum, but I think perhaps we want to have a more general discussion.

I think we're talking, I think for the 2 to less than 12 year old, for multiple ingredients versus the single ingredients first and then if it plays out that we feel differently by age, then we can vote separately by age, but there would have to be some compelling physiologic reasons for that.

Any general discussion?

Dr. Parker, Dr. Will Shrank and then Dr. Newman. Dr. Shrank.

WILL SHRANK: Just a suggestion on the labeling of combination products, it's clear that

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frequently patients and families don't know what's in them and I would suggest that any combination product have some sort of label on it that says do not take with any other cough or cold medicine.

MARY TINETTI: I think that's our next question, we haven't gotten there yet, that's B, but hold that thought, thank you.

Dr. Newman.

ANN McMAHON: Yeah, I just wanted to mention that on the serious review of errors, looking at the serious reports, that over 75 percent of the serious reports were related to combination use.

MARY TINETTI: So your point is that they're at least as common as their prevalence of their use?

ANN McMAHON: Well I, I don't know about denominators, you know, because we don't, we didn't, we don't have direct evidence of the denominators based on this database, but I just wanted to point out that they were, that the serious adverse events in this particular study were frequently with

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combination product.

MARY TINETTI: I think if industry has a short response to that, actual data with numerators and denominators.

MS. KUFFNER: Yes, slide on, please, we didn't get a chance to discuss this yesterday but we do have reporting rates for the single ingredient and the combination products and you see those reporting rates up there broken out in the different age groups. And what you do see is that reporting rates for both single and combination ingredients were low, and let me remind you, these were reporting rates for a million units distributed and what you see is you have a similar rate for a single ingredient and combination products and these are based upon distribution data. And again, this is out of the McNeill database.

MARY TINETTI: Thank you. Dr. Neill.

RICHARD NEILL: I'm curious to hear from the pediatricians on the panel with regard to the actions that you take when patients come to you as a result of recommendations on the label saying ask

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your doctor, given, you know, my experience that I never recommend combination products and in those rare instances where I in my mind begin to consider it have to add up now which one was that and is that still the active ingredient and how can I find that information from the drug store that they're going to go to, is that product going to be available. This is a phenomenally difficult process for me as a prescribing clinician, is it different for you folk, do you ever recommend combination products?

ROBERT DAUM: I can answer in a word, no. No.

JESSE JOAD: And I would have to say

yes, that there are, that drugs are hard to give to children and, and when combinations come along that are prescription drugs where I know I want to give both of them, I'm very happy to have a combination, so combinations do make a difference in adherence for children in my opinion.

ROBERT DAUM: But he's asking about cold and cough combinations.

JESSE JOAD: Just for cold and cough,

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yes, and then I can't, you know, I can't tell you, although I could see the, if the drugs work, which I'm not sure they do, they each do something different and some of them have such a short half life you have to give them every four hours and if they're ever going to work you probably would have to view them as a combination. And if the safety data in our big safety study turns out that they're just as safe, then I would be in favor of combinations.

RICHARD NEILL: Well this, to me, gets to the issue of Dr. Daum's comment regarding, you know, just cutting to the chase and using single data discussion and vote that we've taken. If there's a difference for me, I think that's the difference, that it's quantitatively and qualitatively a different phenomenon for me to consider combination products in my patients and if it's qualitatively different for me, how can it not be qualitatively different for patients, consumers walking in doing self-selection and as a result, I would be hard pressed to advise that we continue to

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consider combinations for that 6 to 12 age group, that's all.

MARY TINETTI: Dr. Newman, did you have a --

TOM NEWMAN: Yeah, I think for me it's difficult because I, I don't think they're effective so I don't prescribe them at all, but I think that the combinations, my impression is that if they were shown to be effective, the combinations could end up also saving the consumers money because my

impression is that the, the packaging is such that most of the expenses for the, you know, the bottle and the space on the shelf and so on and that if, you know, it would probably be less expensive for consumers to get both their Acetamitophen and their Dextromethorphan or whatever in a single package, so I'm, I'm concerned about the cost and my concern is really I don't think there's strong evidence that they're, that they're less safe. They're certainly way more confusing.

MARY TINETTI: Dr. Rappley.

LAURA MARCIA RAPPLEY: I would have to

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say that I would not usually recommend a combination for 6 to 12, but I have, don't feel that I've seen anything to make me say that they should not be available to people.

I don't think, and correct me if I'm wrong, but I don't think we've seen a risk higher in this age group and in fact some of the adult data shows that combinations are more effective.

So for me it's in that same, I'm thinking about this issue the same way I'm thinking about a need for better studies and a certain time frame in which we might allow that and ask the companies to come back and present that to us.

