on pulse and systolic blood pressure. Most of the studies only reported data on the means for pulse and systolic blood pressure and did not report individual patient data.

In the 10 studies that reported data for pulse, seven studies showed no statistically significant or clinically relevant difference between phenylephrine 10 milligrams and placebo. In one study, there was a mean decrease in pulse of two beats per minute in phenylephrine treated subjects, in two studies; there was a mean increase in pulse between about two and eight beats per minute in the phenylephrine treated subjects.

In the 11 studies that reported data for systolic blood pressure, 9 studies showed no statistically significant or clinically relevant difference between phenylephrine 10 milligrams and placebo. In one study, there was a mean decrease in systolic blood pressure, and in another study, there was a mean increase in systolic

blood pressure in the phenylephrine treated subjects. Importantly, the mean increase or the mean decrease was not greater than three millimeters of mercury.

With respect to vital signs, in most studies, there was no difference in pulse or systolic blood pressure between phenylephrine 10 milligrams and placebo. When there were differences, the changes from baseline were inconsistent, were minimal, and were unlikely clinically significant.

I would now like to turn your attention to the clinical trials safety data from post-marketing safety databases. All spontaneously reported adverse events in the United States that were coded as serious from the post-marketing safety databases of individual companies participating in the phenylephrine task group were provided to, and reviewed by toxicologists at the Rocky Mountain Poison and Drug Center.

The combined post-marketing safety

database includes companies distributing approximately 76 percent of all over-the-counter phenylephrine containing single ingredient medicines in the United States. This represents about 280 million dosages distributed between -- since 2005.

The analysis found that serious adverse events with over-the-counter single ingredient phenylephrine containing medicines are very rare. The reporting rate for reports coded as serious was 0.15 reports per 1 million doses distributed. Dr. Richard Dart, a medical toxicologist and director of the Rocky Mountain Poison and Drug Center is here today so he can answer any questions that you have with respect to their analysis.

In summary, reported adverse events in placebo- controlled trials occurred at a similar rate between phenylephrine 10 milligrams and placebo. With phenylephrine 10 milligrams, there was no clear pattern of pulse and blood pressure changes. When

changes occur, they are inconsistent, small, and unlikely clinically significant.

Based upon available data, it appears that events may be dose related. The findings from the review of spontaneous reported adverse events from the combined post-marketing safety databases of the majority of companies distributing over-the-counter oral phenylephrine in the United States, is consistent with the FDA's conclusion that there are no significant safety concerns with oral phenylephrine.

Overall, given that there is more available data with phenylephrine 10 milligrams compared to 25 milligrams, in both clinical trials and post-marketing safety databases, moving to a 25 milligram dose at this time does not appear to be warranted. The currently available dose of phenylephrine, 10 milligrams, is well tolerated and appropriate for over-the-counter use.

I would now like to introduce Dr. Cathy Gelotte, who will discuss pharmacology and the pharmacokinetics of phenylephrine. Thank you.

MS. GELOTTE: Good morning, I'm Cathy Gelotte, senior director of clinical pharmacology at McNeil Consumer Healthcare. I will briefly highlight the pharmacology and pharmacokinetics of phenylephrine that support the following key points.

The first is that phenylephrine is a selective and potent alpha-1 adrenergic receptor agonist that causes vasoconstriction in the nasal mucosa leading to decongestion. After oral absorption, phenylephrine rapidly distributes out of the blood, into tissues and the site of action. Phenylephrine's pharmacokinetic profile supports the current OTC dosing regimen of 10 milligrams every four hours. And finally, the temporal relationship between plasma concentration and effect shows a classical lag time.

Doses of phenylephrine are well absorbed orally, but phenylephrine has low systematic availability due to extensive first-pass metabolism. It is markedly conjugated with sulfate in the intestinal wall. The absolute bioavailability of the drug may be estimated from the ratio of the area under the curve, when administered as an oral dose to area under the curve when administered as an IV dose.

We are aware of only one published study by Hengstmann and Goronzy in which the absolute bioavailability of 1 milligram of phenylephrine was estimated at 38 percent using a radio label technique. However, this estimate has not been confirmed with contemporary assay methods, which measure the unchanged parent phenylephrine directly.

I'd like to clarify what you heard earlier today about estimating bioavailability based on the ratio of the parent phenylephrine to total phenylephrine

derived from cleaved metabolites. This ratio was not valid because total phenylephrine is a surrogate for the conjugates and we don't know their distribution of volume.

Absolute bioavailability should be estimated as the ratio of the parent drug concentration from an oral to IV dose. Nevertheless, oral bioavailability is not a surrogate for relative drug efficacy and it is inappropriate to compare the bioavailability among drugs. Comparative efficacy depends on other important factors, including relative potency, drug concentrations at the target site and receptor affinities.

It is noteworthy that there are a number of effective drugs on the market with oral bioavailability less than 40 percent. As you can see, lovastatin's bioavailability is less than 5 percent but its efficacy is well known. At least one example listed here, chlorpheniramine is a systemically

active OTC ingredient.

Contemporary assay methods that measure plasma concentrations of unchanged parent phenylephrine are commercially available or have been published recently in the literature. Using liquid chromatography with mass spectrometry, the lower limits for these assays are 10 or 50 picograms per milliliter.

As we heard earlier today, some published pharmacokinetic studies report higher total phenylephrine concentrations in the nanogram per milliliter range, because older assays did not have the sensitivity to measure picogram concentrations of unchanged phenylephrine. Instead, plasma samples were digested with enzymes to cleave conjugate metabolites and then assayed for total phenylephrine.

Such methods obscure the true pharmacokinetic profile because the formation and clearance rates of the conjugates are

depicted rather than the kinetics of unchanged phenylephrine.

In two recent pharmacokinetic studies in healthy adults that use contemporary assay methods, plasma concentrations of unchanged phenylephrine after a 10 milligram dose range from 400 to 3400 picograms per milliliter for individual subjects. And they peaked between 15 and 60 minutes. The beta or terminal elimination half life was 2.5 hours.

The mean pharmacokinetic profile for unchanged parent phenylephrine after a 10-milligram dose is shown here in two figures. Plasma concentrations are plotted on the regular scale, and inset on the log scale for comparison. This profile is consistent with phenylephrine's 4-hour dosing interval.

It is important to place the pharmacokinetic profile in context with known scientific data of a given drug. For

example, the profile of unchanged phenylephrine shows a steep distribution phase that corresponds to its large volume of distribution estimated at 340 liters.

This volume considerably exceeds body weight indicating significant storage in the tissues. The rapid uptake of phenylephrine by transporters into adrenergic storage vesicles is consistent with less drug circulating in the blood and with this pharmacokinetic profile.

Another important point with regard to the pharmacokinetic profile and picogram plasma concentrations is that phenylephrine exhibits highly selective and direct action on alpha-1 adrenergic receptors. These receptors in human nasal mucosa preferentially constrict nasal arteries resulting in decreased blood flow. After a single dose, the rapid distribution of phenylephrine into tissues leads to nasal decongestion, which has been demonstrated in

multiple clinical studies in adults with viral colds.

A higher dose of 25 milligrams phenylephrine has been proposed to achieve greater efficacy. However, increasing the dose would be expected to increase Cmax and area under the curve without a proportional increase or extension of the 4-hour dosing interval.

To illustrate these non-linear changes, phenylephrine concentrations from the recent adult study were modeled using a pharmacokinetic software program. The blue curve, fitted to mean plasma concentrations is shown here for a single 10 milligram dose.

Next, the same parameter estimates were used in the model to simulate the pharmacokinetic profiles for two higher doses. The model assumes that the pharmacokinetics are dose-independent without significant changes in total amount of phenylephrine absorbed.

The simulated profiles for 20 and 30 milligram doses show relatively large increases in the peak concentrations in area under the curve. Yet the concentrations at later times do not increase as greatly and are closer to those of the 10 milligram dose. Typically, concentrations of drugs with short half-lives like phenylephrine may be increased at these later times when formulated into extended-release dosage forms.

Although, it's informative to measure or simulate plasma drug concentrations after a given dose, we know that the time course and intensity of drug affect depends on the concentrations at the site of action. Plasma concentrations are related to concentrations at the site and thus to pharmacological effects.

But the temporal relationship is often different. Available data for phenylephrine across pharmacokinetic studies

and clinical studies indicate a classical delay between plasma concentrations and the time course of effect. Specifically, changes in objective and subjective measures of nasal decongestion after a single dose in multiple clinical studies appear to lag behind the more rapid changes in plasma concentrations.

