of this newsletter an article appears entitled "The Top Smart Drugs & Nutrients." Mentioned in this article is piracetam, a bulk drug substance nominated by compounding pharmacists. The article describes piracetam as "an intelligence booster and CNS stimulant with no known toxicity or addictive properties. Piracetam has been described by many people as a drug that 'wakes up your brain.'"

Piracetam has never been approved for use in this country and there is no legitimate medical use for this drug that we could find.

In some Third World countries, it is promoted for the treatment of memory loss, in others for lack of concentration and in still others for intellectual deterioration. In India and Thailand, piracetam products are promoted for the treatment of mental retardation or learning problems in children. In Malaysia, Singapore, the Middle East, Mexico and Colombia, they are recommended for the treatment of alcoholism or alcohol addiction.

Two boxed advertisements appear on page 4 of the newsletter in close proximity to each other in the same style and with the same color highlighting. These ads are reproduced below without color.

Briefly, the first ad, "How to Find a

Compounding Pharmacy." The easiest way to locate a compounding pharmacy is to contact the Professional Compounding Centers of American, Inc. or the International Academy of Compounding Pharmacists. They can be contacted as follows -- and their phone numbers are given and then parenthetically you can also ask these organizations for a referral to a physician near you.

The second adjacent ad is "How to Find a Knowledgeable and Understanding Physician." The quickest and most efficient way is to visit a medical doctor or osteopath, who is a member of the International College of Advanced Longevity Medicine or the American College for Advancement of Medicine. All members of these professional organizations are skilled and knowledgeable in the prescription and use of natural hormones and other alternative compounds.

These two advertisements show the completion of a treacherous triad between compounding pharmacists, complementary/alternative medicine practitioners and an unwitting public. Public Citizen strongly believes that the FDA and the members of the Pharmacy Compounding Advisory Committee must consider that some of the nominated bulk drug substances you will be discussing have no legitimate medical use and will be compounded by some pharmacists to exploit the public while making

exploitation appear as a noble cause.

Thank you very much for your attention.

DR. JUHL: Thank you.

We will, of course, take your comments into the suggestion hopper for future meetings of this committee.

Agenda Item: Discussion and Vote on Dermatological Products

We now will move back to a discussion and vote on the product compounds that we have discussed in the morning. Let me ask if there are general comments before I suggest a way of proceeding.

Carmen.

MR. CATIZONE: Mr. Chair, I have two points of clarification I had raised earlier. The first, I would ask representatives of the FDA to respond to, please. That is the question of if this committee recommends that a product not be included on the list of substances to be compounded and the FDA approves that recommendation, does that exclude that product entirely from practitioners and prescribers and patients or does it allow that product to be used to a more controlled system, such as the IND process?

DR. DeLAP: I think we are not interested in withholding products from people that may benefit from them. So, I would like to put that out first.

I think there are different mechanisms that people can access products. This is one mechanism we have discussed a little bit about the IND mechanism. And I think if there are products that people need to have access to, but it is your sense that you would like to see them accessed with a little more involvement of the FDA under the IND process, you certainly could give us that message.

I don't think you have to simply say "yes" or "no," this product should or should not be available because I don't think that is -- I don't see that as being what the discussion is about today. I think really it is should it be available under this mechanism and if you feel strongly that it should be available, but you think we should work on perhaps a different mechanism, then that is a message you can give us, too.

MR. CATIZONE: Mr. Chair, with that answer then, a question to the committee in terms of what is our responsibility. If we agree and accept the fact that by not placing a substance on the list, that we are not excluding the availability of that product to physicians, prescribers and patients with a demonstrated need for that substance. It is not our responsibility, as somebody mentioned earlier to decide what the availability of those products should be, based upon the

criteria, which the FDA has established.

So that if we place the substance on the list of substances that can be compounded, we are saying that that product is perfectly safe for any practitioners, duly licensed or registered to compound that product to use in any situation, including based upon information that was presented to us this morning to allow patients to home treat and titrate themselves with those medications or are we saying to ourselves we need to distinguish between products that are ultimately or perfectly safe and those products, which the FDA has produced data that indicate there is a concern and problem with safety and, therefore, we should allow those products to be available through a mechanism that addresses and manages those safety issues so that the public and practitioners involved in the compounding of these substances are safe and protected from the concerns, which have been noted and published.

DR. JUHL: Well, with the exception of using the words "perfectly safe," which I don't think any -- is used any time at the FDA or elsewhere, I think that is the sense of the issue.

David.

DR. LIEBMAN: Piggybacking on Carmen's question, you have said that there is a mechanism whereby

an IND can be obtained, give me a sense of the time frame. If I were to apply for an IND or if M.D. Anderson would apply for an IND today for one of these drugs, give me a time frame as to when they would have it such that it would be available and they could then dispense the product or the medication.

DR. DeLAP: Well, that is -- it varies to some degree, based on what the need appears to be in the particular situation. If it is a situation where there is an individual patient, who greatly needs to have a product and they need it today or tomorrow, then we do have mechanisms for that, for approving an IND and approving availability literally within a day in those situations.

The more standard approach is if we are getting a protocol in that deals with the treatment of potentially a large number of patients and it is a new IND, then under our regulations, we have 30 days to review that and respond. Again, that is more for the situation where there is a research program that is being submitted with a protocol that we are reviewing and providing comments on. And, again, the timetable there is for us to respond within 30 days.

DR. LIEBMAN: Let me see if I heard you correctly then. If we were to put these on the non-

acceptable list -- and Dr. McBurney has patients or Dr. Rosenberg has patients and they want to use either one or both of these drugs, they could put an application to your offices and within 30 days, they would have approval?

DR. DeLAP: Well, 30 days is the review time for an IND. The great majority of INDs are accepted within the first 30 day cycle. There are some that come in with some significant problems in the proposals that need to be worked through and there is a little back and forth that may take a little longer. But the great majority are finished within that first 30 day period and people can go ahead and start using the product and treating patients.

DR. LIEBMAN: One last question. Dr. McBurney has to put in an IND. Dr. Rosenberg has to put in an IND. Every physician who treats alopecia would then have to put in an IND if they wanted to continue using one or more of the products that we talked about this morning. I need a sense of clarification. I don't know the process.

DR. DeLAP: I think we would want to work with people to see if there was -- what was the most efficient way of dealing with this. If in fact there are a large number of individual physicians, who would want to be

able to use these products under an IND mechanism, our preference would be to work with people to find some umbrella mechanism such that not each individual person would have to go through the IND process, but there would be some centralized mechanism such that people could participate in a consortium, as it were, and individually have access to the product without having to go through the IND process individually.

DR. LIEBMAN: One last question. For the two physicians involved, does that sound reasonable to you?

DR. MC BURNEY: I have a couple of questions just to follow up on what you said. If it is decided not to include it on the bulk list and that is upheld by the FDA, the decision of the committee here, then it is my understanding that immediately it will no longer be available to legally compound. Am I correct on that?

MS. AXELRAD: I would say once we -- once November 21st, 1999 comes, because we have this one year grace period, once we published the final rule and we pass that November 21st, 1999 date and assuming it is no longer under consideration, then strictly speaking it shouldn't be used for compounding.

DR. MC BURNEY: With that in mind then, all of the patients who are using it or who potentially would be using it by then. For each patient we would have to

submit an individual IND. Am I correct on that?

MS. AXELRAD: No.

DR. MC BURNEY: As a physician, if I am, say, treating 10 patients that way, what would be my recourse of action as a practitioner?

DR. DeLAP: I don't think we would envision people submitting INDs for individual patients. I think that we would envision people submitting INDs for their entire group of patients in their practice. Again, I would prefer that we could come to some way of having further organizations, such that people collaborate in this process and have mutually agreed upon programs, such that, in fact, we could have one IND that would cover multiple physicians and practices.

DR. MC BURNEY: My experience as an individual in practice, having applied for individual INDs for thalidomide before that was approved and so forth. We did it on an individual patient basis and the turnaround time I will say from the FDA was very prompt and they were very good about it and within 30 days I had my approval and so forth.

But even doing those, it takes about five hours of time to get everything together with the review -- you know, the hospital review board and everything else and to get the pharmacy and everything set up, the

pharmaceutical company. With these products, would we be held to a more intensive -- not having seen the forms that would have to be filled out, for, say, to treat ten patients with it, would it be a more extensive form? Are you going to, you know -- I am trying to get a feel for how complex it would be, I guess, is my question.

DR. DeLAP: Well, we have, really just one set of forms for INDs. You know, whether it is an individual patient or a group of patients or a major, you know, multi-center protocol, it is basically the same kind of paperwork involved in an IND process.

I think the thalidomide, of course, had some special issues and I think that we were trying to be attentive to some of the special concerns with thalidomide. So, you might have experienced a little more paperwork with that in some respects.

DR. MC BURNEY: So, actually, you would say that it would be less for -- if I wanted to do ten patients, I could do it as a group and not need individual patient data?

DR. DeLAP: That is my expectation. And, again, I think we have an interest here, too, that we don't want to go through a lot of paperwork from multiple investigators about a lot of individual patients. So, we really try and work with people to do this as efficiently

as possible. Again, I think, thalidomide raised some special issues and we spent a lot more resources internally on that and ended up collecting a lot more paperwork from people externally than we might have otherwise done.