MARY TINETTI: Right, which I think was Dr. Daum's point that when we word this question, we'll certainly have to word it similar to the limitations we've put on the other question.

Dr. Shrank.

WILL SHRANK: Yeah, I think it's actually easier to take, so I -- the risk I think is when a patient or a family buys three or four different medicines and are trying to dose them all

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simultaneously, so I bet there's a safety advantage in some cases of using the combination product.

MARY TINETTI: Any further discussion?

So going back to Dr. Daum's point, we, I guess it probably might be good to vote on this by the age, do we need to do the under 2? I think that under 2 we've said no for everything so there's no

use in doing that. So I think it was the split vote where the 6 to the 12, so for children between 2 to 6, should marketing of combination of products be allowed for children, and I think we limited it for the next three years until the efficacy studies are completed, yes or no.

Those who would say yes, raise your hand. So the question is should marketing of combination products be allowed for children between 2 and less than 6 for the next three years, pending efficacy studies and safety studies, those in favor?

LAURA MARCIA RAPPLEY: I want to point out that the previous question was not be allowed so when we look back on our previous votes, that would be --

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MARY TINETTI: So you want to --

CHARLIE GANLEY: Well I think you're taking it too far in terms of the immediacy of it and this is more, you know, if we're going to propose a regulation, it's more geared towards that and it was based on the recommendations in one of the reviews is that should there be limits on what combination products can be used in and the main issue of concern has been is that you may have the same ingredient on two different products, but the symptoms on the front of the panel are different.

There's a lack of consistency there and so you have this use of two products because it may be taking it, the emphasis on one product may be cough, the emphasis on another product may be stuffy nose, yet they both contain Pseudoephedrine or something because it's a combination product and that's where, so I think the --

MARY TINETTI: Some of that will come out I think in our next point, the labeling question, I think.

CHARLIE GANLEY: Yeah, but the interest

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is more on what is the long-term view rather than what to do in the next three years.

MARY TINETTI: Well I think the long-term view is we've already answered, we want

efficacy studies, I think we've already answered, answered that question. I think, I think the question here is if we say yes, I think it's still pending results of efficacy studies.

CHARLIE GANLEY: So if, you're comfortable with if they have efficacy studies and somehow we improve the labeling that's going to decrease the number of misdosing, because that's where some of the problem seems to be occurring with these multiple ingredient products, that you would possibly be comfortable with that --

MARY TINETTI: Well I think we, it's more the opposite, that we would not be -- if there's no -- yes, yes, this is, this is predicated on the fact that there's clearly efficacy data, would we be comfortable with, with combination products, correct.

CHARLIE GANLEY: That's the question we

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need --

MARY TINETTI: Okay.

CHARLIE GANLEY: -- the answer on, we don't need it, we don't need the immediacy question.

MARY TINETTI: Okay, so is everybody clear on that question.

Dr. Daum, you seem not --

ROBERT DAUM: I guess I'm not and I apologize. We voted before on the single agents, if I understood the procedure correctly, without the efficacy part in the question and so I'm a little concerned that we're now voting on the combination for the same two age strata with the efficacy stuff in the question and we might end up with an internally inconsistent view here where we say we can't, we don't want single agents sold but we --

MARY TINETTI: I don't think we voted specifically on, it was not, our previous vote was on the products with these ingredients, we did not specify whether there were single ingredient or multiple ingredient.

ROBERT DAUM: Oh, okay.

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CHARLIE GANLEY: I think the way that

you have to look at it is we're going to have to write a proposed rule, okay, so if we come out and say that there shouldn't be combination or multi-ingredient products for children less than 6 years of age, unless we get some compelling data that they can be dosed correctly and, you know, go, because I think it is a little more complicated to use multi-ingredient products than it is to use single ingredient products, okay.

So, you know, I'm thinking of, you know, what is it we have to put out there that they're going to have to respond to that will force them to provide data that gives us a comfort level that we're comfortable with these multi-ingredient products.

It doesn't have to apply to less than 6, it could be all, for children 12 and under, okay, and it's really this concept of, you know, obviously if he have efficacy data that supports, you know, that these products work and, you know, they, we can combine these two and we think they'll work, but you

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still have the problem with misdosing that we have to get.

And, you know, so there have to be some data for us to say that you need to provide us with data, whether it be consumer behavior data or some other data, you know, that makes us feel comfortable that these products, these combination multi-ingredient products can be used correctly in children, whether it's labeling that needs to be done or some other, that's really what the heart of it is and to me it's that when we go to propose this in a rule, the proposal may say that multi-ingredient products shouldn't be provided, you know, for children less than 12 years of age unless something.

