flags, and that's why physicians are not advised to get radiographs routinely in patients who present to the office in the absence of significant trauma with new onset of low back pain.

So certainly we've already accepted that patients with new onset back pain can treat for 10 days with acetaminophen or ibuprofen. The risk is no greater presumably if they have spasm.

DR. BRASS: Yes, Dr. Hamilton?

MS. HAMILTON: I always love it when you promote me to a doctor at these meetings.

(Laughter.)

MS. HAMILTON: A general observation. As you pointed out numerous times, a common point of discussion among the OTC Committee members, but I'd like to suggest that the FDA at some point consider some general studies that aren't specific to products or symptoms that help us determine a consumer's general ability to self-diagnose. This is a consistent question, and we tend to deal with it on a per-product or a per-symptom kind of basis, and in the absence of data on this, I have an instinct that most consumers are probably more accurately tuned in to what's wrong with them and what might be hurting them to at least present in a reasonably helpful way initially to physicians.

But we consistently don't have general research and data on which to make some of those suppositions. So just like I tend to ask general questions about how useful inserts and package labels are, which we can't determine if we don't have hard and fast data about consumer utilization and the depth to which they're willing to go to get educated, I think we need the same sort of basic information about a lay person's ability to self-diagnose.

DR. BRASS: Yes, I would just endorse that recommendation, and I think the FDA in many of these areas has the opportunity to provide very important general data that no sponsor is ever going to generate that would really help the agency, but also the advisory committees advising the agency. When we do these risk-benefit types of subjective assessments, implicit in them always is what percentage of the consumers are actually going to do what they're supposed to do, and the risk-to-benefit changes dramatically if you knew that consumers behaved in certain prototypical kinds of ways. I think the absence of that data is constantly crippling to the committee.

Yes, Dr. Harris?

DR. HARRIS: Just a minor note, though, that in terms of self-diagnosis, certainly if one has a headache or menstrual cramps, I think that that's self-diagnosable. That's much easier than something like muscle cramps or

muscle spasm. This is really where I have some difficulty, because there are certainly some conditions that I feel relatively confident people can easily self-diagnose. This one is, in my mind, in a separate category. So even with the proper studies, we still may have some difficulty with this.

DR. BRASS: Again, this goes back to how consumers -- and as long as we're giving our editorials, I will again say the editorial about ethnic diversity and what these terms mean to different ethnic groups, because it's vastly different in terms of what is common, mainstream usage for what those same words will mean to a Korean immigrant or other ethnic populations.

But again, it seems to me that if you knew that when a consumer said "I have back pain," that in fact independently you could say that 98 percent of them have muscle spasm, that would relieve your concern. But I'm not hearing any data set that looks like that, and it sounds like we're all kind of just presenting our individual anecdotal experiences.

DR. GANLEY: Are you asking that we generate those studies or that the sponsor generate those studies?

DR. BRASS: Well, I think both Ms. Hamilton and I were making a global, cumulative, four years worth of experience generic comment, not about this indication, not

about this label, but about the paucity of information that in general allows us to make predictive decisions about consumer behaviors in the diagnosis and following directions and obeying instructions and warnings type of categories. I think it was a global thing, and I don't think any sponsor is going to do it except under some very specific categorical diagnosis type of situations. Somebody's got to do it sometime if the information base is going to get better.

Yes, Dr. Yocum?

DR. YOCUM: I guess going back to one of the original questions from the FDA a little bit ago about this mean difference versus categorical, I think we're focusing that categorical may well be better, and I think we're kind of saying that and focusing in on specifically back spasm, neck spasm, which here is kind of handled globally. Gee, I would love to see the separation of neck and back, aged versus non-aged, and so on and so forth. That would give me a better feeling, but we just don't have that data. I share the FDA's concern that this rather mean response score is very difficult to assess.

DR. BRASS: Yes, Dr. Koda-Kimble?

DR. KODA-KIMBLE: Well, I would be really very interested in the study that you suggested, which is that someone who self-diagnoses with back -- and the indication

here on the label is muscle spasm or strain. It's not just spasm. How they respond to these agents based upon the analysis that was -- because I am not convinced that a patient is ever going to be able to diagnose spasm. I mean, from what I'm hearing around the table. I think most people can say, "I've got a crooked neck, a stiff neck, acute back pain," or something like that, and then the question is to what extent is this drug effective.

I was very impressed by the fact that of those patients who self-referred into the 008/009 studies, only 6 percent were not included. That was impressive data to me. So I do not think spasm -- anybody is going to ever be able to indicate that a patient can self-diagnose spasm.

DR. YOCUM: Again, I am concerned about the data that you just talked about, because it's not blinded data, and the physicians obviously need to get patients in the study. So during a lot of these studies, I'm not sure I can trust that data at all.

DR. BRASS: Yes?

DR. LOVELL: The study you just proposed, or the question just proposed, which is if you take patients who would self-refer themselves to be put on this drug and then just have them evaluate to see how many of them had muscle spasm, I think it would be a very informative and straightforward and simple test or study to do. I don't

think we're talking about a huge, incredibly expensive undertaking. I think as a sponsor who is coming in with the first drug in a potentially new class of OTC drugs, that perhaps it's appropriate to ask the sponsor to perform that rather straightforward, simple study.

DR. BRASS: Since it's now my study --

(Laughter.)

DR. BRASS: -- I will play devil's advocate very quickly and say why do I care. If I do 009 placebo-controlled and patients get better based on the self-referral pattern, do I care whether or not they had physician-diagnosable, confirmable muscle spasm?