DR. MC BURNEY: Can I ask you one other question? Would the FDA consider giving, say, a blanket one to something like the National Alopecia Areata Foundation and have physicians go through them in an approved source of getting the medicine if that organization was willing to oversee that.

DR. DeLAP: I think we would be comfortable with some kind of overarching organization like that, managing an IND if they want to take it on. I don't want to say that the paperwork is trivial because it is not. There is some paperwork involved, but it is a lot more efficient to have kind of an overarching organization with a lot of participating physicians than to have everyone going through it individually.

Obviously, we have a great vested interest in getting done what needs to get done, but getting it done with the least amount of paper that we have to look at, too. So, we are not interested in having things happen that would require more paper.

DR. JUHL: I think, unlike term papers, there

is an advantage that the INDs all be the same. That has the opportunity to maximize the public benefit. I mean, that would be one of the purposes. So, it wouldn't be necessary or even desirable for individual physicians to ad hoc write their own IND. It would be useful to use the same kind of information.

DR. ROSENBERG: Thank you for letting me come back, but someone asked a question. As someone who has written INDs, they are not trivial. That would be one thing. And as someone -- and when they get it, the Agency, they get a level of review, which is not superficial. So that my reaction would be to use the IND route as a means for us to continue what we are now doing, which is treating patients, because we think it is all right, would not be right. That is not what the INDs are for. It would be -- it is not fair to the IND process, which is much too important for that.

Very few physicians will fill these out. Those that do, they don't want to read them. I think individual physician's IND kind of behavior would be wrong on -- for several reasons. I haven't thought long enough. I am sure I could come up with more reasons but I think these are two good ones. I think it would be just not the -- INDs should be treated with more respect than that, both coming and going.

The second thing is, you know, what is an IND really trying to tell you. Is this drug safe and effective? And in terms of safety, how is it going to come up with safety? I mean, the doctor has no idea what company supplied the chemical. He doesn't know how it has been analyzed. He doesn't know anything. So, when the doctor writes an IND, we are not going to know anything. If we wanted to talk about having an organization sponsor something, I think we could talk about it.

If we wanted to go back to the point I tried to make before was if we are talking about safety and efficacy, I think -- I did not prepare myself -- I must say, I did not understand the nature of this meeting precisely, that I would need to, you know, bring in all the efficacy data, as if I were bringing the drug before -- as a drug sponsor. I was speaking of the interest of the practicing physicians and I think did that fairly, but I think if you said let's have somebody who really wants to be a sponsor of this come in and present the case for it, I think the Alopecia Areata Foundation -- I can't speak for them, but I think it would be something they would certainly consider doing.

I believe with all my heart that this group or any other reasonable group would say the stuff seems safe

enough and I think the people around this table and both the Agency and within the pharmacy review experts could tell us about the safety, in theory at least. In terms of experience with safety, I think there is no -- the whole question of Phase 4 study is, of course, an enormous one. Whether you would want a registry or not, I don't think so. I am repeating myself.

Thank you.

DR. JUHL: Loyd, other questions of clarification before we begin the discussion formally?

DR. ALLEN: Yes. For the presenters this morning, if the IND/NDA approach is used, the source of the product, as it is now for your standard INDs that comes from a manufacturer or single source, you know, maybe three lot, single source type product, if we look at a compounded product, would this be limited to coming from a single source, at which point it would then become a manufactured item or would it come from pharmacists throughout the U.S. that were participating in these studies? Would they be working from the same formulation or just how would this all work down at the bottom line level? Because we are almost moving it from a compound to a manufactured product.

DR. JUHL: Want me to offer an opinion on that? I believe the IND asks you to specify your method of

manufacture, with a small "m." And I think to whatever level the group who was sponsoring or individual was sponsoring wanted to delineate that, it could be useful. And it may mean that they would say that the bulk compound should have a model certificate of analysis of whatever the most precise one is that we have and then that would allow multiple sources, as long as they met that standard with a similar certificate of analysis.

And then any pharmacist, who was operating under that IND would be obligated to follow the manufacturing process that is specified, whatever it is. So, I think there is a great deal of flexibility in that, but it would allow the setting of standards and perhaps ameliorate some of the concerns that we have over the impurities and their possible contribution either to ineffectiveness or side effects.

DR. ALLEN: I was primarily referring to formulation instead of the source of the raw drug material.

DR. JUHL: And how it could be compounded could be specified.

DR. DeLAP: I think that is exactly how I would envision it. You would have some way of saying what your expectations are regarding the bulk substance and then you would also describe in the program what are the

acceptable range of practices, as far as compounding it, to make the final product.

MR. TRISSEL: Yes. There are examples of products that have gone through the Agency that way. 2CDA, when we first had it at Anderson, we had to compound it under a set of instructions from a sponsor. But they had no product at that point. In fact, the first three or four batches had to be compounded before they finally had a product to test. That product, I believe, now is commercially on the market. So, there is an example of how it progressed. There is a mechanism for specifying or allowing compounding pharmacists to do that through the Agency and the IND process.

One question I would like to ask about the three compounds that we have been discussing have been generally classed together, but one of our speakers, Dr. Rosenberg, seemed to make a differentiation between DNCB and the other two products. I was wondering if our other dermatologists would care to agree or disagree that there is a difference between DNCB and its safety and toxicity versus the other two in clinical use.

DR. MC BURNEY: I think what has happened is that when the Ames test data was made -- was widespread knowledge, was made available to everyone, everyone backed away from it clinically as a general group. As

David has mentioned, there are people in his area that are still using it, but I think as a group they backed away from it and not because there was data about problems with its safety, but because of the fear that there could be potential danger and move to the other two products, either the squaric acid or the DPCP.

In more recent years, I think people are using more of that than the DNCB and that is -- I don't have any hard numbers on that, Larry, but that is just my impression in talking with people, who do this kind of therapy.

But there are still very good clinicians in medical centers, who are using DNCB, not frequently but for very difficult cases.

DR. JUHL: David.

DR. LIEBMAN: I am sorry. As a practicing clinician who compounds, if an organization has an IND, clarify for me what that means to me at the compounding level. Can one of my physicians write for it because there is an IND somewhere out there? Do I need special permission to make it? Does he need to be a member of that association? Do I need to get it from a particular source? Lots of questions. And I need to know what that means to me as a practitioner.

There is one thing -- let me just say when M.D.

Anderson is doing it, it is all in one building. That is kind of easier. If you have got 50 or a hundred or 200 or 500 pharmacists around the country, who are going to be impacted by it, but individually, give me a sense of how we are going to be impacted, what this means to me at the patient level.

DR. JOHNSON: Well, both of these, both the physician and the pharmacist need to be tied to the IND in some way.

DR. LIEBMAN: Does that not create an automatic nightmare? Do you send a list around and say how many compounding pharmacists in the country would like to be tied and if I want to be tied, if I don't want to be tied now and a year from now, one of my docs says, David, can you do so and so, where does that place me?

DR. JUHL: I think the tie goes through the physician.

DR. LIEBMAN: Does the physician have to be a member of the National Association of Alopecia Treaters, blah, blah, blah? I hear lots of -- I don't mean to be a pain. Okay? I am a practitioner. I need to know exactly what this means to me, to my doctors and to my patients and I need for you all to understand clearly that whatever -- you know, in your wisdom you decide this is the best way to go, that is fine and I will have to

live with it, but I need to know that you know that when you vote for something or when you agree to something, these are the ramifications and I am at the patient level. I am at the doctor level. I am at the patient level. I am at the compounding level. So, I am going to be impacted very clearly by whatever decisions the committee makes, whatever recommendations you do to the FDA.

DR. DeLAP: I think the way it is usually done would be to have a list of the participating physicians on the IND and then those would be the people that are empowered to write the prescriptions and add the patients to the program. I am not sure -- you were describing your M.D. Anderson experience. I mean, ordinarily, I think, the people that the physician works with professionally don't really need to be specified to the level of detail, as long as you have someone that is identified as being the responsible person at that site.

Again, often times it is just the physician who is actually writing the prescription and administering the treatment. So, we don't ask for information on who all might be involved in preparing the product for the administration, for example.

DR. JUHL: The only responsibility would be to the pharmacist, who was preparing it, would follow it

according to the manufacturing process.

DR. DeLAP: We would expect people would be appropriately licensed and follow their usual, you know, good practices, but we don't ask for that kind of information ordinarily.

MR. LIEBMAN: My last comment and I will let you go. If the Alopecia Society does this, what does that do to Dr. Buddy Cohen at Johns Hopkins, if he is not a member? Ergo, he can't participate? If I don't get asked, do I want to be one of the participating pharmacists? A year from now, what happens?

What I am hearing is you are about to create a nightmare. If you want to go with saying, oh, we will vote it off the list but we will do an IND, when you start looking at the mechanics of it, it is a monstrosity. I think the voters need to think about that. It is one thing to do it in an enclosed institution. There is something very different about doing it to a physician group nationwide and a pharmacist -- 50,000 pharmacists, pharmacies nationwide.

I envision lots of problems.