RUTH PARKER: Charlie, is it possible to look back and say that you actually would need data like the kind that could be attained in label comprehension and actual use, could that be a reasonable thing for the kind of thing we do with other over-the-counter products, to say because of

concerns about the ability to safely self-diagnose
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and administer combination products for cough and cold in the outpatient setting for this age group, we recommend label comprehension and actual use studies that demonstrate adequate label understanding and actual use of combination products?

CAROL HOLQUIST: Hi, Carol Holquist, yeah, that's exactly what we would look for because a lot of the errors that we've seen are that people just don't know, they're going by symptoms, not by active ingredient, so they buy these multiple products by symptom alone and don't know what they're getting and they get into trouble.

MARY TINETTI: Okay. Dr. Calhoun.

WILLIAM CALHOUN: Thanks. So I think there's one other consideration here which is that with combination products, there is the potential for kids to get medication that they don't actually need because the marketing might be a brand name something and brand name something and then brand name max that has everything in it and so mom or dad will pick up the brand name max because that must be
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the best and, you know, the kid might only need one or two of the components and I guess that parents aren't reading the fine print as carefully as perhaps they might in order to sort out exactly what their child needs.

So I think that's my level of concern about the multiple combination products.

MARY TINETTI: And I, I think as we vote on this we need to weigh, again, that I think clearly there's advantages and disadvantages and the question are do the advantages outweigh the disadvantages. I think we may be able to address that a little bit in the next question, too, because they specifically ask us about the number of ingredients and certainly the labeling issues.

So, so, Charlie, would this be a reasonable question that would be useful to you, assuming that the clinical trials support efficacy

and safety in this, in this age group of these ingredients, should marketing of combination products be allowed for children and I think we will break it down into the age groups of 2 to less than

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6; is that -- okay. And then we'll do it from 6 to 12.

CHARLIE GANLEY: Right, and again, it gets back to what the original intent of the reviewers was that we need to understand how these products can be marketed safely and, you know, we understand there may be some benefit for multi-ingredient.

MARY TINETTI: Could we do a yes or no and then if the question is, if the question is no, then it's a moot point. If the question is yes, then we can discuss ways to make it safer; is that, does that -- is that okay? Okay.

The question is just a yes or a no, because if it's a no, then label comprehension becomes a moot point. If it's a yes, then we'll address issues that will make it safer, including labeling.

WILL SHRANK: Just a clarification, so we're assuming that the drugs are effective for this?

MARY TINETTI: Right, my question was

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assuming that the drugs are shown to be effective, should marketing of combination products be allowed for children between 2 and less than 6.

CHARLIE GANLEY: It may be easier to just, rather than have it as a two-parter, just try to capture it in one and I think Ruth was trying to head that way, is that if there, should, should -- for the marketing of combination multi-ingredient products in children, should there be data to support the ability of the parent or caregiver to identify the products and ingredients and things like that, because it, you know, if it's a yes or no, if someone, for example, that we, there's efficacy established and then they through consumer use or consumer labeling studies or actual use

studies show hey, really, parents really understand now because we've done this, this, this, this to the packaging, we have standardized everything and they really understand how to use these, that eliminates the problem.

MARY TINETTI: So let's work on the wording here then.

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Assuming that studies show effectiveness and safety, should marketing of combination products be allowed for children if they are found to, to finish the question, Dr. Ruth.

RUTH PARKER: I would say should marketing of combination products be allowed for children 2 to --

MARY TINETTI: Less than 6.

RUTH PARKER: Less than 6 pending label comprehension and adequate use studies, done in the right order I might add, you have to use the right label in the actual use, you can't do them in the reverse order, so adequate results of label comprehension and actual use studies that demonstrate acceptability to self-select safe and effective use of over-the-counter products.

CHARLIE GANLEY: You just broke your own rule.

RUTH PARKER: I'm changing it to make it simple.

MARY TINETTI: Are you going to help us clarify or make it more confused, Dr. Daum?

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ROBERT DAUM: Well you'll have to tell me what you think. There's 800 products on the market now we've learned in the last day and a half and the 800 are there because every combination imaginable is being sold.

I'm looking at a world now, I think I finally understood, we're looking at a world where the efficacy of individual components is demonstrated, now should we sell them in combination. I'm not sure we have to address that now because I'd like to see the efficacy data and see what they look like, first, but I'm a little

concerned about going back to a world where there's 800 products on the shelf.

So I don't want to, I don't think we have to take a rigid stand right now because the efficacy data that we'd love to have and wouldn't consider moving forward without are not there, so think about the shelf in the Walgreens and the 800 products and that's what we're voting for, without any data at all about the efficacy.