DR. LOVELL: I think you do care because once you approve a drug, you're going to open the floodgates to a huge number of patients. This is a very large denominator we're dealing with here. So it's one thing to say in the numerator group it is an effective drug, but it's also I think important to see if we can accurately define the denominator population that will be taking this drug.

DR. BRASS: To minimize risk of exposure unnecessarily.

Yes?

DR. SHERRER: And I would say that as a physician and consumer I would care, because if it's a

matter of Flexeril really having an analgesic effect, then I could just optimize analgesics, which may not have the same side effect profile.

DR. BRASS: I'm a lot more skeptical of analgesics than the rest of you, but I'll go on to Number 3, then, and I'm actually going to editorialize Question 3 because it segues nicely.

"Can consumers" -- and I will say or physicians -- "identify when Flexeril should be used, as opposed to other products such as OTC analgesics? Can they adequately assess whether their condition is responding to treatment? Were these conditions identified by a significant number of subjects where Flexeril use was considered when it should not have been?"

DR. GILLIAM: I remember reading in some of the background material that the patients responding in these studies were asked: How much did your back pain really bother you? If I remember correctly, most of them said just mildly or just a little bit. I've looked for that today and I can't find it, so I hope I'm remembering correctly.

That goes back to an early question that I had. I'm wondering if Flexeril adds that much more benefit than just using Tylenol and/or NSAIDs in helping these people, and whether from that aspect, if it's only bothering them

mildly or a little bit, if it's worth having this new class of OTC product put on the market, and that using NSAIDs or Tylenol and physical therapy or other modalities might be just as beneficial. I would like to see some data along that line.

DR. McNEELY: Correct me if I missed it, but I don't think this question was ever asked in any of these studies. Am I wrong? Because if you look at the pattern of use study or the actual use study, they didn't query the patients as to whether they should use Flexeril as opposed to an analgesic. Am I right or wrong?

DR. BRASS: Yes, you're right. Again, we're being asked as esteemed experts with vast experience to help the agency extrapolate this aspect of the database, and to the degree it is unanswerable and it is important to answer, to convey that to the agency for future considerations.

Did you want to follow up?

DR. McNEELY: No. I mean, it wasn't part of the study. So that's something that's been repeated here several times as something we have to address.

DR. BRASS: Yes.

Dr. Sachs?

DR. SACHS: I think the real practical point, though, is that this isn't prescribed in a vacuum. I mean,

even the prescription is used in combination. So the reality is that this medicine, if made over-the-counter, will be used in combination with an analgesic such as NSAID or aspirin or Tylenol or Advil, whatever.

So, in a way, maybe what's important to know is whether it should be marketed that way too, as an adjunct in addition to. I think that's the one thing, just being very practical, I actually would have liked to have seen data on nonsteroidals alone, this alone, even Benadryl alone if the sedation is a big deal. If you have muscle spasm and pain and you take Benadryl before you go to bed, is that as effective in getting you a good night's sleep? If you relax, maybe your muscle does relax, and you take your Advil during the day so you're awake. That actually would have been very practical.

DR. BRASS: Again, just to make sure I understand, are you saying that given that real use will probably be in combination with classical analgesic class drugs, that it's important to show incremental benefit on top of them, so that if it's used, there will be a rationale for it?

DR. SACHS: Actually, as someone who really doesn't use these, as a pediatrician I don't use this, to me that was something I didn't know and that I would like to know. And as a consumer, perhaps someone who might go

out to buy this, I would like to know is it better, should I use it with it. Just common sense from what I've heard and seen and experienced, it's been that it is actually used with. So recommending it alone doesn't seem to really make sense.

DR. BRASS: Dr. Yocum?

DR. YOCUM: Is there any -- this is a question to the sponsor. I see baseline demographic data, but only do I see baseline data on the physicians' scoring of the degree of muscle spasm, which is relatively mild to moderate. Do they have any baseline data of how severe these patients were when they came in? The FDA has kind of thrown this question out, and it suggests they may have some knowledge that this was mild back pain, or is this just a shot in the dark?

DR. KORN: Okay. To answer Mr. Gilliam's question, in Protocol 9, in the use study at baseline, there was a question: How much has the muscle pain impaired your usual activities? That was asked not at all, a little, somewhat, very much, extremely, and there was a bell-shaped distribution, 41 percent of the patients said somewhat, 23 and 24 percent on either side of that. So that's the data, but the question was not asked at follow-up in that study.

Asking, though, Dr. Yocum's question, the

patients did provide a rating of baseline pain severity in the pivotal trials, and looking at Protocol 6, on a 5-category scale, zero to 4, the patients in all three treatment groups rated themselves similarly, approximately 2.3 on the zero to 4 score.

DR. BRASS: Dr. Blewitt?

DR. BLEWITT: I just wanted to clarify a point on what data are required versus what data people would like to see. In terms of the incremental value of a product such as this, I don't think that I can say that it is not the charge of the company or the sponsor to prove this. The charge is to prove whether the product works in and of itself. So I think there's a need to differentiate the need to know versus like to know.

DR. BRASS: Yes, Dr. Lovell?

DR. LOVELL: I would like to question the FDA as to what their intent was in Question 3A, because it would seem that a number of studies have shown that patients are reliable reporters of self-pain, and in the functional assessment scales that were mentioned in our discussion here, that patients are reliable reporters of functional ability. So I was wondering if there was another issue that was being addressed in 3A that I wasn't aware of.