DR. DeLAP: I think there are definitely tradeoffs and I think you have eliminated some of the issues very clearly. I don't think anyone would have a monopoly on this kind of thing. I mean, if there was an

AA sponsored program that served as an umbrella for many physicians across the country to do this with minimal personal paperwork, that wouldn't mean that someone at Johns Hopkins couldn't say, well, I want to be on this and then if for whatever reason they couldn't just get added to the AA sponsored program, they could -- you know, they could file their own protocol and do it if they wanted to.

So, there is no law that says that if there is one umbrella organization that is doing it that nobody else can. I agree with you that there are some very real logistic questions that come up and I think I would say that it is not our interest anymore than it is yours to have it be onerous or impractical. We do have to do the best we can to manage those issues. There is a little time, as Jane was saying before this actually takes effect anyway, but not a lot and we have to do the best we can to get things organized so that it wouldn't be -- wouldn't disrupt people's lives too much.

The only other thing I would add is, obviously, the compounding list is a living document. It is not set in stone and if it was decided later on that the public health advantage was to just put one or two of these compounds on, even if they hadn't been put on originally because it was just not working otherwise, you know, we

could always revisit the issue, too.

MR. TRISSEL: To address your concern at many sites, it was M.D. Anderson, but it was also a number of other hospitals that were participating in this early phase study of 2CDA. So, we had different pharmacies and different physicians from different institutions all listed on the same IND. The pharmacies were not cited by individuals. The IND just said that the product would be made according to the set of instructions in the institutional pharmacy. That is about as far as it went.

To add physicians was a matter of adding a name to a list, along with their C.V. to show appropriate credentials, if you want to add an investigator to that list.

DR. LIEBMAN: That is easy to do at an institution. Independently, it is hard. I know you don't mean to make it difficult and I know you are not trying to exclude anybody and I know that we don't set it up in terms of, well, we can do it but nobody else can do it and we are going to exclude everybody else, so our members have control over it.

Forgive me. It gets worse and worse as I listen. It just gets more and more difficult, more and more complicated and the ones who are going to suffer are the patients. That is my real concern is patients are

not going to be able to get what they need and physicians are not going to be able to treat their patients.

DR. JUHL: Who are prescribers in your experience for this? Are they primarily dermatologists? I would expect so.

DR. LIEBMAN: They are all dermatologists. One is a dermatologist, who teaches at Johns Hopkins in the medical school. Another one is a community dermatologist, who teaches at the University of Maryland. There are other practitioners, who have --

DR. JUHL: I think there is no denying that it will offer an extra level of bureaucracy, but I think you are going far off the edge of the fence on how bad it is going to be.

DR. LIEBMAN: I would love to be wrong on that issue.

DR. JUHL: Let's assume that it is dermatologists and they need to be part of this process. It would be a simple matter, as Larry said, of them submitting their C.V. to whatever organization this is and being listed on the IND. That would take care of the physician. From your perspective, all you would need to know is that the physician is on the IND and what the protocol for preparation is. I can see that being widely distributed to all compounding pharmacists all over the

country.

DR. LIEBMAN: And to all dermatologists across the country to let them know that if they choose to use this, they need to have their name -- because I think if we do that, that needs to be a condition.

DR. JOHNSON: Well, absolutely, absolutely.

DR. LIEBMAN: Okay. If you can work it out, I think it is great. You know, I am not opposed to it, but I think we need to anticipate what are the potential problems and try and figure out how to solve them before it goes into effect. That is all. That is my concern.

DR. JUHL: I agree.

Let me suggest a little -- a path for us to take here. A little bit ago, when Dr. Rosenberg was up, I spoke for the committee and stipulated that I think the committee probably believes that these compounds are useful in some patients some of the time. I want to make sure that I wasn't stepping across the boundary. Is that a reasonable -- can be -- does anybody object to that, I guess?

Well, let's make that assumption that that is the case and you will all just have to stop me when I get too far down the road here. And, again, looking at the drugs as a class and we do need to do some individual things, but as a class, we also see if we examine our

four criteria of chemistry, historical use, safety and what is in the literature, that there is some difficulties in chemistry.

One of the foundations, the bedrock of drug development is to get a drug that you know what it is. You know exactly what it is. You know its impurities if there are any and you use that all throughout to do your clinical trials so that you can relate back to -- this is actually what happened and how and why it happened. We don't have that with these compounds in that there is variability in what comes down the pike and in some instances we may not be concerned about that, but with these drugs, I think we may be because the impurities may be carcinogenic or have other problems.

So, there is -- in my mind, some chemistry problems. I am satisfied with the thorough work that the Agency has done. Does that reflect the view of the committee at this point?

Loyd.

DR. ALLEN: Yes. I will just go ahead and add that if you recall the USP has stated that they will go into the adoption of any standards that might be required for these. You know, and also keeping in mind that there is a number of products that we have currently in use, that we don't have the full information on. So, these

four here may be -- the three here may be just a little bit different. But as far as the standard setting, I don't see that that could not be done within a reasonable, you know, length of time.

Then to our issues of safety, I think there is particular concern here about not only the safety of the patients, but also health care workers. This seems to be in my mind a bit special compared to other products that we have worked on.

I think then the issue before us is whether or not we would like to recommend that these products be listed or not and if we recommend that they not be listed, is the attraction of the IND route one that could be turned into reality without creating a nightmare for patients, as well as practitioners, keeping in mind that the FDA cannot force someone, any group, to submit an IND. They can use friendly cooperation and persuasion, but the Agency isn't in a position to be able to mandate this happens. So, we would be -- if we were going to recommend that they not be listed with the hopes that an organization come forward to develop the INDs, we would be taking a little bit of an act of -- a leap of faith to assume that that would occur.

Now, having gotten to that point, are there differentiations that you want to make between the

compounds before we actually take a vote on them? DNCB seems to have fallen by the wayside because of some of its special toxicity situations, although it is still being used.

The question I have, do we want to lump them as three and act on them in general or do we want to do them one by one? I am seeing heads shake "no" about doing them as a lump and to do them one by one. Is that -- head shakes don't do well on the transcript.

DR. MC BURNEY: I would request that we do them one by one.

DR. JUHL: Okay. Then, in turn, let's start with DNCB and dare there any additional items of discussion on that?

Are you ready for the question? My assumption is that the question is to recommend that it be listed or recommend that it not be listed with the hopes that an IND process can be worked out. Is that the question you want answered? Okay.

Let's have a call for the question. Those who are voting members, let me remind myself that David is an industry representative and Joan is an industry representative and the rest are voting members up through Loyd.

Call for the question. Those that favor list

-- recommendation to list DNCB, please raise your hands.

Seeing none, those that to not list DNCB, please raise your hands. I see that as a unanimous recommendation from the group to not list the compound.

Moving to our next alphabet soup, DPCP, let's follow the same process. Discussion?

DR. MC BURNEY: I cannot speak for the American Academy of Dermatology. I am only sitting here as a member of the committee, but I can give some opinions about what their approach would be having sat on their board of directors.

The American Academy of Dermatology is an educational organization and that is what is so stated in its mission statement. There is no organizational structure nor fiscal notes available to support a study that we are proposing. Ideally, it would be a very good place to have it and certainly we could approach the executive committee of the American Academy of Dermatology, but I doubt that that would receive a very high priority. I could be wrong on that. We certainly would need to look at it, but I think on the list of projects before them, that would not be put very high for the reason that it would not affect the majority of its members, would look at it that way.

And that there are more pressing issues, such

as skin cancer that they would -- there is a greater number of patients that we treat with that disorder that they would want to put their dollars toward. So, I don't think it is realistic to look to the American Academy of Dermatology. If we did look to the National Alopecia Areata Foundation, certainly that would be very nice for our patients with alopecia areata, but what about all our other patients with warts?

We would then have to look at other individual physicians or institutions. There is no National Wart Society. There should be because there are a lot more warts than there are alopecia areata, but there is not. So, we have got -- we still haven't addressed all those other patients that it is being used for.

As I said, this is only my personal opinion on that.

DR. JUHL: Let me ask you, are the majority of practitioners, who would use these products to treat warts the same people who would probably be using the products to treat alopecia? Are they primarily dermatologists?

DR. MC BURNEY: They would all be dermatologists, I think, generally. Now, some of the warts, they may -- I think the other groups we would need to include, of course, would be our family practitioners

who would probably perhaps use some of this. There might be some internal medicine people who would use it.

I cannot speak for pediatricians. I do not know any pediatricians and I couldn't speak to infectious disease. The buck stops with the dermatologists, I think.

DR. JUHL: For the record, Dr. Rodriguez said he would refer those patients to a dermatologist.

Let me ask the question of the Agency. It would seem to be some extra work but not much for an IND to include both. Could the same mechanism be used -- the same IND be used?

DR. DeLAP: Certainly in principle. I mean, we do have INDs that cover multiple indications and don't require additional -- you know, another IND and another set of paper work. Again, I would like to stress that our interest in this is really not to deny this approach to anybody that really looks like they need to have it. Our interest really is just to do what we can to address some of these -- the chemistry concerns and the safety concerns and to learn a little more about the products as time goes on.