To illustrate the temporal relationship, the pharmacokinetic profile of phenylephrine from the recent adult study is shown here over 4 hours. Data on nasal airway resistance, a measure of nasal congestion were obtained from the four positive clinical studies that reported effect measurements up to 4 hours. These data overlaid on the same figure where the Y axis on the right side shows the percent reduction of nasal airway resistance inverted for an easier comparison across studies.

We see that the time course per plasma concentrations of unchanged phenylephrine are related to pharmacological

effects, but there is a delay in response. The time course curves for changes in nasal airway resistance are shifted to the right.

In summary, the pharmacokinetic profile of unchanged phenylephrine that is derived from contemporary sensitive assays supports the current OTC indication, which is the temporary relief of nasal congestion for a 10 milligram dose taken every 4 hours.

It is consistent with the selective and potent direct activity of phenylephrine and also shows rapid distribution of phenylephrine out of the plasma into tissues or the site of action. We could see from a cross- study comparison that the temporal relationship between plasma concentration and its effect on nasal airway resistance shows a classical lag time.

The current dosing regiment for 10 milligrams phenylephrine is suitable alone, or in combination, with monograph, analgesics, and antihistamines that have a

similar 4-hour dosing interval. Typically, the interval between doses of drugs with short half-lives may be prolonged when modified using extended release pharmaceutical technologies.

Product opportunities using this approach include the combinations of phenylephrine with analgesics and antihistamines that have longer dosing intervals from 6 to 12 hours. Now, I'd like to introduce Dr. Dretchen, who will review the clinical efficacy of phenylephrine.

MR. DRETCHEN: Good morning, I'm Ken Dretchen, professor and chairman of the Department of Pharmacology at Georgetown University Medical Center. I would like to review the efficacy of phenylephrine 10 milligrams in placebo-controlled trials.

There are 22 studies which could have potentially provided efficacy data in the public domain. Eight were excluded from further analysis for the following reasons.

The two studies from Schering have been previously presented today, and I did not have access to data to use that in my analysis.

Three studies did not use a 10 milligram dose of phenylephrine; one study was an abstract which contained little data; two published studies were primarily methodological papers and contained little efficacy data. The remaining 14 studies met the following criteria. All studies had at least a phenylephrine 10 milligram arm and all subjects had nasal congestion due to upper respiratory infections or allergic rhinitis.

Of these 14 studies, the FDA reviewer found that demonstrated a statistically significant effect on nasal airway resistance, commonly referred to as NAR. Of these seven, five also demonstrated statistically significant efficacy based upon subjective endpoints. Seven others did not

demonstrate a significant effect on either endpoint.

The FDA has a group of studies slightly different than the sponsor's briefing book. However, in an attempt to organize this data in a consistent fashion, I also used the FDA classification. The FDA reviewer pointed out several limitations in all of these studies. In the next series of slides, I will review both the positive and negative studies in greater detail, and my findings from the review of the available data.

This slide presents the results of 13 studies which evaluate the efficacy of phenylephrine 10 milligram using percent reduction of nasal airway resistance as the endpoint. The AHR G1-A study was not placebo-controlled and therefore could not be plotted.

The first column is a descriptor of the study. The next column indicates the

number of subjects that received phenylephrine 10 milligrams. The next figure portion of the slide provides a point estimate for the percent reduction and it is 95 percent confidence interval. Points that lie to the right favor phenylephrine over placebo, points that lie to the left would favor placebo, points that lie on the line show no difference between treatments.

Here is a table that presents all seven trials that demonstrated the efficacy of phenylephrine 10 milligrams in individuals with upper respiratory infections. I will also be showing you a similar table when I review the negative trials.

All of the trials were properly randomized and six of the seven trials were double-blind placebo- controlled. Four of the seven studies had active comparators which also separated from placebo. And all studies were either a parallel or a crossover design. Here you see the results of these

studies were all positive for the objective measure of NAR and five of the seven studies were also positive for the subjective scores.

I am now going to present the time-action curves for nasal airway resistance. And in a few minutes, we'll review the time-action curves for the subjective scores where the data is available. The key objective measurement from these studies was nasal airway resistance, which is derived by monitoring nasal airflow at a given pressure.

There are many factors that may affect the accuracy and reproducibility of NAR measures. Measuring nasal airway resistance accurately requires training and calibration of the operators. In addition, nasal airway resistance can be influenced by the nasal cycle, the presence of mucus in the nose and the fit of the mask over the nose.

Two alternative objective measures that occasionally appear as dependant

variables are peak nasal inspiratory flow and peak nasal expiratory flows. Nasal airway resistance, however, remains the predominant measure used across these studies.

Here is the first of the seven studies I have reviewed. To orient this is future slides the vertical axis is mean percent change in nasal airway resistance; the horizontal axis is the time point that nasal airway resistance was measured. I'll use light blue for phenylephrine 10 milligrams and grey for placebo. A downward deflection in the curve shows improvement.

The study by Cohen in 1975 is different from the other studies in that it was a parallel rather than a crossover design. In addition, it was a multi-dose study in which phenylephrine 10 milligrams was given every 4 hours over a 12-hour period.

This slide shows the data for nasal airway resistance, which was collected on 50

individuals, 25 controls and 25 treated. Phenylephrine reduced nasal airway resistance for the entire 120 minutes of this phase of the study.

The next slide shows NAR in the A.H. Robins 4010 study. Although the study included six centers, nasal airway resistance was only monitored at one center. There was a significant reduction in nasal airway resistance at 15, 45, 60, 120, and 180 minutes compared to placebo.

The third study shows the data from Elizabeth, Number 2, in which three doses of phenylephrine were evaluated and compared to placebo for an effect on NAR. As can be seen from the light blue line, the dose of phenylephrine 10 milligrams produced a significant reduction in nasal airway resistance from 15 to 120 minutes. The maximum reduction of 40 percent was observed at the 45 and 60-minute time points.

In the Elizabeth Number 5 study,

three doses of phenylephrine were evaluated and compared to placebo using a crossover design in 10 subjects with head colds and confirmed nasal congestion.

The 10 milligram dose produced a significant reduction in nasal airway resistance from 30 to 180 minutes. And the maximum reduction of 29 percent was observed at 60 minutes. Here we see the data from the Cintest 1 study where doses of phenylephrine 10 and 25 milligrams were compared to placebo for changes in nasal airway resistance. The results show significant improvement for phenylephrine 10 milligrams with 30, 90, 120, 180, and 240 minutes.

Cohen 72 also studied the efficacy of three doses of phenylephrine versus placebo in subjects with nasal congestion due to the common cold. This dose produced a significant reduction in the nasal airway resistance from 30 to 120 minutes. This is the seventh study in my review, the AHR-G1 A

study.

Phenylephrine 10 milligrams was compared to pre- drug levels. Phenylephrine produced significant reductions in nasal airway resistance at 60, 90, 120, and 150 minutes. However, this study did not include a placebo control. Next I'll review the positive studies for nasal airway resistance that also had sufficient data measurements to create a response curve for subjective measurements.

Subjective assessments include the use of a five-point ordinal scoring scale with zero representing clear or normal and increasing numbers signifying enhanced levels of nasal congestion. This study also represents the Cohen 72 study. The vertical axis is the mean percent change in subjective scores. The subjective impression of congestion improvement was noted from 30 to 120 minutes post dose.

The maximum reduction of

approximately 50 percent was seen at 60 minutes. The time action curves for the subjective scores and the reduction in NARs are consistent. A comparison of a solid and dashed blue lines show similar time courses and similar magnitude of effect.

In the Cohen 75 study, phenylephrine was given every four hours over a 12-hour period. The vertical axis represents the level of improvement as described by the subject. If there was a one unit change, it was scored slightly better. If there was a two unit change it was scored moderately better.

Phenylephrine 10 milligrams given every four hours produced significant improvement over the entire 12- hour study period. This study shows the efficacy of phenylephrine 10 milligrams on subjective scores in the AHR-G1 A study. Recall that this study lacks a placebo arm and the comparison is made with pre-drug levels.

Significant improvements in subjective scores were seen at 60, 90, and 120 minutes post dose.

Now, I'd like to review the seven studies that did not demonstrate the effectiveness of phenylephrine 10 milligrams and explain some of the reasons that the authors themselves reported as to why these studies might have failed to demonstrate efficacy. The first two Huntingdon Number 1 and AHR-7032 had no apparent deficiencies and in both cases, the active arm separated from placebo.