DR. BRASS: And let me just add again that to

the degree that we have data for 3A, it's that the physician's exam did correlate to the patient self-assessment over the course. It was not a perfect correlation, but there was a correlation.

So, Dr. Katz, do you want to comment on that?

DR. ELASHOFF: Not only not perfect, but not high.

DR. KATZ: Part of the intent behind the question was, in a sense, if you look at Questions 1, 2, and 3, they are all related to the efficacy and the data presented to be able to say whether or not consumers can adequately pick up the product and be able to make the distinction, and whether, again, the committee felt that the data presented not only in the efficacy trials but in Trial 009, which was the actual use trial, and in the label comprehension trial, could actually give the information enough that people could feel comfortable that consumers could use the product adequately and safely.

DR. BRASS: Dr. Elashoff, could you just expand on your comment? It's important, and that's why I highlighted that data, because it is the data that we have available to our already-defined apparent gold standard of physician examination.

DR. ELASHOFF: As I recall, some of the correlations ran around 0.3 and some of them ran around

0.6. 0.3 explains about 10 percent of the variance, and 0.6 explains a little bit more than a third of the variance. Those say that there is some general relationship, but it is not a strong relationship between the two.

DR. BRASS: Can the rheumatologists help me clarify if there are any patients for whom the use of a muscle relaxant would be used as first-line therapy before initiating or at the same time as initiating analgesic therapy?

DR. YOCUM: I suspect that there's a significant portion of rheumatologists who may well use this to treat fibromyalgia first line, and I think Dr. Moore alluded to that earlier, that many rheumatologists will go to a drug like Flexeril or amitriptyline first-line over an analgesic. But in my practice, other than that, unless I detect clear muscle spasm that I feel comfortable with, which again even from my perspective is difficult, I would go to an analgesic. Even in the case of muscle spasm, I might do that anyway. So I would say a majority of patients, other than the fibromyalgia group, are going to get analgesics first, but other rheumatologists may have different perspectives.

DR. BRASS: Even in the prescription dose or for any other drugs that are in the "muscle relaxant

class," are there any data that would address at any dose, in any population, the relative response to NSAIDs for muscle spasm versus muscle relaxants? Again, I'm trying to establish whether this is a black and white decision or a consumer/marketplace type of decision between the different agents.

DR. ABRAMSON: The easy answer is there's no data to address the question. I think the reason this is so nebulous is, again, when one is treating these conditions, one doesn't know exactly where the pain is coming from. I think the reason we may often use analgesics first or anti-inflammatories is that the muscle spasm oftentimes we think is secondary to whatever the primary problem is. So if there's arthritis or some mechanical joint pain, there may be secondary muscle spasm.

So I think, as David said, the first inclination, without really knowing where the pain is coming from, is to treat with analgesics or anti-inflammatories. In some people with very severe pain in whom you may think there's some muscle spasm, you may add Flexeril to that. It's often in people who you want to calm down a put a little to rest, so you're relying a bit on the sedative component of it, rightly or wrongly. But it's uncommon in the straightforward neck or back pain, which we think is coming not typically from the muscles

first, to just go right to a muscle relaxant.

DR. YOCUM: I would agree, Steve, that that's true, and even in the fibromyalgia group, I think most rheumatologists are relying on the cancer data for relief of pain and it has nothing to do with muscle spasm at all.

DR. BRASS: Would that clinical assessment be true if there was an identifiable acute precipitant in a 25-year-old laborer?

DR. LOVELL: May I make a comment? I think perhaps Dr. Abramson and Dr. Yocum are -- perhaps your populations are skewed. Perhaps this question would be better answered by primary care physicians who would be the ones to which this 25-year-old laborer would be more likely to go to see for his kind of acute onset back pain in an otherwise healthy lifestyle. So I'm not sure that a rheumatologist gets very many of these virginal patients with acute back pain with muscle spasm related to sprain or injury, that sort of thing. I pose that question to you guys.

DR. ABRAMSON: Well, we'd be happy to teach the primary care physician the correct manner of treating these patients. You may be right to some extent, and I don't know the acute spasm of a laborer. I'm not sure what the right treatment for that is. We don't clearly have data from this data set to say that it's Flexeril. It may be,

but there are no data to really address that.

DR. BRASS: Again, what I'm trying to crystallize is the issue of the NSAID analgesic versus, and the degree to which, if it is gray, it is proof of efficacy of Flexeril against placebo in a gray area sufficient to say that, well, we don't know any better, but at least we know this works, again going back to all our other caveats about efficacy, or is there a genuine concern that there's reason to believe that there is some reason that we should not be even considering the use of Flexeril as initial sole therapy? That's what I'm trying to differentiate.

DR. ABRAMSON: I think the dilemma is what you were alluding to before. I think the data speaks to the fact that the drug is efficacious in the population that was studied. The dilemma I think is that it's restricted in the way the data was presented to muscle tightness and strain and spasm, and to exclude people with other kinds of chronic neck or back pain, and the question is do we know whether it works in that population. Does 009 shed some light on that, as you were suggesting?

I think the concern is if you take a very narrow view of what the drug is indicated for, then the concern is that there are many more people who don't have that particular condition but have chronic backache and other concerns who will get exposed to the drug because the

criteria for entry here would not be the criteria for use in the population. So I think that's where the problem is. If a drug is only indicated for muscle spasm, tightness, and strain, and people over 65 should call their doctor first, then there's a potential problem with putting it OTC. If it was shown to work in backache and nondescript and didn't have those caveats, I don't think there's any question that the drug has a role. But as narrowly constructed here, the problem is that it may get utilized in people beyond where it's been shown to work.