So, that is really where we are coming from and we don't want to limit the ability of somebody who really needs these kinds of treatments to get it. And we are

very concerned -- again, I come back -- we are very concerned about logistical issues and we will look at these issues as carefully as we can and try and minimize them to the best of our ability. Again, we can -- I would say, again, we can revisit this whole subject if it turns out that logistically that it is too much of a problem to do it the way that we start.

MR. CATIZONE: Mr. Chair, I think there are two issues here and I would ask for some assistance with trying to understand how we differentiate or complement the two. One would be the question of safety. If this committee has a concern with the safety of a product and not addressing that safety by placing that substance on the list means that it is free for use for everyone, every practitioner duly licensed or registered to do so, including patients to self-medicate or self-treat, versus the issues raised by David and Elizabeth, which is access to those medications, can't our recommendation be that if we have those safety concerns, we separate that issue and recommend that those products not be included on the list, with the proviso that these medications be made available through the IND process or through working with the Agency.

If that doesn't occur, if we receive information that the process is too burdensome or

patients are being denied access, could we revisit the topic and then place those medications or those substances back on the list?

DR. JUHL: I think that is what was suggested. I think that is reasonable.

MS. AXELRAD: Can I make one comment?

With regard to self-medicating and taking it home, I would remind you that we propose to limit the use of some of the other products that we addressed at the last meeting for office use only. So, we think that that is an option and that would address some of the safety concerns.

DR. JUHL: Other comments on DPCP? Are you ready for the question? Same question?

DR. MC BURNEY: Can I make an amendment to the -- can I make one of them be that we would include -- if we are going to talk about DPCP -- be administered in a physician's office and be put on the bulk list, as we did with cantharidin. Can that be one of those?

DR. JUHL: We could, indeed. The question that we will answer is, number one, to recommend that DPCP be added to the bulks list with the restriction that it be limited to application in the physician's office or, secondly, we could recommend that DPCP not be added to the bulks list with the expectation that if there is

sufficient interest, that the Agency would work with a willing group to go the IND route.

Clear on the question?

All those who would favor recommending DPCP be added to the list with restrictions, please raise your hand. We have five voting for that option.

Secondly, those that would recommend that it not be added to the list, please raise your hand. We have five with that option. The chair breaks the tie by siding with the second option of "nay." So, it is 6 to 5 for option 2.

Let us move then to squaric acid dibutyl ester. Is there anything that we haven't covered in the first two that you would like to cover with this one or any difference in the chemical itself that we should consider?

Bill.

DR. RODRIGUEZ: I want to raise a question. Assuming that IND doesn't go through, how long would it be before we get the screamings, for example, to let us know that the system isn't working? In other words, I am just sitting over here, again, as somebody who has no direct effect in terms of my patients, but on the other hand, I am just thinking over here, saying, gee, how long is it going to take before we know that 50, 60, a

hundred, 250, for example, and what the mechanism is going to be.

DR. JUHL: I think we have between now and November 21st to get an indication that the process is not only possible, but it is something that can be workable and the Agency has expressed their concern that they want to make sure that this happens in an appropriate way. So, I think between now and then, we would be able to tell that the process could work were the situation such that -- it is not going to get completely done by then. There would be ways to make sure that it happens in a way that it doesn't disadvantage people. I don't want to speak for the Agency, but that is what I thought I heard you say.

DR. DeLAP: I think, again, our primary goal here is that the patients get the best possible advantage out of this. I mean, the best possible advantage for me is that they have access to the product and they have access to it in a good form. It is a good chemical. It is well-formulated. It is well-administered and that they get the best possible results as a result and that we learn more about it along the way.

I don't think it is a black and white situation in the sense that things will -- you know, that November will come and it will be absclutely a total flop or that

it will be totally working. I think we will probably be somewhere in between, but we will have to look and see how much of a burden it appears to be placing and if there are limitations on access, we have to look at that very seriously. It is not -- I am sure it is not going to be perfect going in, but we will do our best to make it as good as possible and, again, we can always come back here for discussion if it seems to be just too far out.

DR. JUHL: I believe the committee's next meeting will be in the fall, prior to the November 21st deadline, and, obviously, we would be interested in a report back on that as to whether or not --

DR. LIEBMAN: Point of information.

DR. JUHL: -- we should reconsider the issue.

DR. LIEBMAN: If between now and the fall meeting, someone tries to get an IND and there is a problem, could we possibly look at these drugs again since we now know that the -- if we find that the IND mechanism is not going to make them available?

DR. JUHL: Yes. I think that is what I said. Yes.

Elizabeth.

DR. MC BURNEY: I am sorry to be so persistent, but I just want to be sure we haven't -- I don't want us

to blind ourselves that there is not another option, another way of doing it so our patients can still have the medicine.

Is it possible since what I am hearing from our distinguished people at the FDA, who have spent a considerable amount of time looking into the safety data -- and I have great respect for that -- is it not possible to somehow limit it to a mono source for the next drug we are going to look at so that what is available for bulk compounding comes from only one source? Is that possible? So that we could say not only does it have to be done only in a physician's office, but only from one -- we will allow bulk from one area, from one source.

MS. AXELRAD: I am hardly the expert on this, but I would say that it could possibly come from multiple sources, but we would look at the source and we would -- I mean, the way we usually do it for an IND is that they provide information on what the source of the drug is and the method of synthesis and the impurity profiles and we would look at that. If someone wanted to propose two sources or three sources, that would be all right.

We would still be able to look at that and make sure that it was acceptable. We wouldn't want to say it has to be only one source. It might be perfectly fine

for it to come from two or three different sources, as long as it is produced in a way that provides a quality product.

DR. DeLAP: I think you are talking about under IND, though.

DR. MC BURNEY: Yes. I was talking about under bulk.

DR. DeLAP: She was asking about under bulk, compounding, whether we could specify a limited number of sources where it was acceptable for compounding purposes.

MS. AXELRAD: No. I am sorry. I misunderstood the question. Compounding, as long as it is a registered manufacturer and it is provided with a certificate of analysis, that is what the statute requires.

DR. JUHL: Other questions?

We shall then move to squaric acid with the same question. We will use the same options. Option No. 1 is to recommend that squaric acid be listed on the bulks list with the restriction that it be used only in the physician's office. Option No. 2 is that squaric acid not be recommended for the bulks list.

All those that favor recommending listing, please raise your hand. We have six.

All those who favor Option 2 of recommending not to list the drug, please raise your hand. Four and

the chair votes "no." Five. So, it is 6 to 5 in the other direction, squaric acid being recommended to be listed.

Any final comments?

[There was no response.]

I would like to add my thanks to the Agency for all the reviews that were received. It has been a tremendous amount of work on your part and it has required work across the disciplinary lines within the Agency and I know that doesn't always work smoothly. It certainly doesn't at my university. It requires some extra effort, things that you probably didn't plan on doing. So, I really appreciate the effort that it took to put that together.

We will adjourn for lunch and reconvene at 5 minutes to 1:00.

[Whereupon, at 11:55 a.m., the meeting was recessed, to reconvene at 1:00 p.m., the same day, Thursday, May 6, 1999.]

A F T E R N O O N S E S S I O N [1:02 p.m.]

DR. JUHL: We will reconvene. The group will now make a flawless transition from dermatology to neurology. We have a number of new people from the Agency at the table and I would ask you to introduce yourself in the microphone.

DR. BEHRMAN: Rachel Behrman, deputy director, Office of Drug Evaluation 1.

DR. KATZ: Russ Katz, acting director, Division of Neuropharmacological Drug Products.

DR. FEENEY: John Feeney, medical officer, Division of Neuropharmacological Drug Products.

DR. SOSTEK: Andrew Sostek, clinical reviewer, Neuropharmacology.

DR. JUHL: We have a series of presentations this afternoon on 4-aminopyridine and 3,4-diaminopyridine. These are drugs that are used to treat very serious conditions for which there are few options. At present, these drugs are not of the USP monograph or an NDA'd product and they are made available to patients sometimes through pharmacy compounding and sometimes through the IND route.

We will be reviewing a number of issues regarding these drugs and Dr. Feeney will begin the presentation. I will turn it over to you.

Agenda Item: 4-aminopyridine

DR. FEENEY: Thank you.

My purpose is to give a brief overview of the aminopyridines. Additionally, we have various specialists here today, who will also speak to their personal experience with the use of the aminopyridines, both 4-aminopyridine and diaminopyridine.

Dr. Sanders from Duke will later talk about the use of diaminopyridine in a rare disorder, -Eaton Syndrome and Dr. Bever from the University of Maryland will hopefully share his experience with the treatment of MS patients with both 4-aminopyridine and diaminopyridine. Then we also have three commercial sponsors, who will talk to you.

Again, my purpose is to provide a brief overview of both drugs, first for 4-aminopyridine . 4-aminopyridine is a potassium channel blocker that can be used to enhance the propagation of action potentials along injured axons and to enhance synaptic transmission. It has been used in patients with MS to improve neurologic function, as well as patients with chronic spinal cord injury.

4-aminopyridine is commercially available as a white to off-white crystalline powder. It is unstable at room temperature if exposed to light and humidity.

Special care may be needed for handling bulk material because of potential toxicity if inhaled, absorbed through the skin or swallowed.