The next is the Lands study. In this report it was stated that most of the subjects did not appear to have congestion at baseline, and that hardly any further shrinkage of the nasal mucosa could be expected. In a study by McLaurin, there were two issues; the first issue is that congestion was caused by mixed ideologies ranging from the common cold, allergic

rhinitis, the hypothyroidism.

The second issue is that one-third of the initial participants dropped out of the study. In the Huntingdon Number 2 study, the Cintest Number 2 and Number 3 studies there were not positive controls questioning whether or not there was assay sensitivity. In addition, in Huntingdon Number 2 the authors mentioned that insufficient training of technicians, and the use of different technicians, pre and post dosing were possible explanations for the failure.

Next, I'd like to show two representative time action curves from these negative studies. This slide shows the results of the Huntingdon Number 1 study where neither phenylephrine 10 milligrams nor 25 milligrams separated from placebo.

The Cintest Number 3 study also failed to show a significant effect for any dose of phenylephrine compared to placebo. In addition to the individual clinical

trials, 2 meta-analyses of phenylephrine study data have been published, these are from Dr. Hatton and the CHPA. I agree with Dr. D'Agostino that individual trials should be considered as primary when evaluating the effectiveness of phenylephrine.

And that the meta-analyses should be considered as supportive. The only reason that we are presenting this today is because Dr. Hatton represented this as a significant component of the citizen's petition. Based upon the FDA guidance, clinical end point selection is a critical factor in meta-analyses. The FDA recommends the evaluation of treatment responses over time.

Hatton found that phenylephrine 10 milligrams, was ineffective while CHPA found it to be effective. The more significant difference between Hatton meta-analyses and the CHPA meta-analyses was the end point selected. Hatton used a maximum percent reduction in nasal airway resistance

regardless of when it occurred during the first 120 minutes.

Where as CHPA analyzed treatment differences in nasal airway resistance from baseline at all available time points up to 240 minutes. There are some other differences in methodology. However, as I will show, the critical difference is the choice of end points. CHPA conducted an additional meta-analyses using the Hatton methodology, but evaluated the area under the curve which is weighted average of the individual time points.

Using the Hatton methodology with the AUC as the end point this meta-analyses showed a significant treatment effect for phenylephrine 10 milligrams. Therefore, the clinical endpoint selected is the major factor of the differences in conclusions between Hatton and the CHPA meta-analyses. This slide shows the farthest plots for all 14 placebo-controlled studies using AUC

reduction in nasal airway resistance as the end point, similar to the one that I presented at the beginning of my presentation.

The studies shown in yellow are those used in the Hatton meta-analyses. Looking below the line at the combined data for these studies, it can be seen that there was a significant improvement. Furthermore looking at the line in blue when all 14 studies are included in the results, the results still favor phenylephrine 10 milligrams.

In conclusion, phenylephrine 10 milligrams has been shown to be an effective over-the-counter dose for treating nasal congestion in adults, based upon the following. Seven randomized double-blind, six of which were placebo-controlled clinical trials demonstrating the efficacy of phenylephrine 10 milligrams, five of seven trials demonstrating efficacy for subjective

scores, and meta-analyses confirming the effectiveness of 10 -- phenylephrine 10 milligrams. Now, Linda Suydam will summarize the presentations made today.

MS. SUYDAM: Thank you, Dr. Dretchen. You've seen in her data on safety, pharmacology, and efficacy of phenylephrine 10 milligrams, I'd like to take a few minutes to summarize a few points. While we are committed to adding to the body of evidence for phenylephrine and we'll work with FDA toward that goal, we have shown that there is sufficient data to support phenylephrine 10 milligrams as an effective and safe over-the-counter monograph ingredient for the temporary relief of nasal congestion.

Dr. Kuffner presented data from the body of clinical trial evidence for phenylephrine 10 milligrams, which showed a favorable safety profile. This is consistent with the FDA's conclusions on safety. Dr. Gelotte presented the pharmacology and

pharmacokinetic profile of phenylephrine that shows that phenylephrine is potent and highly selective, rapidly distributed into tissue and appropriately dosed at a 4-hour interval.

Dr. Dretchen stressed that the efficacy of 10 milligrams phenylephrine has been demonstrated by multiple double-blind randomized placebo-controlled trials in adults with colds using both subjective and objective end points. These positive studies were conducted in three independent research centers. We thank you for your time and attention and we would be pleased to take your questions.

DR. TINETTI: Thank you, again, before we break for lunch, just points of clarification; I used to have a question on the pharmacokinetics for those of us who are biochemically challenged. Can you translate for us picograms and nanograms; those are data that were presented on two different scales that showed drastically different

things and for those of us who are challenged can you translate for us?

MS. GELOTTE: Okay, let me see if I can do this straight off the top of my head. One milligram equals 1000 micrograms, equals, add three more zeroes, it's nanograms, and add three more zeroes it's picograms.

(Applause)

SPEAKER: So, probably -- thank you.

DR. TINETTI: Thank you, looks like those data are much closer when one thinks of it that way, thank you.

DR. FITZGERALD: Okay, I might have a slightly more challenging question, and I applaud the effort to relate plasma concentration to response using contemporary methodology and I'd just like to comeback to the question that I posed to Dr. O'Mullane previously, and that is, when you showed the data in response to 10 milligrams, the plasma concentration data, the Cmax was around 700

picograms per milliliter on average.

But the intra-individual variability in this very small study, ranged from 400 to 3400 picograms per milliliter at Cmax, and to put that in context when you simulate it, the Cmax for 20 milligrams and 30 milligrams of phenylephrine; the Cmax was roughly where 1300 and 2000 picograms per milliliter.

In other words, falling within the range of the intra-individual variability in response to 10 milligrams in a very small number of people. Now, given that we have heard earlier that there isn't one study designed appropriately to look to evaluate the impact of 10 milligrams or any milligrams of phenylephrine delivered orally on blood pressure, do you have any data that relates the upper bound of that range of Cmax after 10 milligrams to either a vascular reactivity or that can be interpolated on the plasma concentration response relationships of

phenylephrine to blood pressure after parenteral administration?

MS. GELOTTE: So to answer your question first, no, we do not. And one point I'd like to clarify in your questioning, in the slide it says the range is from 400 to 3,400 and that was the range across the two studies, the McNeil study and study published by Potasik. In the McNeil study with the model simulation it's still a board range, it's about 400 to 2000 picograms per milliliter. So still a broad range and that's really reflective of this significant variability and high first metabolism.

SPEAKER: Sure.

MS. GELOTTE: So the point of the -- these simulations was to look at what the dose would do on an average, for folks who aren't used to looking pharmacokinetics curves it doesn't necessarily push the curve out, it will push it up and then if you look at someone who is at 400, they'll move up if

you double it, maybe into that range, but someone at the high end, when you start pushing the dose to move up, but we don't have any cardiovascular data.

DR. FITZGERALD: Yeah, I mean I'm not challenging the use of the simulations and as I say, I come back to applauding the attempt to relate plasma constriction response, but the point that I'm making is there is variability in response to this as everything else. We have no information around a reasonable estimate of blood pressure impact of 10 milligrams, never mind 20 milligrams, and I certainly don't view adverse response reporting as a reasonable way to detect an estimated impact of around three or four milligrams, which can -- millimeters in mercury which can be clinically significant.

MR. KUFFNER: There were multiple studies where they did look at blood pressure with the 10 milligram dose.

DR. FITZGERALD: Yeah, sure.

MR. KUFFNER: And the vast majority of those studies didn't find a difference between --

DR. FITZGERALD: Well, just to put it in context, as I described earlier this morning, there hasn't been one study designed to look at blood pressure, paired appropriately to detect what would be a reasonable estimate of an impact on blood pressure which would be by back extrapolation from that high oral dosing that we saw this morning in the FDA presentation and effective around 3 to 4 milligrams on average -- millimeters on average of mercury.

And so the only way that you're going to pick that up is actually design a study appropriately to pick it up and obviously with hypertension, something that affects around 30 percent of the population, and you anticipating that such an effect might be exaggeration in a hypertensive

patient. The design of such a study in a hypertensive population would also be appropriate. So I don't think we've ever actually addressed the question.

DR. TINETTI: I think we'll be addressing more this afternoon, appropriate studies, so you -- let's focus specifically on clarification.

MR. OWNBY:: Dennis Ownby, I had a question for Dr. Kuffner and that is on, excuse me, your slide depicting the adverse events in Cohen 72, you listed the number of events, but it's not clear whether that each person had one event or whether there are multiple adverse effects for each individual in the study. So that makes a difference when you calculate the percent reactions.