CHARLIE GANLEY: Yeah, I'm not sure if

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you didn't have multi-ingredient products that you wouldn't have 800 single ingredient products.

MARY TINETTI: You might have 2,400.

CHARLIE GANLEY: Yeah, and so I think the one way is assuming that efficacy data is provided, should there, should there be additional data to support the correct use of the combination products, okay.

TOM NEWMAN: To finish your sentence, should there be additional use before they are allowed to market them, that's what you mean.

CHARLIE GANLEY: Yeah, consumer use studies and we understand that they can be used correctly.

MARY TINETTI: Dr. Bier.

DENNIS BIER: Well I don't, I don't see them -- I see two things here, one is should you have combination products at all, I mean we haven't, that was the first level of our question. The second is if you do, should you make sure that they're done properly.

CHARLIE GANLEY: But again, it becomes a

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data issue. If they establish that it's efficacious and they provide data that they've done standardized -- you know, they've standardized dosing, they've standardized the container, they've improved the labeling so that consumers understand it, there's ways to do studies to understand whether, you know, how that's going to work.

ROBERT DAUM: I appreciate that, but that comes if we, you know, I think there's a

question first, some of us don't necessarily believe there should be combination products.

CHARLIE GANLEY: Okay, that's fine.

ROBERT DAUM: That's the first level of the question. If we don't believe there should be combination products, we don't have to worry about how you label them.

CHARLIE GANLEY: Okay, that's fine.

MARY TINETTI: Well then you would, then you would vote no. There was a proposal here to defer this question until the efficacy data are in, but I guess my question to you, Charlie, I mean some of these changes, some of the requirements to do the

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labeling and comprehension could actually occur now, right, they could occur simultaneously, potentially, with the efficacy, so that would be a potential reason for addressing this now.

So, could you tell us again your, your wording of this question.

CHARLIE GANLEY: Well, I appreciate Dr. Bier's view and, you know, in that situation he would be voting no because there's no data that would support his, so again, it goes with the assumption that if there is efficacy, should there be additional data to support the use of combination products, consumer data to support the use of combination products.

So it's not only just establishing efficacy and, although I understand you could say that, no, I don't, the no answer could mean no, I don't need additional data.

ROBERT DAUM: Well I'm just looking at your question here, A, should marketing of combination products be allowed for children, yes or no, that's the one I want to answer first.

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CHARLIE GANLEY: Okay, we can do that.

MARY TINETTI: Very good, let's do that first, then.

Should marketing of combination products be allowed for children, we will, there was a sentiment for breaking it down to age so we will do

that, from 2 to less than 6. All those in favor?
UNIDENTIFIED SPEAKER: Are we assuming the drugs are effective?
MARY TINETTI: Yes, assuming the drugs are effective, I think we agreed on that wording. We'll start with Dr. Calhoun.
WILLIAM CALHOUN: Calhoun, yes.
PRESCOTT ATKINSON: Prescott Atkinson, yes.
JESSE JOAD: Jesse Joad, yes.
ROBERT TAYLOR: Robert Taylor, yes.
MARIE GRIFFIN: Marie Griffin, yes.
JAN HEWITT: Jan Hewitt, yes.
WILL SHRANK: Will Shrank, yes.
RALPH D'AGOSTINO: Ralph D'Agostino, yes.

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BEN CLYBURN: Ben Clyburn, yes.
RUTH PARKER: Ruth Parker, yes.
MARY TINETTI: Mary Tinetti, yes.
AVITAL CNAAN: Avital Cnaan, yes.
AMY CELENTO: Amy Celento, yes.
JEFF ROSENTHAL: Jeff Rosenthal, yes, if safety and efficacy is demonstrated.
MARY TINETTI: Yeah, that's part of the question.
Okay, those no?
LAURA MARCIA RAPPLEY: Dr. Rappley, I vote no because I cannot separate the question from the previous vote.
MARY TINETTI: Very good. Any other nos?
RICHARD NEILL: Richard Neill, no.
DENNIS BIER: Dennis Bier, no.
MIKE COHEN: Mike Cohen, no.
MARY TINETTI: Mike Cohen, no.
Any abstentions?
SEAN HENNESSY: Sean Hennessy, abstain.
ROBERT DAUM: Robert Daum, abstain.

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TOM NEWMAN: Tom Newman, abstain.
MARY TINETTI: Okay, so the, the question while we are adding up here is assuming

that these ingredients are proven safe and effective, should marketing of combination products be allowed for children between 6 and less than -- between 2 and less than 6. What's that?