There are two reasonably sized controlled trials of 4-aminopyridine in the treatment of MS mentioned in the literature. This first one is published in detail, while details of the second study are not completely available. In this first study published in 1992, 70 MS patients with chronic stable deficits were treated for 12 weeks with 4-aminopyridine or placebo and then crossed over to the other treatment.

At the end of the study, there was a small but statistically significant benefit seen on the expanded disability status scale, a standard 10 point rating scale in MS studies. Also, while 10 4-aminopyridine patients improved by one full point on the EDSS, no placebo patients did so.

This one point change is generally considered to be clinically meaningful. The dose used in this study was 0.5 milligrams per kilogram per day, which for an average adult would be about 35 milligrams per day. We know that during the open label extension study, two of these patients went on to have convulsions.

A second larger study was performed, presumably following up on the positive results already seen. This

second study enrolled 161 MS patients in a six week parallel trial. No difference was seen in the number of patients improving on the EDSS at the end of the study.

Approximately 20 percent of patients improved in both treatment arms. The dose that was used here was 45 milligrams per day of a slow release formulation. Several seizures were also seen in this study.

Now, chronic spinal cord injury can be in many ways analogous to stable MS and 4-aminopyridine has been used in spinal cord injury patients also. While this 26 patient crossover study found no difference on its specified primary outcome, a composite endpoint, there were trends in favor of the drug seen on a sensory scale, as well as a patient global assessment scale.

The dose that was used here was 35 milligrams per day, again, of the slow release formulation. Later today, hopefully, Dr. Ron Cohen can talk about a larger, 60 patient study that was performed also in spinal cord injury. Those results are not yet published in the literature.

Here you see the common adverse events that are seen with 4-aminopyridine and I think the same profile exists for diaminopyridine, although with diaminopyridine, you may see more of the abdominal pain and paresthesias predominating. But the two more serious

concerns are listed here. One is a realized problem and one is a possible problem that really merits further evaluation before we can say much about it.

Seizures are the major concern with the use of 4-aminopyridine. In our literature search, we found a total exposure across all diagnostic categories of 409 individuals. That would include patients with spinal cord injury, MS, botulism, anything. The individuals were treated with different doses, ranging from 15 to a hundred milligrams per day. Likewise, they were treated with different formulations, varying from immediate release to slow release and peak blood levels would be expected to be lower with the slow release preparations.

But ignoring all those differences, we found six seizures for an overall risk of 1 in 68 for a risk of convulsions.

The QT interval on the electrocardiogram is directly related to potassium currents in the heart. It is strongly predicted that a potassium channel blocker, like 4-aminopyridine or diaminopyridine, would prolong the QT interval and put patients at risk for cardiac arrhythmias that could in some cases lead to sudden death.

While QT interval prolongation has not been reported with 4-aminopyridine or diaminopyridine, we are

not sure that it has been adequately assessed in the experience to date. There are two reports that raise concern. Both are with diaminopyridine. The first is the report of a death attributed to MI in a middle-aged patient, newly exposed to diaminopyridine for -Eaton Syndrome.

Unfortunately, the details of that case are unavailable. The second case is that of an older woman with an inadvertent overdose of diaminopyridine. Initially, she had convulsions, but four days later, as she was recovering, she had an unexplained cardiac arrest. Fortunately, she was resuscitated and survived without sequelae.

Diaminopyridine is also a potassium channel blocker that can be used to enhance the propagation of action potentials along injured axons and to enhance synaptic transmission. It has been used in patients with MS to improve function, but its main use has been in the treatment of -Eaton Syndrome.

-Eaton is a rare disease, which can occur either spontaneously or in the setting of cancer, especially lung cancer. Antibodies are produced, which affect the calcium channels on presynaptic neurons. Synaptic transmission is reduced and patients experience muscle weakness and autonomic symptoms. Perhaps only 300

patients are affected in the United States at any given time.

Diaminopyridine is also commercially available as a white crystalline powder. Like 4-aminopyridine, it is also unstable at room temperature if exposed to light and humidity. In 1989, McEvoy, et al., published this report in The New England Journal. The authors enrolled 12 patients with -Eaton in a crossover trial with three day treatment periods. Not only did symptoms improve, but there was good electrophysiologic correlation with the doubling of compound muscle action potentials.

The dose that they used was a hundred milligrams per day. One of their 12 patients had a convulsion after ten months, but was able to continue successfully on a lower dose of the medication.

Donald Sanders, who is here today, recently reported on his ten year experience at Duke University treating Lambert-Eaton patients with diaminopyridine. Roughly half of his 40 patients returned to normal levels of functioning. In his report, Dr. Sanders mentioned an ongoing trial, which, hopefully, we will hear about more today.

Diaminopyridine, like 4-aminopyridine, has been studied in MS patients. Dr. Bever performed a 36 patient crossover study. Treatment periods were 30 days long,

with a 30 day washout period. The dose used was a hundred milligrams per day. Favorable results on measures of leg strength were seen in the trial.

Paresthesias and abdominal pain, limited dosing in seven patients and one convulsion was recorded. So diaminopyridine, we have the same two safety concerns that were discussed for 4-aminopyridine; namely convulsions and QT prolongation. For diaminopyridine, we had a total exposure in the literature of 300 individuals.

Ignoring one convulsion that was in a patient with brain cancer and a convulsion attributed to theophylline toxicity, we found three other convulsions, which would leave a risk of about 1 in a hundred for convulsions.

It is because of the risk of convulsions and our concern about QT prolongation with both of the aminopyridines that the Division of Neuropharmacologic Drug Products believes these drugs should not be put on the compounding list at this time.

We believe that current experience with both of the drugs should allow for the accumulation of more data to hopefully improve their later safe use. And as the afternoon goes on, alternative distribution mechanisms that have been proposed will be discussed in more detail.

Thank you.

DR. JUHL: Thank you.

Are there questions on the presentation -- and, I guess, before I get to that, let me welcome Dr. Sid Gilman to the table. Dr. Gilman is the chairman of neurology at the University of Michigan and chair of the FDA Advisory Committee on the same topic.

Welcome, Sid.

Questions for Dr. Feeney?

MS. HOPE: I have one question. Do I understand correctly that there are two of these studies that use this slow release form?

DR. FEENEY: No, I am sure there -- I know there are more smaller studies that have used the slow release form.

MS. HOPE: And this was a commercially available slow release form so that I guess my relation to this is that if this were to go on this list, that then compounding pharmacies would not necessarily be compounding a slow release formulation that was comparable.

DR. FEENEY: That is correct. I would guess that most of the compounded product would be immediate release and Dr. Bever has studied the relationship between C-Max and convulsions. He may talk about that

today. He believes that there is a relationship between the two and with the slow release formulation, there may actually be a lower C-Max and less of a risk.

DR. JUHL: Other questions of clarification?

[There was no response.]

Thank you. I am sure we will be calling on you again later.

Next is Dr. Chris Bever of the University of Maryland, professor of neurology.

DR. BEVER: Good afternoon. I have been asked by the staff to discuss our experience working with 4-aminopyridine.

DR. JUHL: By the way, those slides were handed out at lunch to the committee members. There should be a piece of paper that the first slide has Dr. Bever's name on it.

DR. BEVER: And it is my responsibility that they didn't get to you until lunch. So, I apologize for your not having more time to go over them.

I thought I should review just briefly some things about multiple sclerosis. I wasn't sure how much all the members of the panel knew about it.

There are about 250 to 350 thousand cases of multiple sclerosis in the United States. It is a disease that has its peak age of onset in the twenties and

thirties. It generally does not significantly reduce life expectancy. So, it is a significant cause of neurologic disability, beginning in young adulthood.

It is a chronic inflammatory, demyelinating disease of the central nervous system. It can follow either a relapsing remitting or a slowly progressive course and it produces a wide range of neurologic symptoms, which relate to the location of lesions within the central nervous system.

Okay. There are treatments for multiple sclerosis and there has been quite a lot of interest in those treatments, but the newest treatments on the market, I would like to point out are preventative treatments, not restorative treatments. So, they do not offer symptomatic relief to patients with deficits from multiple sclerosis.

There are no treatments for some of the most common and disabling symptoms of multiple sclerosis, such as weakness and many patients have multiple symptoms and the available symptomatic treatments are generally effective only on one symptom.

The pathology of multiple sclerosis is one of inflammation with demyelination and accidental loss. Conductional abnormalities are produced by demyelination with swelling of action, potential propagation and

blockade of actual potentials in some situations.

There is evidence that some deficits in MS patients are physiologic; that is, not anatomic loss, but physiologic derangement of nerve functioning. That comes primarily from studies of the effect of cooling and warming MS patients; that is, symptoms in some patients improve with cooling and they worsen when patients' core temperatures are elevated.

There are two mechanisms related to demyelination that are proposed for 4-aminopyridine in MS patients. The first is improving action potential duration amplitudes and velocities in demyelinated axons and the second is to increase transmitter release with reduced numbers of axons and synaptic endings.