MR. KUFFNER: For here you could actually determine whether it was one event per person for Cohen 72. There were some studies where you couldn't figure that out where there were multiple events reported and

you weren't sure if there were multiple events reported by one individual patient. But for Cohen 72 you could determine that incidence.

DR. TINETTI: No further questions? We will break for lunch and we'll reconvene again in, and at the time that we are set for, which is 1:25. And please take any personal belongings with you, the ballroom will be secured by the FDA and you won't be allowed back in until we reconvene.

(Whereupon, at 12:25 p.m., a luncheon recess was taken.)

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

(1:35 p.m.)

DR. TINETTI: So if everybody would please take their seats. Thank you. There is no one who has signed up for the open public hearing. If there are people in the audience, I am told that you can have a minute or less to make any particular statements that you might want. Is there anybody that would like to take the opportunity to say anything?

(No response)

DR. TINETTI: Okay, thank you. Then we can move on to the question period. And what we'll do is take the next several minutes for the members of the panel to ask any further questions of the FDA, the petitioner, or industry. Does anybody have any questions they would like to ask?

While people are thinking, I have a question for industry that relates to marketing of the products, and a couple of

months ago when we did have our presentation for the children, I remember a couple of graphs that were shown. And I don't remember the exact details, and I could be incorrect, that if you look at the percentage of the market that was -- pseudoephedrine versus phenylephrine, that has changed dramatically over the last few years, as pseudoephedrine became less actively available. And I don't remember where propanolamine was on that list.

But my question to you is, if the industry has felt that the 10 milligrams was effective, what is the historical reason why propanolamine and the pseudoephedrine had much larger share of the market until it became, obviously, external events changed that.

MS. SUYDAM: The Combat Meth Act, which passed in 2006, did in fact require pseudoephedrine to be put behind the counter, and PPA, FDA had asked to be removed from the

market. So -- but you know, we -- I think it was just a question of practice. And when it became unavailable to have a decongestant in front of the market -- in front of the counter, I think, people felt very strongly that there should be something that people could use, that they didn't have to wait in line. And so that's why reformulation happened. And so, you know, globally, PE -- many of these companies are global companies, had a PE product in their global markets, and then just decided to move PE into this country.

DR. TINETTI: But my question was why didn't the U.S. have PE on the market until the other two drugs were either no longer available or more complicated to be available? Why wasn't PE a larger share with the market before?

MS. SUYDAM: You know, I think -- as I said, I think -- I don't really know why it wasn't, but I think it was just common

practice that these products had already been -- Sudafed and PPA had already been in use in this country.

DR. TINETTI: But why was that? Does anybody --

MS. SUYDAM: Yeah. No. I think there is one other -- one thing is that it is easier to formulate the other two products rather than -- I think Dr. Gelotte pointed out that this is a highly active ingredient.

MR. DANZIG: So if you look back at the history of a product like Dimetapp, it actually had phenylephrine in it. There was the Bickerman study, and after that phenylephrine was removed, and it left phenylpropanolamine. And when the FDA began deliberations about that, they switched it to pseudoephedrine, and then now they've switched it to phenylephrine. So I think -- there were very few products. There was Allerest and Dimetapp were the only ones that had phenylephrine in it, and I think it was

because of the data, of Bickerman and some of those studies that came out in the late '70s.

DR. FOLLMANN: Yeah, Dean Follmann. I have a question for the FDA. And I'm trying to, sort of, calibrate a bar for what I think effectiveness means. And I was curious to -- well, it was interesting for me to read what the chair to the old panel was, and I'll reread it here. A reasonable expectation that in a significant proportion of the target population, the pharmacological effect for the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. So that's a certain, you know, verbiage to describe effectiveness. And I wondered -- it seemed to me different than the verbiage people would use for prescription drugs. So my question is, what is the standard for effectiveness of prescription drugs, or is it the same?

DR. TINETTI: You are addressing your question to the FDA?

DR. FOLLMANN: Yeah, I seem to, you know, recall like two well-controlled studies or multiple studies --

DR. TINETTI: Okay. Who wants to take that?

DR. FOLLMANN: -- and I think, the bar for that.

DR. JOHNSON: I can take it up. I was hoping that our folks from DPAP would be back to --

DR. TINETTI: Do you want to defer that until -- there's other questions?

DR. JOHNSON: Well, let me just say, while you're -- before we have a chance to have them back, in general, an NDA would be supported by two adequate and well-controlled studies. I think the DPAP folks made the point that for seasonal allergic rhinitis, you'd need two natural seasonal allergic or perennial allergic

trials, and that the EEU studies wouldn't be considered anything but supportive in that circumstance.

The reason that the monograph looks different is because the whole process for putting drugs into the monograph was different, and it was based on literature on existing data at the time.

DR. FOLLMANN: So that was sort of a historical definition of ineffectiveness. My question now is, so is there a distinction between over-the-counter drugs and prescription drugs? And I guess you are saying there isn't.

DR. JOHNSON: In general, if a phenylephrine product came in today, and was entrusted in, for example, an immediate release product or a sustained-release product, we would be looking at a bioavailability comparison. And that came up with Combat Meth. We were specifically asked how we would go about enhancing the process

to reformulate and make it more efficient. And we responded that basically that would be based on biocoolants.

DR. FOLLMANN: So that sounds different than sort of two well-controlled studies with a clinical endpoint.

DR. JOHNSON: Well, the assumption there is that based on the findings in the monograph, that the phenylephrine dosing is safe and effective. And that if you match it with bioavailability data, bioequivalent data, that you are set.

DR. FOLLMANN: So in some ways, maybe it's sort of grand-fathered in or it was accepted based on that old definition, and therefore it just needs to show it's bioequivalent.

DR. JOHNSON: Well, in the NDA world there is an application called a 505B2 that is reliant on data that isn't submitted in that application per se. And what's not submitted in an application like that, for a

phenylephrine extended-release product would be what was found in the monograph. They would be relying on that.

MS. PARKER: I just wondered if someone could speak specifically to any of the -- what would be considered the most recent -- and this would include whether or not there's anything ongoing currently -- effectiveness look at the 25 milligram dose. It seemed to me that the more recent studies focused on, I guess, the twelve, just because maybe that was the EU formulation of it.

But given, sort of what, you know, the safety profile that's been presented historically about it, this whole idea, particularly as the market has shifted with what's happened with other products, to looking at the 25 milligram dose and whether or not there is anything ongoing about that?

SPEAKER: Slide on please. Slide on. Slide on. Oh, I'm sorry. So much for my commands.

(Laughter)

DR. TINETTI: Are there any other questions while we are waiting for our projector to wake up?

MR. OWNBY:: I have one for Dr. --

DR. TINETTI: We will solve here this -- sorry.

MR. OWNBY:: Dennis Ownby. I just had one question for Dr. Dretchen is, unless I missed something, it looks like in terms of efficacy and the nasal airway resistance test, it's only the Cintest 1 that showed efficacy at 240 minutes or 4 hours. Is that correct?

MR. DRETCHEN: On the single-dose study -- on the single-dose study, you are correct that the Cintest 1 is the only one that went out to 240 minutes, showing effects. On the other hand, some of the other studies still showed effectiveness at 180 minutes over there. Do we have the -- and can I comment on the multi-dose study?

Can I show the --

SPEAKER: The Cohen 75 --

MR. DRETCHEN: -- the Cohen 75 study? Slide on please. The reason I wanted to just bring this one up is that this was a -- this was the multi-dose study that the -- the Cohen study, and this one was, dosing every 4 hours. And so I would ask you to pay attention if you will to the four-hour mark, the eight- hour mark, and the twelve-hour mark, because each of those represents the end of a four-hour dosing period. And you can see that throughout each of those four-hour dosing periods, by the blue stars, that in fact there still was a significant effect at the 240 minutes. So I would say that, in addition to the Cintest No. 1 study, this study also shows an effect, over the -- over a four-hour time period.

DR. TINETTI: Do you want to go back to your previous --

MR. DRETCHEN: Oh yes, I forgot.

The -- no, not that one, the -- slide on. These are the ten studies that I was able to come up with, where a dose of 25 milligram was evaluated. And you are correct that if you look at the studies, I mean, they are the -- some of them are the original studies, and they are studies that were done in the, you know, in the '60s and the '70s. And in this case as be -- the FDA also saw that seven out of the ten studies showed an effect on NAR with the 25 milligram. And there were three studies that showed an effect on the subjective measurement.