DARREL LYONS: I'm missing Daum and Dure.

MARY TINETTI: Daum was an abstention, Leon Dure is gone.

DARREL LYONS: Okay. For the record, there was 14 yes, 4 no and 3 abstains.

MARY TINETTI: I think we'll do the next age group before we add the next point, so should marketing of combination products be allowed for children, assuming they are proven safe and effective, should marketing of combination products be allowed for children between 6 and less than 12.

All in favor, raise your hand. Okay. Starting with Dr. Calhoun.

WILLIAM CALHOUN: Calhoun, yes.

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PRESCOTT ATKINSON: Prescott Atkinson, yes.

JESSE JOAD: Jesse Joad, yes.

ROBERT TAYLOR: Robert Taylor, yes.

MARIE GRIFFIN: Marie Griffin, yes.

JAN HEWITT: Jan Hewitt, yes.

WILL SHRANK: Will Shrank, yes.

RALPH D'AGOSTINO: Ralph D'Agostino, yes.

BEN CLYBURN: Ben Clyburn, yes.

RUTH PARKER: Ruth Parker, yes.

MARY TINETTI: Mary Tinetti, yes.

AVITAL CNAAN: Avital Cnaan, yes.

AMY CELENTO: Amy Celento, yes.

JEFF ROSENTHAL: Jeff Rosenthal yes, with the same stipulation.

MARY TINETTI: Yes, that's part of the question.

Okay, for nos, Dr. Rappley, did you --

LAURA MARCIA RAPPLEY: I'm voting yes, Rappley yes.

MARY TINETTI: Okay, Rappley yes.

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Okay, nos?
MIKE COHEN: Mike Cohen, no.
DENNIS BIER: Dennis Bier, no.
RICHARD NEILL: Richard Neill, no.
MARY TINETTI: Abstentions?
SEAN HENNESSY: Sean Hennessy abstain.
ROBERT DAUM: Robert Daum, abstain.
TOM NEWMAN: Tom Newman, abstain, I just don't feel like I have enough data to say.
MARY TINETTI: Okay, so the question was assuming the products, or the ingredients are proven safe and effective, should marketing of combination products be allowed for children between 6 and less than 12 and the vote?
DARREL LYONS: 15, 15 yes, 3 no, and 3 abstentions.
MARY TINETTI: And so now we're asked to say assuming that, that the marketing is -- well I guess the, clarify maybe, Dr. Parker, again, the wording that you want for the follow-up question.
RUTH PARKER: So it should be that, do you want the question -- should label comprehension

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and actual use studies for combination products be done. How's that?
MARY TINETTI: Okay. Happy to say no to that, right.
Dr. Newman.
TOM NEWMAN: Should they be done as a prerequisite before the combinations could be marketed, that's what you mean.
MARY TINETTI: Thank you, okay. Okay.
So we understand what the question is, should labeling and comprehension and actual use studies be done prior to allowing marketing for combination products.
Okay. All in favor, requiring, requiring the studies? Okay. We'll start over here, Dr. Hennessy.
SEAN HENNESSY: Sean Hennessy, yes.
JEFF ROSENTHAL: Jeff Rosenthal, yes.
ROBERT DAUM: Robert Daum, yes.
AMY CELENTO: Amy Celento, yes.

RICHARD NEILL: Richard Neill, yes.
AVITAL CNAAN: Avital Cnaan, yes.

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DENNIS BIER: Dennis Bier, yes.
MARY TINETTI: Mary Tinetti, yes.
RUTH PARKER: Ruth Parker, yes.
BEN CLYBURN: Ben Clyburn, yes.
RALPH D'AGOSTINO: Ralph D'Agostino, yes.
WILL SHRANK: Will Shrank, yes.
JAN HEWITT: Jan Hewitt, yes.
MARIE GRIFFIN: Marie Griffin, yes.
ROBERT TAYLOR: Robert Taylor, yes.
JESSE JOAD: Jesse Joad, yes.
PRESCOTT ATKINSON: Prescott Atkinson, yes.
MIKE COHEN: Mike Cohen, yes.
TOM NEWMAN: Tom Newman, yes.
BILL CALHOUN: Bill Calhoun, yes.
MARY TINETTI: Dr. Rappley?
LAURA MARCIA RAPPLEY: Yes.
MARY TINETTI: Okay, any nos? Any abstentions? Okay.
RUTH PARKER: A comment, I think that these label comprehension and actual use studies

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actually represent what I will call a golden opportunity to advance our ability to set forth the language that could be used and adopted in a standard if we're able to come to that language and demonstrate adequate understanding of the targeted consumers and their ability to self-select based on this language. And the labeling comprehension study could also target the ability to look at the consumer's ability to act appropriately on warnings, in other words, not self-select to use it if your child is under 2, so the language of that warning, the symbol that draws attention to someone attuned to that symbol and the opportunity is really here to make tremendous improvement in labels and in setting standards.
The other thing would be to look at the dosing device, perhaps, in the label comprehension

in actual use and not just, can you, can you tell us that you could take it correctly, but can you demonstrate it using the new standard dosing device.