DR. YOCUM: I think Dr. Lovell's comments are well taken, but I think it also emphasizes that there are whole books on back pain, and different ages, different ethnicities which you talked about earlier, different educational levels -- I think it's one of the things we've all struggled with today here. We've compressed a very complex area into three global categorical analyses, expecting a broad range of patients over 50-some-odd years to respond, and I think the FDA's concerns are the same way. It's categorical analysis versus a mean analysis of a very complex area. So it's just not easy to approach.

DR. HARRIS: At the risk of jumping a few steps ahead, I want to come back again to a point made earlier by Dr. Sherrer, that in a number of these circumstances, one would probably want to use an analgesic first -- strains,

sprains, spasm, whatever. I think as long as that option remains viable and safer, then there is the issue, again coming back, as to the use of Flexeril.

DR. BRASS: I would point out that there's no data that it's safer. I know an awful lot of people with adverse events from NSAIDs presenting to my hospital every day. So I think you hit the paradox and how we set the bar.

Yes, Dr. Koda-Kimble?

DR. KODA-KIMBLE: I forgot your instructions. We were provided with AHCPR guidelines on acute low back problems and pain, in which they do not recommend muscle relaxants at all for this problem. They did a very thorough review of the literature at the time and indicated that at least muscle relaxants were no more effective than NSAIDs. So given that the first question, if we accept the AHCPR guidelines, we could say the answer is no to your question, that physicians aren't using them properly either.

DR. BRASS: You caught the attention of one of our consultants -- one of their consultants. Sorry.

DR. BORENSTEIN: I just wanted to make a comment about those guidelines. I think that you have to remember from where they came and what they were based on. They were based upon whatever evidence was available. Lack

of evidence doesn't mean that it did not work. What it basically said is that it was not available. Now, in fact, we have some evidence, from whatever viewpoint you may take of the data, where in fact these drugs have been tested, particularly Flexeril has been tested by itself to see if it's efficacious.

So now, in fact, if this were published in a journal, that same group could now go back and say the muscle relaxants might work because of this very study if it was in fact in the literature. So I think those guidelines are very important, but they did not come down from Mt. Sinai. They're sort of guidelines which will change, and this group I believe will be looking at other guidelines which may change over time. So I think that although we like evidence-based medicine, it's important to remember that we're only doing as well as what evidence we have available. The fact that we don't have evidence doesn't mean that it doesn't work. From a practical standpoint, I can certainly tell you, as a physician who sees the whole range of low back pain problems, that these are agents which work.

DR. BRASS: Just for clarification, you are now referring to the medical school in New York.

(Laughter.)

DR. BRASS: Dr. Blewitt?

DR. BLEWITT: I was going to say the same thing as Dr. Borenstein, but not as well.

DR. BRASS: Other comments about Question 3?

Yes, Dr. Blewitt?

DR. BLEWITT: I can't find it now, but you had mentioned about concomitant use, and it seems to me that in 009, as they enrolled studies, there was a certain percentage of people who were taking them concomitantly, and it wasn't 100 percent. In fact, it was fairly low. Again, I can't find the page, but it seemed to be a rather low percentage, 20 or 25 percent, something like that.

DR. BRASS: Yes, it was in there. Twenty or 30 percent is my recollection. But again, there was no efficacy assessment, so to the degree that's a question, that becomes a concern.

Other comments or questions about Question 3? Is the agency satisfied with the discussion?

Question 4. The reason we're not taking a break is I'm hoping we're going to be done in 30 minutes.

"Has the metabolism and excretion of Flexeril been adequately characterized? If no, what additional information should be obtained (for example, better characterization of the metabolic pathway, drug-drug interactions)? Are there any potential or known drug-drug or drug-food interactions that may impact on the safe use

of this drug in the OTC setting?"

Perhaps I just want to ask one additional question of the sponsor. In particular with respect to drug-food interactions, is there a potential to get accelerated absorption with certain types of food from this formulation that would give you higher peak, earlier peak concentrations, and then for more acute sedation?

DR. KORN: Nothing that we're aware of.

DR. BRASS: Because again, as you're aware, there are certain types of formulations where ingestion with fatty foods, et cetera, will change and lead to an accelerated -- and this is partly going back to why I asked about the three times a day dosing. You're clearly concerned about high peaks, and anything that would accelerated absorption therefore would be of some concern.

Other comments or questions about this issue?

DR. PUCINO: If you have a wish list of things, it would be nice to know the metabolites, if they're active; if they are, then to know the kinetics of the active metabolites. It would be nice if they co-model some of the psychomotor effects with steady state concentrations, CPmax, areas under the curve. It would be nice to have some pedes data. It would be nice for the drug interactions, at least for things that are over-the-counter -- grapefruit juice, H2 antagonists like

cimetidine. Because it's highly protein bound, it would be nice to know about free drug kinetics, particularly as it relates to malnutrition, elderly patients, liver dysfunction, and so on and so forth.

DR. BRASS: I'm going to ask you to expand on that because having what's nice is useful. Having what's really critical differentiated is going to be helpful to the agency, and I think there are a couple of points you hit upon that I would just like to highlight and then ask you to comment on.

The first is the issue with the elderly. We know that total drug concentration is significantly increased. The free drug concentrations for the reasons you alluded to may even be more dramatically increased, and the same thing with liver disease, incidentally. Understanding the free drug-disease/age interaction I think would be, to the degree that's going to matter in the labeling, I think would be important.