And just as a point of comparison, if you recall with the 10 milligrams, it was seven out of fourteen for nasal airway resistance, and five out of -- and five studies showing an effect on the subjective evaluation.

DR. KOENIG: The last 25 milligram study, I agree with you, was the Cohen 72.

MR. DRETCHEN: Yeah.

DR. KOENIG: I'm not aware of any other studies that have looked at twenty five --

MR. DRETCHEN: I've not seen anything past the Cohen 72 study.

DR. KOENIG: And the other question that I wanted to address was the question about the duration or the last effective time point. According to our -- and were you asking about -- I forget who asked the question. Was it about the 10 milligram dose or 25?

MR. OWNBY:: It was about the current 10 milligram dose.

DR. KOENIG: I show that three different experiments that had it at 240-minute time course, the effect -- the last effective time point was at the 180 minute. That's in terms of reducing NAR.

DR. TINETTI: So you are saying that there are -- no studies show effectiveness at 240 -- four hours?

DR. KOENIG: I guess not -- not at the 10 milligram dose.

DR. TINETTI: Not at the 10 milligram dose. Okay.

DR. KOENIG: There were some at 25 milligram.

DR. TINETTI: Right. But not at the 10 milligram.

DR. KOENIG: Right.

DR. TINETTI: Okay.

MR. DRETCHEN: Can I just comment -- slide on, please. Yeah, but again, as we were just saying before, the Cintest study -- it's on the screen now -- it shows a significant affect at the 240-minute period with the 10 milligram dose.

MR. WYETH: When this study was analyzed, reanalyzed, we included baseline in the model, which I do not believe was included in the original analysis. So that probably accounts for the slight discrepancy.

DR. TINETTI: Well, can you say

that again?

MR. WYETH: When this study was reanalyzed for the presentation, baseline was included in the model. And it probably was not included in the original analysis. So that could be explaining the discrepancy.

DR. TINETTI: So you reanalyzed --

MR. WYETH: Yes.

DR. TINETTI: -- data that had been -- okay.

DR. JOHNSON: I'd just like to make a comment about end-of-dosing-interval efficacy. Where phenylephrine to have consistently shown efficacy at four hours, I think the original advisory panel may have had to look at giving it a longer dosing interval, one of the reasons why the dosing interval on the label is limited to four hours is because you are seeing that trailing off, perhaps at the end. So if we were to say, get a brand new NME and it were still to show efficacy at four hours, we might

consider whether or not it should actually have a longer dosing interval. If it were still statistically significant at the end, and a lot of it would depend on what precisely the data looked like, whether efficacy was curtailed close to four hours, a little after four hours, that sort of thing. So the fact that there aren't a lot of four hours, I don't think necessarily means that it works a lot less long than that.

DR. D'AGOSTINO: Are we still giving our names? Ralph D'Agostino. I wanted to second that, because we went through that with some of the analgesics and so forth, and if they maintain over the time period, then why would you give another dose. And so you are looking for a falloff where you can justify giving another dose without beginning to overdose.

MS. HOFFMAN: Ruth Hoffman. My question is for the industry. So just to follow up with the 25 milligram dose, you

mentioned that actually it showed better efficacy with the NAR seven out of ten versus seven out of fourteen studies. So is -- I guess, is there a lack of push to, you know, favor that because of the 80 percent AE reported. So patients, you know, might not want to continue to take it because there are higher incidents of AEs?

MR. DRETCHEN: Slide on please. So there were -- of all these studies, there were four studies in which there was, if you will, a head-to-head comparison of the 10 to the 25 milligram study. And I have shown those on the screen. And as you can see it, the one study, the Cohen study, there was insufficient information to compute, you know, the standard errors. So I really couldn't make that point of comparison. But if you look at the other three studies, in only one of the three studies, the Elizabeth No. 5, was there a significantly greater effect of the 25 milligram over the 10.

And in the other two studies, the effects between 10 and 25 were not significantly different from each other. So the point I was trying to make in looking at the slides that in both subjective and objective scoring, that both 10 and 25 are shown to be effective. But from a viewpoint of a statistically significant effect, there is no difference between the 10 and the 25. And coming back, you know, the 10 milligram dose is the lowest effective dose that there is, and it's safe and it's effective and that's the point.

MR. KUFFNER: Yeah, from a specific safety perspective, when you look at the body of the data and you look at all the adverse events, and I showed the -- one Cohen study where they directly compared the adverse events with 10 milligrams and 25, there is a suggestion that there are a greater incidents of adverse events with the 25. That being said, all of those adverse events, whether it

was 10 milligram or 25, as Dr. Koenig pointed out, really were non-serious adverse events. When you look at all of the vital sign data across the board, there is a suggestion for pulse -- that increases in pulse occur more frequently with the 25 milligram dose compared to the 10 milligram dose. And when you look at mean increases in both blood pressure and pulse, although those mean increases are smaller, they are higher with the 25 milligram dose.

Again, that being said, across all doses, the mean increases in pulse were less than 11 beats per minute, and the mean increases in blood pressure were less than 4 millimeters of mercury. When you look at all of the post-marketing safety data, it doesn't suggest a signal for 10 milligram, and that's where we have the most post-marketing safety data. And in terms of safety data, there is five times as much safety data from these clinical trials for the 10 milligram dose.

So when you ask me as a toxicologist, is there a difference, I feel very comfortable with the 10 milligram dose. In terms of the amount of data that we have for the 25 milligram dose, we don't have as much data. And certainly, it doesn't seem warranted at this time to go to a 25 milligram dose.

DR. TINETTI: Nelson.

DR. NELSON: Yeah. Nelson. Yeah, I'm trying to remember my name now. A question for Dr. Hendeles. In your -- given all the data we've seen or heard today, and had in our packages, where obviously it seems like the same number of studies show efficacy at 10 milligrams, and there are studies that show 25, and you can do NAR and you can do a subjective, why didn't you propose offering a 10 and a 25 and eliminating the dose which we know is safe and effective, or at least, based on all the data that we've seen in this review?

MR. DANZIG: After our -- we deliberated this issue, and it was our -- I was really convinced, especially after seeing the Schering data that if you have a stuffy nose, and you take 10 milligram, you are going to still have a stuffy nose.

DR. TINETTI: Marie Griffin.

DR. GRIFFIN: I just wondered if we could have a little more discussion from the FDA about the efficacy question about -- when we are answering these questions, what is -- is the definition that we are supposed to look to the one in the monograph about that Dean just quoted about being significant -- in a significant proportion of the population, clinically significant effects, or is the question -- does it have any efficacy?

DR. JOHNSON: I think the first question -- and we haven't gotten to actually reading the questions -- is designed to address that. Because one of the things that

we need to hear from the committee is what your level of comfort is with this data, and what data amongst all of these studies helps you understand what's supportive, what's not supportive. I think in terms of a statute regulation, something that expressly says what threshold we need to meet. We don't have one for the monograph except what's been written down in the codified section, and that was a charge to the advisory panel. And they though they'd met it with the data that they had.

DR. FITZGERALD: So I would suggest that the message from the absence of a clear dose response relationship on the efficacy side which we've heard both from the group data presented from the FDA, and most recently at the slide that was just last shown. Really, it is entirely consistent with the most elegant plasma concentration response data that are available and that were shown to us earlier this morning,

whether it's a high degree of heterogeneity in the plasma concentration response to delivery of 10 milligrams, and almost certainly, a high degree of heterogeneity in response to 20 milligrams, although we don't have the data. And given that the sample sizes of these studies are so ridiculously small, the likelihood of being able to detect even a dose response relationship with respect to efficacy would a priori, be extremely low.

And as for the safety issue, I'll come back to the fact that we don't have a study that addresses the likelihood of the most plausible increase in blood pressure in any convincing way as any dose, and to say that the absence of a signal, given the fragmentary information that we've got, means that there is not a cardiovascular effect, is at odds with reality.

DR. FOLLMANN: You know, I wanted to talk a little more about the dose response

effect between 10 and 25 milligrams. And if the slide that was just up there which showed the four head-to-head studies, head-to-head comparisons, I guess, the point I want to make is it's not so clear to me that there is not a dose response relationship. If you go through the -- just the tally, which is not sort of a great way to summarize all the data, but if you look at what's significant, there are more instances where the 25 milligram is significant compared to placebo than the 10 milligram.

Similarly when you look at the meta-analysis done by the petitioner, they get a much, well, a stronger and significant effect of the 25 milligram dose using their random effects meta-analysis, using the maximal difference as the outcome.