So these are options that would be made available and would represent an enormous

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opportunity to improve public health and I think what require courageous leadership but perhaps the type that the industry has, has stated that they're willing to take on. So I think it's a great opportunity.

MARY TINETTI: Thank you. Dr. Calhoun, did you --

WILLIAM CALHOUN: Yeah, so I guess the outcome here would be the proportion of people who took the medication correctly or et cetera.

Would it be useful in that sort of a study to have a control group which would be comprised of people who read the label on a single component product and I guess the issue here is, for me is whether combination products are more or less confusing than single agent products for consumers and in order to get that notion, you almost have to gather the same kind of data with single agent products. I think that would actually be pretty useful.

RUTH PARKER: The question that is posed here about indications for each ingredient appearing

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on the label and the ability to understand that and sort of the clarity of understanding an ingredient and this, this issue of not taking multiple products with the same ingredient and even ingredient category and the overlay of that is going to be very important.

I think to answer the question it's going to take a narrow focus on a well-designed label comprehension study that could, here again, set a great example for the kind of work that we want to do on all over-the-counter products and a great example and lead from industry on this would be, would be very welcome to the world of OTCs.

ROBERT DAUM: I think it might be a very

nice thing to put into the record for this meeting that at least the Pediatric Advisory Committee, and perhaps both committees, would like to sit and reflect on the data when the efficacy studies are done and revisit this issue so they'd have an opportunity for an update.

MARY TINETTI: Fair enough, you're invited back. I think that's an excellent idea.

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The -- yes, Dr. Joad.

JESSE JOAD: With regard to the single dose versus the multiple combination products, somehow to really get at the whole issue you'd have to see how a parent did over a day -- a caretaker did over a day giving single ingredients, three different single ingredients all at once at least three times a day and how often were they successful at doing it and not making mistakes with multiple giving of the drug versus somebody who, I mean that has to go along with the label comprehension because that's another place of error or lack of being able to administer a drug.

MARY TINETTI: Right, I think that's the actual use part of it and I think you're right. Okay. We're asked to comment upon if, if yes, we agree that there can be marketing of the combination products, should the number of active ingredients in combination products be limited in order to reduce the use of overlapping ingredients in different products.

BEN CLYBURN: Shouldn't the actual use

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studies and label comprehension tell us that, I mean it should tell us how many ingredients the public can reasonably take in.

MARY TINETTI: So you're saying that we really can't address that question as of yet, that it really depends on the studies, okay.

Does anybody else have any other comment on that? Dr. Atkinson.

PRESCOTT ATKINSON: Yeah, I'd like to propose at least for consideration that we consider pulling antihistamines out of, out of these

preparations just because they have a, they have a, you know, we're really talking about congestion and cough, mainly, and there we're really looking at the anti-cholenergic, you know, side effects of the first generation antihistamines as a sort of adjunct treatment anyway and they have different toxicities, they've been noted to have different potential for overdose, they're used for sedation and maybe that would reduce some of this toxicity issue.

MARY TINETTI: So you're actually proposing that antihistamines not be allowed as part

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of combination --

PRESCOTT ATKINSON: If we were going to restrict any of the combo medicines, it seems like that would be the one to try to think about pulling out.

MARY TINETTI: Okay, we may want to come back and vote on that specifically. Okay.

Dr. D'Agostino and then Dr. Shrank.

RALPH D'AGOSTINO: Yeah, I'm a big advocate of actual use studies but you have to careful in terms of what you can get out of them and to look at the combinations, you know, how many ingredients can you have, you oftentimes do the actual use studies that there's something that's being planned to be put forth and not what's the maximum that you can get out of it, you know, can you put seven ingredients in and so forth.

So while conceptually you can use the actual use studies, I think the, and I'm not asking that we take a vote, but I think the interpretation of how many ingredients can be in it, it's not going to be a simple thing to just say we'll let the

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actual use studies determine that for us.

MARY TINETTI: Charlie.

CHARLIE GANLEY: I'll just mention now that as per the regulations, you can only have four ingredients in it already and so I think this was trying to get out should it be less than that, so, or again, is it based on data that --

MARY TINETTI: Okay, thank you.

Dr. Shrank.