Second, in terms of the drug interactions, the argument has been put forth that identifying the diversity of the metabolic pathways is reassuring that inhibition of any one of them is extremely unlikely to cause a clinically significant drug-drug interaction. Do you find that reassuring?

DR. PUCINO: I mean, there's some limited data.

My understanding, at least with fluoxetine, there was some limited data that there could be an interaction, but there were no kinetics to suggest that. There are other SSRIs where there's some concern. We don't know about macrolides. So maybe that's the case, but we don't have any safety data, and that's why I say at least having things that are going to be used over-the-counter -- it would be nice to be reassured, i.e., the grapefruit situation. With some drugs, that's significant. We hope that in this case, that would not be an issue.

DR. BRASS: Again, to make this very specific, my understanding is the grapefruit issue is only clinically relevant, if ever, with drugs that have first-pass metabolism. So that systemic bioavailability is increased during the acute exposure to the flavone, whatever it is in the grapefruit juice. Therefore, one would predict it's unlikely that there would be an interaction with this drug. Similarly, for the macrolides, if you knew that 10 percent of the metabolism was through 3A4, and you knew that as an independent fact, would you still require an erythromycin drug interaction study?

DR. PUCINO: If you knew that. But do we know that?

DR. BRASS: I'm not saying that. Again, I'm trying to differentiate what's necessary versus --

DR. PUCINO: If I were comfortable that there was a diverse metabolism, enough that the 3A4 was not significant, then yes, that wouldn't be such an issue, either if we're talking about the intestinal tract or the liver. But without knowing that, it would be nice to have some limited data at least to support that.

DR. BRASS: Other questions? Yes.

DR. BASHAW: Dennis Bashaw. I wanted to touch on two issues that you brought up in your discussion just recently. There is a commitment for a study to be done with food. That was not part of this package, but there was a negotiated commitment with the sponsor that is in the planning stages. So this touched on that issue.

With regard to metabolism of cyclobenzaprine, it is a first-pass drug because the bioavailability is approximately 55 percent. Yet when you look at its excreted pattern, obviously there is some degree of first-pass metabolism happening there. So grapefruit juice could, in theory, be playing a role there, or could play a role potentially. But when you look at the enzyme systems involved, it's probably not. But that will be addressed, maybe not specifically with grapefruit juice, but with the in vitro methodologies. We're hoping to capture that kind of information.

DR. BRASS: Thank you for that clarification.

Do you think that the radioactivity recovered in the urine was higher than the systemic -- I'm sorry. How did you determine it was first-pass elimination?

DR. BASHAW: Well, when we looked at the excretion and we had an I.V. study --

DR. BRASS: Oh, so you have an absolute bioavailability.

DR. BASHAW: Yes, we do.

DR. BRASS: Okay, thank you.

DR. BASHAW: There was an absolute --

DR. BRASS: That wasn't in here. Okay. Thank you.

Dr. Lovell?

DR. LOVELL: To look at the database, it's overwhelmingly white, and I'm not sure if there's enough ethnic diversity in the database to answer some of the metabolic and safety questions in ethnic groups other than the ones that are overwhelmingly represented sitting at this table.

DR. YOCUM: I share Dr. Lovell's concern. As a rheumatologist thinking about this drug, even as I use it as a prescription drug, it is frequently not able to be taken for extended periods of time, especially in the elderly. At least the hint that we see of the elderly pharmacokinetics is very, very scary to me, of the very

high levels that they can achieve at 5 milligrams three times a day. Based on this data, I would want to say, gee, I think it should be restricted to people less than 65, period, because in practice, a number of elderly people coming in with acute neck and back spasm or strain is relatively low and typically due to chronic arthritis or other problems, which I don't want to use this for. So I have a problem. I would want to strictly limit it.

DR. BRASS: Other pharmacokinetic issues?

Yes, Dr. Harris?

DR. HARRIS: This is somewhat informational to the OTC group. This is an agent that has been around for quite some time. There is extensive clinical experience with respect to its use, side effects, and so on. What sort of additional data one might expect from getting metabolism, new metabolism and excretion data that might not already exist that could tell us something clinically is the question.

DR. BRASS: Yes. I think that's a general comment. It goes back to the degree of confidence one has on our sporadic observation of adverse events as being sensitive to identifying drug-drug interactions. We've seen what is clearly an adverse event profile in all the databases that says a percentage of the population responds differently. There's nothing in those databases that says

maybe they're all taking erythromycin, and unless somebody looked, you'd never find those kinds of things. So I think that our understanding of rational predictive power says that to the degree we can do straightforward things and understand those risks better helps consumers, physicians, and sponsors as well.

Yes, Dr. Koda-Kimble?

DR. KODA-KIMBLE: I don't know whether this is a pharmacokinetic question, but one of the things that did strike me right away is why isn't this drug given as a single dose at bedtime? Because of its long half-life, its effects on sedation, the sedation would occur at night when it's supposed to, and it probably would just mess all of the studies up, I realize that, because everything has been done on a TID basis. But it just seems that it would improve compliance. A lot of potential concerns would be minimized.

So to the extent that pharmacokinetic data that sort of analyzed a single dose at bedtime and the adverse effects that accompanied those pharmacodynamic effects I think could be useful.

DR. BRASS: Does sponsor want to comment on that?