This slide, you know, is kind of interesting. It is true that there is just one out of three that is significant. But if you would combine the studies, if you do a

fixed-effects meta-analysis for those three studies, you get a very significant effect of a dose of 25 versus 10, if you do a random effects, I've done these calculations out, actually because I think the answer is not clear about 10 to 25 milligrams. But if you do a different analysis, it's not significant.

Finally, Wyeth presented a nice table, or figure rather, of the effect size versus the dose. And to me, when you do a plot like this, it's screaming to me that you would do a meta-regression where you try to fit a line through this data and see whether it's significant or not. They presented this figure and just said, basically, it looks like not much is going on. And so the question I have, I guess, is for anyone who has analyzed this data, was meta-regression fit, where you tried to look at a dose response relationship for all the studies in just stead of those, you know, for that

head-to-head.

MR. DRETCHEN: Well, maybe I can take just the first question and turn to my colleagues here for the others. So in terms of the slide, yes, there is only the four studies, and only one shows a significant effect right now. But potentially, there is a trend. And again, if more studies were done, it is conceivable that you might see a greater effect of 25 than a 10. But the issue before us today is, is ten, you know, an effective concentration for the treatment of congestion. And I think that the results of at least the seven NAR studies and the five subjective studies, you know, point out that, in fact, that is correct.

SPEAKER: If you may --

DR. TINETTI: Can I just follow-up a question -- really follow-up a simpler question is, what would have to be the sample size in those studies to have a statistically significant difference if there was one?

MR. WYETH: Okay. Well actually the studies were not quite as powerless as the small sample size would imply, because it was crossover in nature. Every active dose group had its own placebo group. So the error that was contributing to it was within subject error. And that explains why we did have some positive results with the small sample sizes.

DR. TINETTI: So the question again is, if you were to power -- to detect a difference, if there was a difference, what would be the sample size that would be needed?

MR. WYETH: Well, we would have to consider what type of study to do today.

DR. TINETTI: No, I'm talking about the exact studies that you did now. I mean, I'm sure that among -- can we have the slide back on?

Using the design that you had, the crossover, I understand that there is less

deviation, the sample size can be smaller, but what -- I can't believe that one of --

MR. WYETH: Slide on.

DR. TINETTI: -- don't know the answer to that question. So we are seeing a difference of 29 versus almost 39, 11 versus 10, 18 versus 31, and 31 versus 38. To see a difference if there was one, what would the number have to be -- the sample size of these studies?

MR. WYETH: Well, it depends not only on the true difference that might exist. It also depends upon the variability and --

DR. TINETTI: Right.

MR. WYETH: -- it has been mentioned there is --

DR. TINETTI: Right, I understand.

MR. WYETH: -- quite a lot of heterogeneity.

DR. TINETTI: So in other words, you don't know. But is it fair to say that we cannot conclude from these numbers that

there is not a difference.

MR. WYETH: We are not claiming that the analysis disproves dose response. We are just simply --

DR. TINETTI: I beg to differ. And I think the question -- the point we -- was raised is that these data show there is no difference. So --

MR. WYETH: I believe what we were saying was that, at this point the data may not be sufficiently convincing.

DR. TINETTI: Thank you. Okay.

MR. WYETH: Okay.

MR. DANZIG: You may recall when Dr Hatton was making his presentation, he had actually a slide where he drew a regression line against the doses of the Elizabeth lab and showed that the line was flat, whereas there was -- and if you left those off, all the other studies with the 25 had a significantly different slope from zero. I think it was the next to the last slide where

he drew that, if you can look at that.

So our conclusion -- you know, all of the Elizabeth data came up with the same results regardless of what the dose was. And those results were just proportionally large compared to any of the other studies.

DR. JOHNSON: The panel did look at the 25 milligram dose, because there were studies that existed at that time, obviously. They did, in general, find it more effective than the 10 milligram, but had more concerns about the safety, particularly the number of adverse events. And on that limited data set, they were more comfortable with the 10. I also wanted to ask Dr. Chowdhury if he would make comments about dose response in this -- disease states that we are talking about.

MR. CHOWDHURY: I'm Dr. Chowdhury. I'm the director of the division of pulmonary and allergy drugs. I just wanted to make a few comments about dose response of these

types of drugs. And the comment I will make is mostly applicable for allergic rhinitis, because that's where we have more experience. And as a top level I would say that it is very difficult to show dose response for these drugs. And this is mostly true for patient-driven symptom scores.

And for example, for antihistamines, it is not uncommon to see in well-conducted clinical trials in the current standard to have a couple of four differences of drug doses showing flat dose response. And even for another drug class, which is nasal corticosteroids, which is a common drug used for allergic rhinitis, the dose response is actually quite flat.

And to discuss that topic a couple of years ago, we had an advisory committee. And the advisory committee was called upon to see if one could show dose response, and the intent was to use that model for developing of generic drugs. And at the meeting, we

presented data showing that up to sixteen-fold differences of the drug showed no dose response. And we have a draft guidance, where actually we ultimately concluded that you cannot show dose response, therefore we would not expect dose response as part of the development program for developing generic drugs.

So that is for allergic rhinitis, and that usually includes symptoms of sneezing, itching, rhinorrhea, and congestion. And now if you take just congestion as one entity, I would still probably say the lack of dose response problems may still apply. Thank you.

MS. PARKER: I had a question. There was -- this is Ruth Parker. There was -- we heard that there had been 5 billion dose -- over 5 billion dosage units of the oral PE distributed. One question was whether or not that's all single ingredient. I think any of us who ever go to the store

and buy anything for cough, cold, stuffy nose et al., know that we have a lot of choices that we face to try to figure out what -- what happens even if you understand some pharmacology.

So one question I have is whether or not that's all single product -- single ingredient, which I actually think is a good idea, and something that we've talked about at other meetings. But I'm also curious to know whether or not the 10 milligram and the 20 milligram exist in combination products, and how many different types of combination products there are that have those various doses included with them.

MS. SUYDAM: The number that you quoted does include combination products. And the vast majority of phenylephrine products are in fact in combination. And I can't tell you the exact number of how many there are, but obviously a significant number. And it's a 10-milligram dose. There

is no 20-milligram dose -- no 25-milligram --

SPEAKER: In any --

MS. SUYDAM: No.

MS. PARKER: So just to be clear, the vast majority of the product that exist on the market, exist not as a single ingredient, which is really the focus of our meeting -- the single ingredient product. I assume, the vast majority of the compound itself that exist on the market for consumers exist with combination products, and I assume, in various combinations with various products.

DR. JOHNSON: Do you want me to clarify? We are not just interested in the single-ingredient products. We are interested in that dose though. So it's the dose of that single ingredient rather than a product that contains only that single ingredient. The combinations are allowed. Does that clarify?

I think there might be some

confusion because we actually presented the errors data based on the single ingredient products. And that was to begin -- start to limit what is a large database that has many combination products in it.

DR. TINETTI: Is the same also true of pseudoephedrine? Is that primarily as a single product -- single ingredient, or is that also primarily as part of a multi-ingredient?

MS. SUYDAM: I think the slide will show you that both pseudoephedrine and phenylephrine are primarily in multi-ingredient products. So you'll see that combination -- all adult decongestants, 10 percent are single-ingredient, 90 percent are multi-ingredient.

DR. TINETTI: But it's 24 percent versus 6 percent. Why that difference? It looks like 6 percent of the -- only 6 percent of the phenylephrine is a single ingredient versus 24 percent of pseudoephedrine. Why

the -- four times as much. Why is that?

MS. SUYDAM: I really don't know the answer to that, and I don't think anyone else does. We don't have any consumer research on that.

MS. PARKER: So this actually means that if you want to go buy this, it's hard to do it. I mean, because most of the products that you are going to see in front of you are a combination rather than a single ingredient for the 10 milligrams. You could find it.

MS. SUYDAM: There are many single-ingredient products on the market, but it's the percent of sales -- people tend to buy the combos more than they buy the single ingredient.

DR. JOHNSON: I think Dr. Hendeles has -- had probably showed one of the more widely sold and widely marketed products. One of the first products to be reformulated with phenylephrine was the Sudafed product. And the Sudafed PE, not the entire family of

Sudafed products, but Sudafed PE is a single-ingredient phenylephrine product.

DR. TINETTI: I mean, in previous meetings you've made probably a pretty cogent point that people vote with their dollars and they -- if they think something is going to work, they buy it. And I'm just sort of curious. Would you use that same example here that they are not buying the single-ingredient phenylephrine because they don't perceive it's as effective as the pseudoephedrine? I mean, does that decision work both directions?