WILL SHRANK: It seems to me that if there's ever a combination product, it should have a label on it that says you shouldn't take any other cough or cold medicines because the marginal benefit of adding a different product is probably relatively small to an already combination of products and the likelihood of overdosing or having a problem I think is greater and it raises lots of more safety problems I think than benefits.

MARY TINETTI: So you're suggesting on the label should specifically state that do not -- take only one, do not take any other --

WILL SHRANK: If you're taking a

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combination, if it's a combination, right, don't take any other cough and cold medicine.

MARY TINETTI: Okay, that's a good point. Okay.

Dr. Neill.

RICHARD NEILL: We've heard data, it's Richard Neill, we've heard data that some consumers don't buy ingredients, they buy symptom relief and I think that in the same way of having multiple individual ingredients available raises the spector of having six bottles for multiple concentrations, et cetera, I think it's also the case that it may occur with combination medications, I would wager actually that it does occur now with multiple ingredient combination medication that in shopping for symptom relief a parent presents, and this is the economic question, I have five kids and of the five, Johnny and Suzie have cough, but Joey has a stuffy nose. And as I tally up the symptom relief among the possible combination medications what might I get and how is that going to factor in given that Johnny just started right tackle for the

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football team, although he's 12, and Suzie's not quite yet to kindergarten and how are those doses going to change, especially if I've got 10 dollars in my pocket and I can get this for 6 and that other for 14.

And so this is not in any way to minimize what I think are some real concerns about having only single entity ingredients available, but rather to lay out there what I think are equally, if not more, compelling concerns that I have about putting combination medications out in a market where a label comprehension followed by actual use studies.

(Please pardon the interruption, your conference contains --)

RICHARD NEILL: Those label comprehension and actual use studies are commonly going to look at study units in one of -- for that one patient, not households, not grouped family members, certainly not communities that trade across the back fence. I've got some, you know, ingredients X from last month but could I trade you

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for and yet I'm confident that economy exists somewhere.

MARY TINETTI: I think we had one, one suggestion here in terms of a votable question is whether antihistamines should not be allowed as part of combination products.

Dr. Atkinson, are you interested or actually voting on that proposal? Okay.

Okay, so the question is here assuming that combination products are allowed and are shown to be safe and effective, should antihistamines not be allowed to be part of combination products.

Dr. Calhoun.

WILLIAM CALHOUN: Could I just comment that once again for an indication other than cough and cold, that is for allergic rhinopathy, that combination --

MARY TINETTI: All of our discussion is assuming that we're just talking about a cough and cold, cold indications.

WILLIAM CALHOUN: But again, this goes to the question if it's disallowed, does that mean

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that that product disappears from the shelf unless it's labeled something something allergy or

whatever.
MARY TINETTI: Okay, fair enough.
CHARLIE GANLEY: We don't know the answer to that question, but I think the best way to do it is to get a sense as to what the concern is about combining an antihistamine with a decongestant, if you think it's okay for the allergic rhinitis, you have a discomfort level with the common cold, I think you can opine on that, but -- but again, I'm still not clear as to what, if, if the antihistamine is found to be effective in the treatment of a common cold as a single ingredient and then the decongestant is also found to be effective for the treatment of the common cold as a single ingredient, and combining them doesn't seem to add any additional risk, I'm not sure why you would ban that specific combination.
To me it's a data-driven issue, too.
WILLIAM CALHOUN: Yeah, that's not my proposal. I was asking a question why not that --

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CHARLIE GANLEY: Yeah, I don't know why.
MARY TINETTI: Did you want to address that, Dr. Atkinson?
PRESCOTT ATKINSON: I can just say that as far as for use in the common cold it seems like the indications are fairly minimal in kids, certainly for allergic rhinitis, you know, decongestants and antihistamine, you know, both may be helpful.
Looking through the recommendations from the FDA committees, all of them recommended looking at eliminating or reducing the number of combo medications, so I thought it would be worthwhile discussing and see what other peoples opinions about it would be.
MARY TINETTI: Certainly addresses the concern of the potential overuse of the medication for sedation rather than for cold symptoms and that would be, that would be one reason for disentangling certainly anti-cholenergic effects in general are, that would be one compelling reason for doing that.
Dr. Newman.

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TOM NEWMAN: Yeah, it just seems maybe a little premature to vote on this since we don't have the data for efficacy yet and if the antihistamines turn out not to be effective for the common cold, then we don't have to worry about they're effective in combinations.

MARY TINETTI: That's been the point of all the questions we're addressing here, these are all, I mean that's common to all of the questions that we've voted on today.

But this one potentially in general, so I'm certainly fine about deferring this particular vote, if you guys are okay about that. Okay.