DR. KORN: Again, we adopted the historical precedent of the dosing, but we have thought about the

advantage of TID dosing; namely, that a potentially sedating product like cyclobenzaprine may offer an advantage to patients with acute back pain that a nonsteroidal drug can't do. Namely, it may help them sleep through the night. If their pain is bad enough that they cannot sleep through the night, that could be a realistic benefit that could be measured in a clinical trial.

DR. BRASS: Other comments or questions?

(No response.)

DR. BRASS: Okay. Going on to Question 5. "Safety concerns include the adverse reactions associated with Flexeril use (especially adverse reactions similar to those seen with closely-related tricyclic antidepressants); the possibility of misuse or overdose; and any possible drug interactions. Can consumers, including elderly individuals, safety use Flexeril in an OTC setting, taking into account the available data on adverse effects, sedation, overdose and misuse, and concomitant medications? If not, why not? If yes, is any additional information needed on the labeling?"

If I could just clarify, when you say including the elderly, do you mean including the elderly not using it? Are you saying is it clear the elderly will not use it, or if they did use it would it be safe, or that if they were allowed to use it it would be safe?

DR. KATZ: Actually, in a sense, it's all of the above.

DR. BRASS: It always is.

(Laughter.)

DR. KATZ: That's right, because part of the discussion is that even though we may label a product that it shouldn't be used in those greater than 65, they still may use it. So we should have good enough knowledge of what will happen if they end up using the product.

DR. BRASS: Okay, takers for Question 5?

DR. ABRAMSON: I guess one of the problems is that certainly the answer is that consumers can take responsibility for reading the label and being aware of potential side effects and know not to drive. That's their responsibility, perhaps. But some of the side effects that one does see in practice or that have been reported are idiosyncratic, whether it's disorientation or some of the CNS effects, that a person can't change their behavior to protect themselves from, and that's where the elderly issue becomes the one concern and how practical it is to think that people over 65 will call their doctor before they take the medication.

So that's the one concern that I think one has to read into this question, is the idiosyncratic severe reactions, although rare, do happen.

DR. BRASS: Yes, Ms. Hamilton?

MS. HAMILTON: A couple of observations. The question speaks to the possibility of misuse by consumers or elderly individuals, and I think there clearly is the potential. There's been the demonstrated misuse of the product in terms of using it for arthritis or headaches.

I just want to point out that in the label, there might be a real simple explanation for that. Sometimes it's the simplest things that we overlook. The very first paragraph on the label, which is where I believe consumers look -- they go to look at which symptom is this product going to relieve. Is what I'm experiencing relevant to what this product might offer? And the two words in there that seem to me to suggest it could be used for headaches and arthritis are "tension" and "stiffness," and in the context of this discussion, we put that in the context of all those other discussions, but when you tell a lay person that this is something that will deal with the pain of tension or stiffness, if I hadn't been in this discussion, I would have thought this was appropriate for arthritis or a headache. So I think that's one certain clarification that could at least minimize that kind of misuse should this product ever be made available on an over-the-counter basis.

The question I asked earlier about consumers'

ability to recognize the technical names for other prescription products that they're using I think is an important one in looking at this label. I can't pronounce most of what's done there in that very, very last paragraph, but until it gets into a generic description about an antidepressant and psychiatric and emotional conditions, I don't see anything simple to understand there. So I have a real serious question about whether or not an average consumer would recognize a product that they're taking on this label, and whether or not they would then be involved in concomitant use which is not appropriate, because that information is not clearly provided in the label.

The question was raised earlier about whether or not it's not safe or appropriate to use this product in conjunction with antihistamine use. I don't know the answer to that but I thought it was a good question, and that's such a commonly used product that it probably ought to be dealt with.

DR. BRASS: Other comments? Yes.

DR. KRENZELOK: The venue that I practice in is one of high selection bias because we have everyone calling the poison center who has a potential adverse event with a product. They've taken too much, they've taken it unintentionally -- who knows what the reason is, but

generally it's a fairly significant amount, and I have to tell you that in 22 years of watching these types of overdoses, as I mentioned this morning, I'm impressed by the very high safety profile of the compound. It's very rare that you see this drug being abused, and the poison center is often a place where these sentinel events begin to accumulate, and we see them because we're handling a bunch of them all of a sudden. So you don't see it in combination with other drugs, trying to produce a synergistic effect with heroin or something of that nature.

So I think from a misuse standpoint, from an abuse standpoint, from an acute overdose standpoint, where you see very commonly overdoses of 100, 200, 300 milligrams if they get 90 tablets because that's what their HMO allows, you have the potential for having a 900 milligram overdose. I'm not impressed at all with this drug from a negative standpoint. So I think the safety profile, from my perspective, is very, very high, and I don't see a problem with the 5 milligram dosage, whether it be little kids getting into a few extra tablets or whatever.

The only one that concerns me is perhaps the drowsiness from a general consumer standpoint, and I think what I'd like to see would be some quantification of drowsiness, because many of us around this table have had some aspect of drowsiness at some point in time.

DR. BRASS: Including today.

(Laughter.)

DR. KRENZELOK: Yes, and how do you rank that? Does it take three mints to keep you awake or a glass of water or a stimulating speaker? I think that's a difference among people, but certainly I think it would be very valuable to quantify this because I'd want to know if this person was going to take this, now are they going to be dozing off at the wheel or something of that nature. So how profound is the drowsiness? I'd like to see that clarified.

DR. BRASS: Do you want to see it clarified as drowsiness, or is the psychomotor testing more relevant to you?