There were a number of early studies of 4-aminopyridine in multiple sclerosis. The initial was an open label study that was done in the U.K. Then there were a series of partially controlled and partially blinded studies that were carried out by Floyd Davis and Dusan(?) Stephaski(?), at Rush Presbyterial Hospital in Chicago. In these studies, improvement was seen in a variety of deficits in MS patients. It did seem to vary from patient to patient. The side effects were relatively minor in a total of about 59 patients who were treated in these studies and the exposures were up to

about one week.

The only side effects that were reported were paresthesias and dizziness. No serious adverse events.

That work led to the study, which has already been mentioned this morning by Chris Pulman and others in Amsterdam, which was a randomized, double blind, placebo controlled crossover design study, included 68 patients, who were treated for three months, no serious adverse events were reported in a 204 patient month exposure period and there was, as mentioned before, an improvement in overall disability scores in those patients.

This summarizes the side effects from those patients with dizziness being by far the most common paresthesias, fairly common gate problems, abdominal pain and anxiety, less commonly.

Responders from that trial were put into an open labeled safety study. There were 23 patients who went into that trial. Treatment durations were from 6 to 30 months. Most of the patients reported sustained improvement during that time. Two patients, as mentioned before, had grand mal tonicoclonic seizures. One patient was reported to have had a chemical hepatitis.

We were then approached by Elan Pharmaceutical Research Company to do a study, looking at pharmacokinetics and efficacy of 4-aminopyridine. This

was looking at an immediate release formulation. We did a randomized, double blind, placebo controlled, concentration controlled, crossover over design trial in eight patients who were treated for up to 36 hours.

This study, again, was mentioned earlier in that we saw there was a relationship primarily between the area under the curve or total drug exposure and improvement of neurologic deficits. We also saw a single seizure in the patients whose drug levels were being monitored at the time of the seizure. So, we knew that the level was about 104 nanograms per ml. In general, in looking through the occurrence of adverse events and looking at the actual serum levels in those patients, there appeared to be a reasonable correlation between symptoms and peak levels.

DR. JUHL: Could I ask for a clarification on that point?

DR. BEVER: Yes.

DR. JUHL: The people who experience seizures had high peak levels or the seizures occurred at the time you would expect --

DR. BEVER: The seizure occurred at the peak and a number of other side effects also occurred coincident with the peak or close to.

This formulation was then tested in an efficacy

study that was carried out at the University of Rochester. It was a randomized, double blind, placebo controlled, crossover trial. Ten patients were treated for up to seven days with a slow release formulation that was developed by Elan and I believe that they will go into some detail on the issues related to developing that formulation later.

There was improvement in quantitative measures in all the ten patients, who were studied in this and there were no serious adverse events. We enrolled 22 patients who participated in pharmacokinetic studies of the slow released formulation in an open label safety study. And the treatment exposure in those 22 patients ranged from 6 to 42 months. There were a total of 52 patient years of experience in this group. There was long term efficacy in 16 -- that is, greater than two years of efficacy in 16 of the patients.

There was one grand mal seizure, which occurred after the patient had been treated for 24 months. Now, it was mentioned before that the major side effect of 4-aminopyridine is seizures. There is in vitro evidence suggesting that aminopyridine treatment increases both inhibitory and excitatory transmitter release in hippocampal neurons and in other areas.

That is likely to be the underlying basis of

epileptogenesis. Seizure induction is a dose-related effect in animals. The early experience with this was in an outbreak of botulism poisoning in Birmingham, England. 4-AP was given intravenously and two patients in that group had seizures and drug levels at the time were estimated in the range of 35 to 90 nanograms per ml in one patient or 140 to 475 in the other.

There have also been cases reported by poison control in New York. A couple of these were reported in the literature and in one a drug level was available and it was 136 nanograms per ml.

In the concentration controlled trial that I already mentioned, the level in the patient, who had a seizure was 104 nanograms per ml. In the Dutch open labeled study, which I mentioned before, there were two seizures, but serum levels were not available in those patients. It has already been mentioned that there was a U.S. multi-center trial, which has not been fully reported. Three patients in that study had seizures.

The drug levels coincident with those seizures were 47, 7 and 140 nanograms per ml with the 140 nanograms per ml apparently related to an accidental overdose. There are also many anecdotal reports of seizures in patients taking various forms of 4-aminopyridine and I guess to clarify from the compounding

pharmacies, you can get either an immediate release formulation or you can get what is called the slow release formulation, which is basically 4-AP, mixed with carboxymethyl cellulose.

I guess I could add at this point as an anecdote that in our open label safety study, we had to terminate treatment last summer and 11 of those patients continued or were switched over to compounded slow release 4-aminopyridine and one of those patients had a seizure last fall after about three months on treatment. This is somebody who had not had a seizure in over three years of treatment with the other slow release formulation and then was rechallenged and had another seizure after several weeks on treatment and that patient has now been stopped.

Another patient, who I think Ron Cohen will mention, is currently in the hospital in Frederick, after presenting in status epilepticus. So, we had a rather disappointing experience in our patient group switching them over to the compounded drug.

In conclusion, epipletogenesis, I think, is the most serious toxicity that has been demonstrated. Seizures appear to be serum concentration related, but it is important to realize that the seizure threshold appears to vary quite widely from individual to

individual. The toxic, the therapeutic margin, may be very narrow in some individuals. The overall risk of seizures in MS patients, who are appropriately dosed and carefully monitored, is probably under 5 percent, which is comparable to the risk that was found with beta seron(?) treatment, which is a currently approved treatment for MS.

Then the last transparency, 4-AP may produce a modest improvement in some symptoms in some MS patients. For patients with no alternative treatments, these improvements may be highly valued. The efficacy of 4-AP in MS has not been proven in a large, well-designed trial.

I would be happy to take questions.

DR. JUHL: Questions of clarification?

Dr. Gilman, Dr. Katz.

DR. GILMAN: Chris, can you give us some anecdotal idea of what these patients were like on drug? They improved on the functional scales, but what does this really mean translated to the individual patient? Was the patient able to walk on drug and not previously able to walk? Or was walking greatly improved so the quality of life was improved? What did it do?

DR. BEVER: Okay. I used the term "modest" in the slide because we are not seeing the Lazarus effect,

where a patient is non-ambulatory and you give them this drug and they are walking. We have had one patient like that and Andrew Goodman has had one patient like that. But those are patients, who were sort of poised on the brink of just having lost a function and if you gave them back 10 percent, they would be able to do much more.

Typical would be improvement in strength and improvement in fatiguability and endurance. For those of you who don't deal with MS patients a lot, although we speak of this as a disease, a neurologic disease, one of the most disabling symptoms is the fatigue that goes along with the neurologic impairment that patients have. I think if you talk to a broad range of patients, who have been on this drug, that would be the main thing that people would report to you; that is, the woman who is at home is able to do more housework, is able to get up the steps.

We have an example of a patient here, who could walk with assistance around the house and on 4-AP was able to walk in the neighborhood and get out and just in many cases be able to do a full day's worth of activity; whereas, they couldn't without this drug.

DR. LIEBMAN: For your patients who needed a compounded medication, who compounded it? Do you know?

DR. BEVER: I do not direct patients to a

particular compounding pharmacist and I can't tell you which pharmacist provided this drug. I have a list of about a dozen pharmacies and I tell patients to call them and find out what their prices are for what they need and go where the price is best. But maybe that is bad advice in retrospect.

DR. JUHL: Dr. Katz was next and then Dr. Sellers.

DR. KATZ: I am interested in your conclusion that the seizures are concentration related. I am just not clear on what you mean. Apparently, seizures occurred at the concentrations from 30 to 140 or thereabouts. I am just wondering how you come to that conclusion or what you mean by it in some sense.

DR. BEVER: Okay. My thinking is that a given patient has a threshold level above which they will have a seizure and that if your drug level is below that, they will not, but that the level at which you can induce a seizure varies from patient to patient and the reason -- I mean, this makes sense to me in terms of MS because we have a disease, which is randomly causing inflammatory lesions in the brain. Some of those lesions are going to be closer to cortex in some patients than lesions are in others.

There are actually a couple of anecdotal cases

of people, who had been doing well on 4-aminopyridine, who had seizures and we did on one of our patients and another patient that I am aware of had MRI scans, which showed that they had cortical lesions at the time of the -- that were new, basically, found after the seizure occurred and were not present on earlier MRI scans, although we don't know exactly --

DR. KATZ: So, you think there is an interaction between disease location and propensity to have a seizure with treatment? In other words, you have to have a near cortical lesion to have a seizure with this?

DR. BEVER: Well, no. We can make a seizure in a normal person. So, it can't be just that simple. But I think that if somebody has cortical lesions, that probably increases the likelihood of their having seizures.

But I think -- I mean, really what you want is good, titrating up people to when they have a seizure so that I could say the threshold in you was this level and in me was some other level, we don't have data like that.

DR. SELLERS: You are touching on my question there.

Monitoring of the drug level, how routine is that and what is the availability of having levels done

at a lab across the country? I mean, is it something that you have set up in your practice or --

DR. BEVER: Okay. The levels that were done in some of our studies were carried out in the School of Pharmacy at the University of Maryland. Jim Leslie set up an assay. That was done during the period of the concentration control trial and for some time after that. As far as I know right now, the only levels are from Elan and I am not sure of that. There may be another source for them. They can be done, but usually the turnaround time is in a matter of days. It took a lot of logistical support in order to get levels back in three hours, which is what we required for the concentration control trial.