The, we've lost one of our labeling people so until she comes -- I think she's coming, she's gone, gone. Oh, okay.

Well unfortunately we've lost our labeling person, so Dr. Shrank, the next question had to do with labeling changes that can improve safety of combination products and you had mentioned, you had mentioned a couple, if you want to just for the record.

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WILL SHRANK: Yeah, I, well I just mentioned one specific request, that all combination products have some sort of warning that says that you don't take it with any other cough or cold medication. Yeah, I don't have any other suggestions.

MARY TINETTI: There was a question, there was a question raised here whether there should be a direct linkage between the indication and the ingredient, should that be --

WILL SHRANK: Sorry, and one other thing that I, it certainly we have to do a better job of listing the names of the medications that are, both the generic and the --

MARY TINETTI: And linked to a specific symptom, okay.

Anything else? Dr. Hennessy.

SEAN HENNESSY: Sean Hennessy, I'm not sure I can endorse the proposal to label products

containing antihistamines with something like do not use to sedate your child, that sounds like labeling cans of whipcream to say do not suck the nitrous

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oxide to get high.

I'm not sure that it will dissuade anyone from doing it and it may inform people who would do it about the possibility.

MARY TINETTI: Fair enough, well taken, okay.

Let me go back to, in the last couple of minutes here the question that I skipped and see if anybody has anything else they want to add.

Please discuss whether you believe, this is question 4, is that, question 4E, please discuss whether you believe the naming of the products contributes to consumer confusion and again, this is just a discussion question, we don't have to vote.

Dr. Cohen.

MIKE COHEN: I do think it presents a problem, it's not just with the cough meds but all OTC meds when there's a line extension. We heard Mr. Mannello mention the Dimetapp today. Originally that was Brompheniramine and there's several products now, none of them, or only a couple of them have Brompheniramine in them and I think it does

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cause confusion.

I'd like to see, again, you know, some of the things we've talked about, linking the ingredients with the purpose on the label in a more enhanced manner would help, but I do think it's a problem continuing to do this and wonder if there could be at least a moratorium at the very least and at the very least at least assuring that the original ingredient continues in that formula if that name is going to be used.

MARY TINETTI: Any other? Dr. Joad.

JESSE JOAD: I'm responding to your last, about the symptoms, one symptom I would recommend we not say is congestion because at least my impression is that that can mean runny nose, stuffy nose or gurgling out of the chest as it leads

three things that regular people will think means congestion, so I think it goes, you'll probably work on the best terminology, but that's not the right word.

MARY TINETTI: So you're suggesting congestion not be on the label?

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JESSE JOAD: Right, congestion is not a helpful word.

MARY TINETTI: Any other? Dr. Newman.

TOM NEWMAN: Yeah, I think this is clearly a huge cause for confusion and, you know, I guess what I'd suggest is that rather there having been a Tylenol, cold Tylenol, cough Tylenol, there would be, there could be McNeill cold medicine, McNeill fever reducer, McNeill and so on, but the generic name would be prominent because it is very disconcerting.

I just now found out that Sudafed, Sudafed PE is now phenylephrine, so, because you get, especially if you're used to the prescribing world where a brand name means a specific chemical and that's totally not the case in the OTC world where a brand name is for a product line and it's a big source of confusion.

MARY TINETTI: I think we all agree and I think we all have the same sentiments.

Let's see, Dr. Daum.

ROBERT DAUM: I think that's why it

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would be very helpful for this group to reconvene when we have efficacy data because some compounds will be efficacious, some won't. There's many issues that can be explored and discussed at that time and I think should be and I would really urge this to be a two-step process where we meet and discuss those results, efficacy trial results.

MARY TINETTI: Dr. Ganley, is that a, something that we can arrange, I mean that's going to be obviously several years from now, but it's duly noted that, okay. Okay.

Hopefully this will be our last comment, Dr. Rappley.

LAURA MARCIA RAPPLEY: I just agree with what the last two speakers said and so I have no further comment.

MARY TINETTI: You disagree?

LAURA MARCIA RAPPLEY: No, no, I do agree.

MARY TINETTI: Oh, you do agree, okay. Okay.

All right, well I think with that, I

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think we can wrap this up and I want to thank all of you for two days of attention to a very important problem. I want to thank the FDA and the petitioners and the industry and the Committee and hopefully you all get home safe. Thank you.

(Meeting concluded 3:54 p.m.)

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I, Monica Voorhees, do hereby certify that this transcript was prepared from tape to the best of my ability.

I am neither counsel nor party to this action nor am I interested in the outcome of this action.

Monica Voorhees