DR. KRENZELOK: I think the psychomotor testing would be a lot more relevant than drowsiness. That's such a generic term and more difficult to quantify.

DR. BRASS: If I could just follow up on that point, we've all acknowledged that use in combination with other sedating products would be very, very bad. Do we know how bad? I mean, do we know whether this is additive or synergistic? If you drank a glass of wine and took one 5 milligram pill, would you then be completely incapacitated? If you took 4 milligrams of chlorpheniramine and 5 milligrams of this, would you be

completely incapacitated? Do we have any sense of that pharmacodynamic interaction on that safety profile?

DR. YOCUM: From personal experience, 5 milligrams is not sedating. It's an odd effect, and what many of my patients complain about is feeling like a zombie effect. It may not be sleeping, but I find it astounding that this is actually prescribed at 10 milligrams TID. I give my patients 10 milligrams at bedtime. So I'm amazed that patients could tolerate 30 to 40 milligrams a day on a regular basis, because this has quite a sedating effect and psychomotor effects.

My patients don't abuse this drug in the arthritis sense. I don't know why. I don't think it's an abuse-type drug. What I would be concerned about from the pediatricians here, since we have at least two, what would be the prospects of young adolescents who get into "downers," this becoming quite a fun thing to do because, for some reason, there seem to be fads that kids go through, going into downers and some of the stuff that goes on. Is that a potential issue? That's probably far astray here.

DR. SACHS: I actually was going to bring up that there doesn't seem to be a lot of data in pediatrics per se, and that was one thing I was impressed in reading most of this, until I guess one of the FDA looked at some

of the overdose literature, and it was reassuring to hear about the poison control literature. So actually that was just something that I wanted to make sure was still in the committees heads and that the labeling had to be very clear that at this point there is no indication in pediatrics.

The other concern is actually to the potential fetus. There were some reports, though, of problems for pregnant women, and I think that the lay perception is that something over-the-counter is safe and may be safe to a pregnant woman, and if there really is clear teratogenic effects, I do have a lot of concern about making something over-the-counter.

DR. BRASS: I think the sponsor will make a statement about that.

DR. KORN: Slide 428, please. I think neither we nor, if I can be so bold as to speak for the agency, don't see a signal of teratogenicity in the five anomalies that are reported here. Each of these anomalies is reported spontaneously and known to occur at rates of 1 to 350 to several thousand in live births in this country. So we do not see a signal. It's well recognized that retrospective reports of use during pregnancy are much more likely to report adverse outcomes than normal healthy offspring. So we do not see a signal here.

DR. BRASS: And it currently carries a Class B.

Is that correct?

DR. KORN: That's correct. Animal studies do not show any signal.

DR. BRASS: Yes, Dr. Lovell?

DR. LOVELL: There's a concern I have, and that is that in the third through seventh to tenth day of taking this medication, when you're over the acute back pain and are now able to be a little more outgoing and you get back in your car, we have no data about the psychomotor effect of this drug in steady state, which, as you've shown us, is at a much higher drug level than the acute 24-hour dosing psychomotor testing you have.

So I would be very concerned that we would have that kind of psychomotor driving data available to us in the later stages of dosing, and also whether sedation itself is an adequate symptom to indicate to people they should or should not drive.

DR. BRASS: I would just like to come back to -- because it's actually in the question -- the issue of analogy to tricyclic antidepressants, because while it is clear that it is antimuscarinic and anticholinergic, I see nothing else in either the pharmacology or the clinical signals that suggests this has any actions at the molar concentrations that you use this compound that is anything like the more idiosyncratic Class 1A QRS prolongation,

other kinds of things that are seen routinely with elevation in tricyclic antidepressant plasma concentrations.

Does the agency have any reason to continue to sustain that concern? Dr. Neuner or others, is this still an issue, or am I missing something?

DR. KATZ: Basically, what this compound is is structurally related to the tricyclic antidepressants. So because some of the way the data was collected, or the lack thereof, is why the question is addressed, and that's why it was raised, because even though the profile itself is reassuring with regard to some of the effects one would see, we don't have data that actually looked for some of this information, and that's why it was raised to you as the committee to see if you have any concerns that the sponsor should go back and look at some of these issues again, or if there is no concern, then that would be that as well.

DR. BRASS: My level of concern is extremely low. The two pieces of data, if they were available, that would help me feel even more comfortable is if, in the overdose cases, if QRS duration could be examined and addressed whether or not there was any prolongation. If not, then it doesn't have the effects, and if there was anything in that kind of signal, in vitro testing for Class

1A-type EP properties again would clearly differentiate from a cardiac toxicity and arrhythrogenicity standpoint from the tricyclics.

DR. YOCUM: The number of elderly in this situation were relatively few, less than 10 percent in any of these studies. So it's kind of hard to look at some of that stuff. The way the selection criteria went, most of the at-risk elderly is even a smaller portion of this population. So I don't think there's a lot of data there for some of the greatest at-risk patients.

DR. BRASS: I agree. But again, to the degree that it's based on an analogy to the tricyclics, it's easy to differentiate whether or not you have the cardiac effects that tricyclics have. And even in young patients at high concentrations, you get QRS prolongation uniformly, or almost uniformly in the serious overdoses. If it's similar to Class 1A properties would be demonstratable in vitro, and whether there are any other surrogates people know about.

I agree, we don't have the data, but I'm unconvinced that there's a pressing rationale for extending that analogy in these kinds of concentration ranges, as evidenced by the fact that the drug didn't work as an antidepressant either.