DR. SELLERS: It appears that we are looking at a drug that may have a narrow therapeutic index and in that case, it would most likely require routine monitoring of levels.

DR. BEVER: Well, we have thought about that. The problem is that you have some people who had a seizure at 104 nanograms per ml and somebody who also had a seizure at 44 nanograms per ml. So, I am not sure that therapeutic --

DR. SELLERS: Well, you were mentioning titrating the dose based on levels or based on therapeutic response to the drug?

DR. BEVER: Yes. Practically speaking, we would look at therapeutic response in patients and that is how we titrate it.

MR. TRISSEL: I believe you mentioned that you had several patients in your study who dropped out for some reason that was unspecified and you referred them to a compounding pharmacy. Was there no effort to get the Elan product donated for off-study use for these patients to continue them on?

DR. BEVER: WE went through a rather long and protected negotiation, which ended up in my getting an IND number so that we can do that, but it never occurred. We never got drug.

DR. RODRIGUEZ: How useful it was in cases where a patient had seizure, let's say, to try to prevent the seizure? I am talking about other -- in other words, epileptogenic control. Did you try that in some of the patients that you tried to titrate?

DR. BEVER: Okay. I guess the question is if a patient had seizure on 4-AP, would it be useful to put them on an anti-epileptic drug and then put them back on 4-AP. I guess there are two different aspects to that question. The first aspect is it has been tried, not by us. There is a practitioner in New York City, who has prescribed 4-aminopyridine quite widely and he had enough

seizures so that he started putting people on concomitant treatment with anticonvulsants, but from anecdotal reports that I have obtained, he still had patients having seizures, even though they were on anticonvulsants at the same time.

The second issue is that we have actually reported a couple of cases where patients were given carbomazopine for trigeminal neuralgia while they were getting 4-aminopyridine and the patients reported to us without us prompting them at all, I promise, that they saw a decrease in efficacy. Theoretically, if you give a sodium channel blocker, that can undo some of the beneficial effects of the potassium channel blocker.

So, we may be somewhat limited in the drugs that can be used along 4-AP to try to do this. Depacote, valproic acid would be one that has been suggested. That is the situation with the use of anticonvulsants right now.

DR. GILMAN: I would like to follow-up on Dr. Katz's question. I think the advent of seizures in any particular patient is the major concern here with respect to safety. So, the question is, first, do you know whether there is a higher frequency of seizures in MS patients compared to any other group that has tried all this medication?

DR. BEVER: Again, I can't speak in detail about the spinal cord injury studies, which I only know sort of superficially, but my understanding is that they have not had seizures in the spinal cord injury group --

DR. GILMAN: In Lambert-Eaton.

DR. BEVER: In Lambert-Eaton, I am less sure about. Dr. Sanders is here. He can --

DR. GILMAN: I have a communication that I will tell you about in detail later from one of the people at the Mayo Clinic, who did the -- who reported on the 1989 study in Lambert-Eaton Syndrome. They believed that seizures were very rare, as long as you keep the dose under 25 milligrams per day -- sorry -- four times a day. They believe that the blood level, in fact, is key. The question is whether there is a bigger variation in MS patients than in Lambert-Eaton.

DR. BEVER: Okay. Now, they are working with 3,4-diaminopyridine.

DR. KATZ: Yes, I know, and it is slightly different.

DR. BEVER: Our study was mentioned. We had one seizure out of 36 patients, who were each exposed for a month.

So, anyway, to get back to your question, I think that there probably is some difference in the

frequency of seizures in different patient populations and I think, again, we are reviewing the evidence in MS. We came up with a number, something under 5 percent, 3 to 5 percent, something in that range. I think that is higher than has been reported in spinal cord injury.

DR. JUHL: Dr. Katz.

DR. KATZ: Yes. I just wanted to make a comment about whether or not an event is rare, as you suggest it might be with 3,4-diaminopyridine in the Lambert-Eaton patient. "Rare," I guess, is in the mind of the beholder. I don't know what the size of the cohort is that -- even though you showed me that -- what the size of the cohort is, but if you have 50 patients, let's say, even if they have that many, and you don't see a seizure, it could still be fairly common and it might have been missed.

So, I just -- sort of as a word to the wise. I guess we will hear about that.

DR. MC BURNEY: Dr. Bever, the patients now that are on the medication, they are receiving it through an IND from a drug company?

DR. BEVER: No. The patients -- I had a group of patients who were in an open label safety study. The open label safety study was terminated by the sponsor. I applied for an IND in order to try to continue to be able

to provide the drug to them outside that safety study. We were never successful and I got the IND, but I never actually got the drug.

So, those patients were given the option of going on the compounded drug and that group of 11 patients is the one that I mentioned, where we have had a couple of seizures.

DR. JUHL: When you say you couldn't get the drug, you know, the drug product from the sponsor, the same product?

DR. BEVER: Right. We needed to get the drug from Elan. That is what we were trying --

DR. JUHL: The drug product, the final formulation.

DR. BEVER: Right. And we were never able to get that.

DR. MC BURNEY: And that company is no longer carrying out the studies?

DR. BEVER: No. Elan is still the manufacturer of the study. They licensed the drug to Acorda and Ron Cohen will be talking to you later as a representative of that company.

DR. MC BURNEY: Thank you.

DR. JUHL: Other questions of clarification?

[There was no response.]

Thank you very much.

We will now move to Multiple sclerosis. Sharon Hamm, who is a senior vice president, Research and Development Technical Operations for Elan, to talk about formulation issues related to 4-aminopyridine.

Again, that handout was given to you during lunch, I believe.

MS. HAMM: Good afternoon.

I am Sharon Hamm of Elan Corporation. Elan is a leading provider of drug delivery technology. As a pharmacist, I understand both the art and the interest in compounding prescriptions.

My focus for today's meeting, however, is to help you understand why fampridine, which is also known as 4-aminopyridine or 4-AP, should not be considered for routine pharmacy compounding. I would like to provide you with some background understanding of fampridine and the particular difficulties associated with its compounding that could affect its safety and effectiveness in its performance, particularly in patients who are often quite ill and frequently on multiple pharmacologic regimens.

Fampridine, as you have heard, is a potassium channel blocking agent, which is currently in clinical development for symptomatic treatment in multiple

sclerosis and spinal cord injuries. The clinical development is conducted under an IND, sponsored by Acorda Therapeutics.

Dr. Ron Cohen of Acorda will address you as well following my remarks.

Although Acorda is responsible for the clinical development programs for fampridine, Elan has been involved in the dosage form development aspects of fampridine and we supply the clinical trial materials. We believe our experience in the development of the fampridine dosage forms is important to your understanding regarding its suitability for routine pharmacy compounding.

Over the last six years, we have conducted a range of formulation development activities with fampridine covering immediate release, IR, and modified release, MR, dosage forms in both capsule and tablet presentations while the preclinical and clinical development activities for fampridine were progressing.

From our immediate release development experience, we demonstrated product performance, which indicated linearity across a dosage range of 10 to 25 milligrams, a half life of approximately 3 1/2 hours, a considerable food effect with a maximum concentration that was lowered by 50 percent and an AUC that was

lowered by 15 percent, a narrow therapeutic index, particularly evident with significant CNS side effects, which appear dose related in MS patients.

Therapeutic levels, as you have heard, were on the average range, 20 to 70 nanograms per ml, with serious side effects often observed in excess of a hundred nanograms per ml. As Dr. Bever mentioned, this could vary. We experienced numerous formulation challenges in developing either the tablet or capsule dosage forms of fampridine.

For the tablet formulation, there were significant interactions with diluent, loss of potency on stability, which was directly related to temperature, humidity and container. For the capsule formulation, we saw significant excipient interactions as well, stability problems, which included loss of potency and unpredictable product release, along with drug migration into capsule shells.

This experience background led us to develop a specific modified release or you have heard sustained release formulation, which was designed to address some of these features, specifically the modified or sustained release product, provided the same extent of availability as with an IR formulation, although reduced the C-Max, thereby reducing peak-related side effects, providing

minimum peak to trough(?) variability, if you would, smoothing out the curve, a lack of food effect, improved GI tolerability, twice daily dosing and a more stable formulation.

Even during this modified release development, we continued to experience formulation difficulties, which was consistent with our IR experience. This included, again, polymer interactions, excipient interactions, container material interactions and degradation products.

We are aware of the availability of pharmacy compounded formulations of fampridine, both foreign and domestic. We required a random sample of fampridine from two different compounding pharmacies for analysis. We recognized that as these were randomly selected samples, they may not adequately represent the findings of a broader sample. However, we thought the findings would be of interest to this committee.

In the first sample you see here, identified as Colorado, we conducted content uniformity assessments of nine different capsule specimens. Although the target content here was 10 milligrams, actual content ranged from 8.8 to 15.6 milligram per capsule and would have failed USP content uniformity testing criteria.

Upon assay, four unknown impurities were

identified on chromatograms, none of which interfered with the main fampridine peak, which was similar to a known standard of fampridine.