MS. SUYDAM: I'm not sure that people are -- I think people are buying the product because they are looking for other symptom relief, in addition to the decongestion. And that's why they buy the combo product.

And did you want to say something?

MR. KUFFNER: When you actually go -- when you look at consumer satisfaction

data, the consumer satisfaction data is similar whether it's phenylephrine or pseudoephedrine, both on the single-ingredient products and on the combination-ingredient products.

DR. FITZGERALD: So we -- just coming back to this point again -- we saw an eight-fold variation in Cmax for phenylephrine alone. And given that it's mostly sold with -- in combination, have there been any studies by anybody to determine whether those combined products contribute further to variance in the kinetics of phenylephrine or its dynamics?

MS. GELOTTE: No, I'm not aware of any studies. The assays and the methods of the studies you've seen today have been done this year.

DR. HONSINGER: Just a comment to sort of reconfirm what -- this is Dr. Honsinger, what Dr. Chowdhury just said, having done allergic rhinitis studies and

seeing allergic rhinitis patients everyday, patients can claim they are better. They can't claim how much better. And we have tried all sorts of means of identifying with various scales whether you're improved to how much you improve. So it's very difficult to tell dosages, although then you try a patient on a higher dosage and they do do better. So I think clinically we know that some of these things, the higher doses work better, but it's hard to prove it.

DR. JOHNSON: If I could just make a couple of clarifications that may help. One of the issues regarding combinations of phenylephrine is that phenylephrine compared to other monograph, the cough, cold ingredients, has a shorter dosing interval. It is only 4 hours, versus the antihistamines and some of the other expectorants -- cough suppressants have a 4- to 6-hour dosing interval. So you saw fewer combinations in general with phenylephrine, because

phenylephrine would limit the number of doses and number of times a day that you could actually use the product. And so that may have influenced the marketing of phenylephrine.

With regard to the kinetics of the combinations, under the monograph, there were policies set out with regard to what you could combine with what. And I hesitate to use the analogy, but it is a bit of a Chinese menu, one from column A, one from column B is how it was structured because those were the products that were marketed when the monograph was set up. So for product combinations of those ingredients in immediate release dosage forms, you would not need to see kinetic studies.

We are starting to see more of them as there are more extended release formulations being reformulated with phenylephrine. And we may know more in future.

DR. SHRANK: This is a question for industry. It seems that the two recent and larger trials, the Vienna challenge and the Canada trial, both didn't show any effect for phenylephrine, and their older studies that do. And I just wondered how you reconcile these newer results with the older results, and you thought -- and how you think that these newer trials fit into the picture?

MR. DRETCHEN: So the chamber trials, as discussed earlier by the FDA, the chamber trials really are considered to be more of secondary and supportive trials. They are good if they were making determinations of, say, onset of action, or for duration of action. But in terms of looking at efficacy per se, the actual clinical trials are still considered to be the primary source of information.

DR. JOHNSON: Would it be all right if Dr. Chowdhury had a comment -- oh sorry, Dr. Lee.

MR. LEE: I guess I'd just like to, you know, point out, we know a fair amount, and we've seen a fair amount of chamber studies for allergic rhinitis, single- dose studies. And generally, as you are probably aware, there are other symptoms that are followed in these, nasal itching, sneezing, rhinorrhea as well as nasal congestion. The nasal itching, rhinorrhea and sneezing are more directly related to mediator release, whereas the nasal congestion, in addition to some component from vascular leakage over time, there's an element of information that's present.

And in this circumstance, the studies for allergic rhinitis are -- the studies for allergic -- are done for allergic rhinitis. It's not a model that actually is relevant to the common cold indication. In addition, the -- it might be risky to assume that a drug doesn't work based on a negative chamber study showing nasal congestion,

particularly when a lot of these drugs are used for treatment of common cold just as much, if not more, than for the treatment of allergic rhinitis.

Particularly since -- the other thing too is that very commonly in allergic rhinitis we will have studies that may be negative. We can expect some studies to be a negative with a drug that is actually effective. So again, I just -- I think I want to point out that that when we start to look at or draw conclusions from the chamber study for allergic rhinitis for one symptom, it may be a bit of a far stretch to take that all the way to where we are talking about, no efficacy for a drug, for a different indication, the common cold.

DR. TINETTI: Let's have one quick question for the FDA. Are any of the studies that we've talked about today -- are any of them non-sponsored by an industry, or are they all? Do we know?

DR. KOENIG: We have some studies that were in the published literature. I can't say where the funding came from to conduct --

DR. TINETTI: I mean, just -- I didn't necessarily mean where the funding came from, but who performed them.

DR. KOENIG: Oh, well, we have the study by Cohen in 1972 in the literature. And we -- there are also some other published studies in literature -- in the published literature.

DR. TINETTI: Any other comments, or can we go on to the questions? Okay.

So I think if you all have your questions in front of you. The first question is a discussion question. So I'll just read it and make sure that we all understand what we are being asked before we start on the discussion.

So the question read, the many studies discussed today in which the efficacy

of oral phenylephrine hydrochloride as a nasal decongestant was assessed differ in many ways -- include in terms of patient inclusion criteria et cetera, the congestion model, whether it's naturally occurring, induced by exposure to pollen, in an environmental exposure unit, endpoints objective, reduction in nasal airway resistance, and subjective improvement in symptoms, and dose 25 versus 10 milligrams, dosing interval, and endpoint assessment interval.

And also the studies have been considered in several different groupings. Studies evaluated by the advisory panel -- initial advisory panel, discussed in the ANPR, and the two meta-analyses. So the agency would like us to discuss which aspects of the data, if any, that it finds supportive of the effectiveness of phenylephrine for the symptomatic treatment of nasal congestion.

I guess one question I would have,

are you asking us specifically -- data that presently exists that support the effectiveness, or are you asking what data we would like -- we think is most compelling to -- if we were going to assess effectiveness?

DR. JOHNSON: The current data of what you've already heard.

DR. TINETTI: Okay.

DR. JOHNSON: There are questions later that address what you may like to see.

DR. TINETTI: Okay. So this is not a voting question, this is just a discussion question. So any discussion on that point or -- so the question we are asked to discuss, which aspects of the data we've heard today, if any, support the effectiveness of phenylephrine for symptomatic treatment.

DR. D'AGOSTINO: I'd like to -- Ralph D'Agostino speaking. I'd like to just remind the advisory committee as we review this material that the studies we have before us that have been reviewed and the studies

that went into the previous deliberations were basically considered state of the art at that time.

I can remember reading the Federal Register where it said, you need to have objective measures, and you need to do crossover designs. We've dropped the crossover designs a lot earlier than we did the objective measures. So in reviewing these, I think we have to keep that in mind. And also in reviewing these, that no one at that time -- and I was involved with some of these different panels -- no one at that time was talking about the things we talk about today that do you have a generalizable study, do you -- have you covered all the age group, have you covered the genders, have you covered the races.

So there was a very narrow -- could you pull together a group of individuals, and then a crossover design and show an improvement in relief. And we have before us

a number of studies that do that.

I think the positive studies, especially the ones that have active controls involved in them, the results are there. We may ask the question, should we do something better today, or would we do something better today, and whom should we advise. That's a different question. But based on the data and based on the science and what have you, which I think was quite solid, but very narrow, we do have seven studies. I believe the number is -- that do show significant improvements in the particular variables of interest, both the objective and subjective measures.

DR. FOLLMANN: Yeah. So I guess we'll comment upon the question first, and then take the vote. So it's true that there are several studies here which show a benefit of 10 milligrams. And it could be that, you know, this is somewhat influenced by the Elizabeth studies, and it could be that the

technicians there just know how to get a more reliable measurement.

To comment about the meta-analyses, I thought that they came up with a kind of overall similar conclusions, that they're sort of right on the boundary of a PO 0.05. They use different methods. They use different endpoints and so on, and yet at the end of the day, if you look at the meta-analyses, you know, it's a little murky for me, I guess.

You can always pick studies that show benefit, and you can always, you know, and you can also -- always pick studies that don't show anything. And the problem I have is I don't really know which ones to pick. And so I would tend to look at the meta-analysis -- the totality of the evidence more, and for me that's a bit murky.

I think someone -- I think it was Bob Temple gave -- was quoted here earlier, and he said, what good is meta-analysis for.

And he didn't think much of it, basically. You tried it out when you know what the answer is. And I think meta-analysis for me in this case is more to generate hypothesis. I don't really see it as settling an efficacy question here.