DR. KRENZELOK: If they're equimolar potent and

so on, you're looking at serum concentrations that are a few nanograms versus 750 to 1,000 nanograms per milligram, where you begin to see QRS prolongation. So there doesn't appear to be any apparent association at all.

DR. BRASS: That's why I emphasized the molar concentration. The only caveat is that you'd have to do free drug concentrations with the two, to the degree that would make a difference. But they're two logs different league of concentrations on total drug.

Yes, Dr. Lovell?

DR. LOVELL: As the other pediatrician on the committee, I feel compelled to respond to Dr. Yocum's question. It seems as if the acute overdose database, because of the number of prescriptions written and the time that the drug has been available on the market, is very reassuring and robust in terms of safety as far as children getting into their parents' medication. So I don't think that that itself is a concern.

The other thing you think about in pediatric use is off-label use, and the two situations that I would foresee in which this would very likely be used by pediatricians off-label is in fibromyalgia and acute muscle spasm related to sprains, just like the indication says. Both of those are predominantly adolescent type problems. I don't see them being big issues in preschool or in

elementary school aged children. So once you get to be an adolescent, drug dosing and metabolism for the most part is very much like adults, and I don't see that there's a real compelling issue to do pediatric PK studies in this drug.

DR. BRASS: I would just, not as a pediatrician also, respond that the other window to that is the emergency room, and that there are a number of prescription drugs that are sold illicitly on the street to adolescent populations which then present often towed by their parents into the emergency room, certainly haloperidol, diazepam. There's a broad list of such compounds, and I've never personally heard of cyclobenzaprine in that class. Again, the warning system from the EDs would also highlight if there was a significant potential. It doesn't mean tomorrow there won't be, and this is being televised.

DR. KODA-KIMBLE: Is Dr. Andreason still here?

DR. ANDREASON: Yes.

DR. KODA-KIMBLE: Could you please, for my own education, explain to me why you recommend a P of 0.1 in evaluating the adverse effects?

DR. ANDREASON: Well, the way that the sponsor set up the initial statistical analysis was actually to test the efficacy of Flexeril at producing sedation and psychomotor impairment, as opposed to looking at it for a safety concern. At that level, that would mean that there

was only a 1 in 20 chance that these findings were due to a random effect. In that sense, we use the level of 0.1 as an exploratory value, and these are also small studies, so that if in a study that involved 50 people there is no effect, or there's no sign of an effect, that does not mean that there is no effect, especially with a level of 0.05.

At the level of 0.1, which is still fairly conservative with the small study, if there is no effect, that doesn't necessarily mean -- lack of evidence does not necessarily mean that there's a lack of an effect. In this case, at a level of 0.1, with only a small number of people in the study, there actually was an effect.

DR. BRASS: If I could just follow up on that, as I alluded to, I think the psychomotor data are much more relevant than the subjective sedation, and I remain concerned about the relatively small N in those studies identifying the 2 percent in the clinical studies who were self-diagnosed as severely impaired and a 2 percent kind of signal.

Now, while the distribution data was somewhat reassuring, it's still a relatively small N, and whether or not there's an X percentage -- and in terms of setting up a study to answer the question whether the population is affected or whether you could pick up X percent of the exposures who were severely impaired from exposure,

statistically is a very different design.

DR. ANDREASON: Yes.

DR. BRASS: So I have a residual concern in that particular area in the psychomotor testing as to what is sedation and what's impairment.

DR. PUCINO: To respond to that also, four doses, even in the young person, doesn't achieve a steady state. So it would be nice to see the same data at 8 to 10 days out.

DR. BRASS: This goes back to the bias that sedation is a surrogate for psychomotor impairment, and it may or may not be, and it was planned that way based on the time curve of mean sedation, which again doesn't identify cutliers, individuals, and assumes that it is, in fact, a 1-to-1 surrogate for psychomotor impairment, and one could imagine it not being. One could imagine becoming refractory to sedation and maintain a psychomotor impairment.

Yes, Dr. Harris?

DR. HARRIS: The concern I have is about the elderly again, whether or not one should recommend that it be used at all in anybody over 65, given that it's unlikely that many people are going to call their doctors anyway, given the sort of risks that there may well be, and there is not too much data anyway to tell us one way or another.

So the issue is whether or not to recommend the use of this drug, if we get to that stage, in anybody over 65 at all.

DR. BRASS: Could you comment on what risks you're particularly concerned being more of a problem in the elderly?

DR. HARRIS: The psychomotor I think in particular. I can't say the degree to which there is more of a risk based on the data I've seen here, but I think theoretically there could be.

DR. BRASS: So again, sedation which was measured is not an adequate surrogate?

DR. HARRIS: Well, to some degree, I guess. I guess one could say so.

DR. BRASS: Other safety issues or concerns?

(No response.)

DR. BRASS: I think we answered a lot of these issues in the context of some of the other questions.

Anything from the agency's perspective that we didn't cover?

(No response.)

DR. BRASS: Then the final question is, does anybody want to say anything else? That's paraphrasing it. Any other issues or concerns about the discussion today that haven't been brought up that individuals would like to bring up?

(No response.)

DR. BRASS: If not, and if the agency doesn't have any additional issues, I would just like to thank all the presenters who did such an excellent job of presenting succinct, on-time presentations, and all the members of both committees who contributed to a very lively but I think instructive discussion. Thank you all.

The meeting is adjourned.

(Whereupon, at 3:28 p.m., the meeting was adjourned.)