So all in all if I had to really bet whether the milligram work, I would say it probably does. But I don't really know based on the studies I've seen here today. I guess another point I would make -- my comments have been focused mostly on the NAR, the objective measurement, and I think it's even murkier for relief of clinical symptoms. And if that's an important thing that we should rule on, I think the evidence is weaker for that.

DR. HONSINGER: We do have pseudoephedrine as an effective drug. And yet very few of the studies that we have seen, very little evidence has made a comparison between a drug that we think is

effective and have better evidence for than this drug. So I think the one thing we need to do is we need to look at that, and whether a higher dose of this would be beneficial, particularly in the light of pseudoephedrine being converted to methamphetamine and those being put behind the counter. Could a higher does replace pseudoephedrine we wouldn't need them behind the counter.

DR. FOLLMANN: I think that the meta-analysis is probably a very dangerous thing to look at. Some of these studies -- we point out the negative studies, had an active control, and the active control didn't show superiority to the placebo. I mean, that to me is a failed study. It doesn't have assay sensitivity; to somehow or other add it to a meta-analysis is to misjudge, I think, what a meta-analysis should consist of.

We have a lot of fields where -- a lot of studies where you do have to show

assay sensitivity before you can even start talking about the effectiveness of the particular drug you are looking at, and the meta-analysis just ignores all of that. And there were a lot of hindsight statements by presenters in terms of why the studies may differ and so forth. But I think you need to look at studies one at a time, make judgments on them, and then say what you can do in terms of synthesizing them.

I think the meta-analysis works probably quite nicely for safety. We have small bits of study; we have small bits of information per study. But with the efficacy, I think we might not be -- I think we should not spend too much time with the meta-analysis, but look at the individual studies and judge them on their merits.

DR. TINETTI: So to summarize the bio- statisticians, the individual studies are best, the meta- analysis is worthless, or the individual studies are worthless -- I

mean, okay. Thank you. That's my -- summarized bio-statistics.

DR. FOLLMANN: I don't think we are contradicting each other in terms of what we are saying. And if you -- you can do a meta-analysis and you can say it's marginal, then I'm -- what I'm adding to that is that you can understand why it might be marginal. I don't think we are contradicting each other at all.

DR. TINETTI: Any other comments on the -- this is just a discussion question. This is not a voting question.

I guess to summarize the discussion is that the individual studies show some suggestion of the benefit to the 10 milligrams, although obviously they are not 100 percent consistent. The meta-analyses seem to be right on the cusp. And overall, the -- what we know from studies today is that it's murky, that we don't really know from the studies that have been done to date,

whether the 10 milligrams is effective; probably it is. And the data are murkier for the symptoms than they are for the nasal airway resistance.

DR. NELSON: Could I make -- Nelson. Could I make a comment? I would differ with your summation a little bit, and that is, I think there are a significant number -- four to seven -- I'm losing track now -- that show a benefit at 10 milligrams. There are some studies that didn't. But we've heard from people who are much more experienced than I am, that in fact a lot of these studies are negative just by pure, I don't know why, all these allergic rhinitis -- so I wouldn't be as soft as you were with your comment about -- I think you used the term "suggest." I would say that our studies had demonstrated --

DR. TINETTI: Well, if you look at the FDA, I think it was half for positive and half for negative.

DR. NELSON: Yeah. Well -- and that's a lot of positive studies.

DR. TINETTI: And a lot of negative. Fifty-fifty. I think 50-50 -- I mean, basically the data -- the small studies that we have, 50 percent were positive, 50 percent were negative. That is the data that we have in front of us.

DR. D'AGOSTINO: Ralph D'Agostino. I think some of the studies that were positive were basically because they were done in centers and single centers with very well-trained technicians and investigators and so forth. And I think the -- what I'm again saying is, I think the effect is there. They are certainly positive. One can ask the real question about generalizability and all this. But those studies are positive. And to say they are not positive is just incorrect. To say how you take that information and generalize it, I think is really a serious issue.

MR. LEE: I'm Charlie Lee again from Pulmonary and Allergy Products. Again, I just want to emphasize that a negative study is not proof that a drug doesn't work. Again I guess, allergic rhinitis itself being the poster child of a disease where you can expect to have negative studies. So -- and in fact, the fact that some of these studies show evidence of efficacy at the sample sizes that they were done is actually amazing.

So again, I'd be little careful as far as assuming that -- or concluding that the -- a negative study provides evidence that the drug is not effective.

DR. TINETTI: No, I wasn't assuming that. I'm just saying there were seven positive and seven negative.

DR. D'AGOSTINO: That's what -- and I was trying to -- I think you can discount some of those negative studies just on the nature of what happened and so forth. So the tally is unfortunate.

DR. TINETTI: Yeah. But you could -- I'm sure you could do that for the positive as well. I think what we have -- the data we have --

DR. D'AGOSTINO: No, no, no, I don't agree. I mean, there's a methodology. When you have a study -- when you have a condition that has this wide variability, the idea of putting an active control is done. So you can say, well, in this setting, I actually did see something, I have a drug that I'm thoroughly convinced is useful. It beats out the placebo. Now I can go and start looking at my drug.

If you look at the studies where the active control didn't show any effect, you can discount them. I think you have a much harder time trying to discount the studies that show effectiveness. I don't see any of these studies that you say, well, would show effectiveness by random chance.

DR. TINETTI: Parker.

MS. PARKER: Ruth Parker. I just want to step back for a minute and say, the cold is common, and the cold is self-limiting, the common cold, and absent it being something other than erroneous diagnosis, which is why somebody would go to the drug store or a pharmacy or a grocery store, or wherever they go to buy a product for it, it really is a symptom, really, kind of feel a little better without doing any harm.

You know, you framed at the very beginning the monograph indication for the decongestant. And I think one of the interesting things about this is looking at the objective outcome of measuring resistance versus the person who goes and buys a product and says, is my nose a little less stuffy, do I feel like I can get through the day a little less better than I do, did I spend my money wisely, was this a good thing to do or not if it isn't going to hurt me, am I

feeling a little better on the other hand, even though this doesn't have a hard clinical outcome on the other side in terms -- or if something serious like a morbidity or a mortality, certainly.

And so one of the things that's kind of interesting to me is I think -- and one of the FDA presenters talked about this -- this endpoint of scoring of whether or not your nose is more congested or stuffy, to me actually makes good sense. It's harder, because it's subjective, and it's harder to get that. And you know, we both sort of have a cold here, but we -- I don't really know how we'd both score and whether or not that even really matters. And it really is subjective. We'd probably score differently on the machine, but I'm not sure how much that really matters at the other -- on the other side of it.

I think one of the things that I encourage is this temporary relief. I like

those words. It's temporary, if it works. It isn't going to work but for a little while. It's relief, it's not a cure. There's nothing about this that changes the pathophysiology. It's not linked to a chronic condition and a health outcome on the other side per se. So you know, in looking at hardcore things and what you are measuring, even though it makes it a little harder, I like this idea of whether or not at the end of the day I feel a little better.

So I just kind of from a practical sense -- standpoint, want to kind of throw that out there, is something that I think -- is what, you know, buying something for a stuffy nose is probably about.

DR. TINETTI: Marie.

DR. GRIFFIN: I was just going to say I think the seven positives and seven negatives are different if you show that the placebo was better in some of them, where we never do. So that -- I think that's a little

bit different than sort of just saying well, half of them are positive and half are negative, because half are positive and the other half are unable to show an effect.

And I think in a -- because there is a lot of measurement error that biases studies towards the null. So I think for the NAR, it's kind of convincing. I think for the symptoms, we really don't have much data for the things that we would really like to know.

DR. TINETTI: Hoffman.

MS. HOFFMAN: Just in terms again of generalizability, back to this charge to the panel, effectiveness means a reasonable expectation that in a significant proportion of the target population, the pharmacological effect of the drug when used under adequate directions for use and warnings against unsafe use will provide clinically significant relief.

And I guess the significant

proportion of the target population -- I just really, you know, we are talking 5 billion dosage units with trials done on approximately 100 patients or 100 people. And I don't see how we can, you know, generalize to a significant proportion of the target population, 5 billion units, from studies that were done 40 years ago on 100 people. And with 50 percent of those results, you know, being negative and 50 percent being positive, I find that very disconcerting for us to have to vote on that.

DR. D'AGOSTINO: I want to comment. What Ruth had said is very profound, and that what you've said summarized the last 30 years in terms of how we should look at these studies. When the panels were looking at these studies, they were told that the appropriate effectiveness measure had to be some objective measure, and they were even told that there had to be crossover, and the field has moved away exactly as you described