The second sample we obtained, identified as Maryland, again, provides a range of variability on content uniformity testing, which would fail standard USP criteria. Although capsules were labeled as 8 milligrams, they contained a range of fampridine from 3.3 to 9.2 milligram, with a significant variability.

The HPLC analysis of this sample did not indicate any presence of impurities, unlike the prior ones. Both the Colorado and Maryland samples were selected at random and the age of these capsules relative to their date of compounding would not be known.

Although these represent a limited sample, the products demonstrated a failure of the compounded products to meet USP content uniformity requirements, showing significant inter and intra sample variability, both of which could possibly be due to poor homogeneity of the actives in the sample. Unknown impurities were also identified in one of the two samples.

These results are not surprising, given our own experience in formulation difficulties and development with fampridine. We would expect that these results would only worsen if assessed as part of a formal

stability program.

To summarize, our experience has demonstrated significant difficulties in compounding fampridine due to excipient interactions, polymer interactions, drug migration into the capsule shell. In addition, we observed product instability with respect to temperature, humidity and container compatibility.

Recalling that fampridine's pharmacologic, pharmacokinetic attributes include a low dose, high potency, narrow therapeutic index, with side effects related to peak plasma levels, which include serious CNS effects, as you have heard, when combining the formulation difficulties of fampridine with its pharmacologic attributes and the intended patient population for its use, there are significant risks for adverse effects.

We hope that you will seriously consider this background as you deliberate the suitability of fampridine for pharmacy compounding.

Thank you.

DR. JUHL: Well, let me ask the question that is on everybody's mind. Compounded products have significant risk for adverse effects, but, yet, your company took a group of patients who was on your product and hung them out to dry. Why did that happen?

MS. HAMM: I would admit that this is something that I am going to let Dr. Cohen address in more detail as he comes to the podium. It is really not quite as simple as it sounds and it just so happened that we were in a state of transition at the end of Chris's trial, both in terms of some formulation activities, as well as transferring of the ongoing clinical research activity to Acorda. It really was a timing unfortunate circumstance in that particular situation, but I am sure Dr. Cohen can address that as well.

DR. JUHL: Okay.

You understand one of the things we are looking for is the -- for you to inspire us with confidence and that doesn't go in the right direction for us.

Other questions of clarification?

MR. CATIZONE: Mr. Chair, while awaiting the specifics from our next presenter, let me ask the question what course of therapy is left or what alternate is left to patients if the medication is not produced by Elan or not made available? Are there any alternative therapies except for the product to be compounded by a pharmacist?

MS. HAMM: You are asking if I would know if there are alternative forms available? I mean, in a domestic sense, I am unaware of any other source.

DR. JUHL: The information that you provided us is not quantitative in terms of impurities, migration of the capsule, those kinds of things, nor have we seen serum concentration versus time to see the effect of your formulation. I presume that some of that is proprietary? Is that information -- has it or will it or is it being submitted to the Agency so that can be scrutinized?

MS. HAMM: Information with respect to the trials and data that would have been obtained from them would be under the IND. Additional information in terms of the testing outcomes on the compounded samples and any of those details, we would be glad to provide in a confidential manner.

DR. JUHL: I was more interested in your product because there wasn't any information about that. We have more information on the compounded product than we have on yours.

MS. HAMM: Sure. It is in the IND and it was because of the proprietary nature we chose not to disclose more detail today.

DR. JUHL: Okay. I guess we would have to look for the Agency not for disclosure of the information but for scrutiny of the information to be sure that it corresponds with the sense of the qualitative information we have received.

MS. HAMM: Thank yo.

DR. JUHL: Any other questions?

[There was no response.]

Thank you.

Our next presenter is Dr. Ron Cohen, who is president and CEO of Acorda and I guess Andrew Blight is presenting with you as well?

DR. COHEN: Actually, Dr. Andrew Blight is here and can answer questions, but I will be presenting.

DR. JUHL: Okay. Great.

DR. COHEN: Thanks.

I am going to depart from my prepared text for just a moment to say that since this issue has come up, I will address in the course of my remarks this issue about the compounded formulation, switching over from that long term study of Dr. Bever.

Thank you and good afternoon, everyone. My name is Ron Cohen and I am a physician and the president and CEO of Acorda Therapeutics. Acorda is a biotechnology company, which is focused on developing therapies for spinal cord injury, multiple sclerosis and other disabilities of the nervous system. Acorda is sponsoring, as you have heard, clinical development of an oral tablet form of fampridine for both chronic spinal cord injury and MS under INDs in compliance with FDA

regulations.

As you have heard from Dr. Hamm, the formulation of fampridine that is used by Acorda was developed and is being manufactured and supplied by Elan Corporation. Acorda began its clinical development of fampridine in 1996. Initially, we used an immediate release capsule formulation, which was formulated for us under good manufacturing practices by an experienced pharmaceutical subcontractor.

In the course of this program, we were made aware by our subcontractor that fampridine is an unusually reactive compound and that this reactivity poses significant difficulties for manufacture of the stable formulation, using conventional approaches. Our initial formulation effort, therefore, took several months longer than we originally anticipated. In addition, we were concerned by numerous reports from patients, clinicians and the scientific literature that immediate release formulations gave significant variations in plasma levels and that these variable plasma levels led to unpredictability of both therapeutic effects and adverse effects.

We subsequently investigated Elan's sustained release formulation. We concluded, based on Elan's chemistry, manufacturing and pharmacokinetic data, that

Elan had successfully translated fampridine from a compound with significant problems of dosing and side effects to a potentially acceptable therapeutic agent.

We, therefore, entered into a collaboration with Elan, which permitted Acorda to deduct clinical development of this formulation for both chronic spinal cord injury and multiple sclerosis. We also obtained orphan drug designations for both indications to help make it economically feasible for us to develop the compound.

To date, we have completed three clinical trials of fampridine and spinal cord injury and we are sponsoring this year further trials in both spinal cord injury and in multiple sclerosis. We have not yet published these data, but they are in the process of being submitted to the Agency under our INDs.

Based on our own experience and on extensive discussions with clinicians and patients, we believe that the Elan formulation is clinically useful. For example, in a Phase 2 double blind placebo controlled clinical trial that we sponsored, involving 60 subjects with chronic spinal cord injury, we were encouraged to see apparent improvements in outcome measures, including spasticity, clinicians' global impression and control of bladder, bowel and sexual function.

In addition, we interviewed 12 patients, who had experience of both Elan's formulation and the compounded formulations of fampridine. Without exception, these patients said that they tolerated the Elan formulation better and experienced fewer side effects.

However, there do remain issues concerning establishment of both safety and efficacy of fampridine that must be resolved in additional properly controlled and documented clinical trials. We have become aware that increasing numbers of people with multiple sclerosis and spinal cord injury are experimenting with pharmacy compounded formulations of fampridine. We understand that many of these people believe that they receive benefits therapeutically, but we are also aware that there are numerous reports of side effects and significant adverse events, including grand mal seizures and even status epilepticus.

In addition, both physicians and patients have expressed concerns to us regarding what they perceive to be inconsistency and unpredictability of the effects of pharmacy compounded formulations. For example, I received an urgent call from a hospital pharmacist and physician last month, regarding a patient with multiple sclerosis, who had been admitted two days earlier in

status epilepticus.

You heard earlier -- this patient was alluded to by Dr. Bever. This was a patient who had been in the long term study sponsored by Elan with Dr. Bever. I think he had been on the compound for about three years. The Elan formulation, without incident, was then switched over when that study was terminated and within approximately six months had this experience of status epilepticus.

At the time I discussed this his physician, this was two days after admission and the patient was still incoherent and unresponsive, although he has since come out of the hospital.

This patient had experienced tremendous rigidity of his legs, which made it impossible for him even to sit in a wheelchair. He had tried every available anti-spasticity therapy without effect and got relief of his symptoms only from fampridine.

To respond now in more detail to the question that has been raised, the issues surrounding the supply of the Elan formulation here were, in fact, a matter more of timing and circumstance than anything. At the time that the study was terminated, Elan was in the process of transferring its entire dossier, the INDs, all of the documentation, to Acorda.

This is a process that actually took the better part of a year for us to get all the information in house and then assimilated in a way where we felt we had a grasp of it. In addition, this is a drug that is in development. So, we continue to need to have Elan formulate the drug to order so that when a given supply has been -- we run out of a given supply, we then have to place another order for the additional studies. In the process of all that and assimilating it, we felt that we really didn't have the wherewithal to jump in and continue the study.

We needed time really to get up to speed ourselves and then to work with Elan to supply. So, in the process, we did wind up supplying at least one patient with drug because we had enough drug in house for one patient. That patient actually is here with us today and would be available for comment. But, unfortunately, we were not able to get up to speed in time to supply this patient or others.

I will continue my remarks and inform this panel of what our intention is regarding future studies of this kind.

To continue with my prepared remarks in this regard, several leading neurologists, in addition, have told me directly that they have patients who have

experienced seizures and as this panel has heard, on pharmacy compounded fampridine, three of these physicians independently have told me that they most often see problems when patients perceive that they are experiencing a waning of therapeutic effects within a given prescription. Then they self-medicate, doubling or sometimes even tripling their dose on a given day, at which time they sometimes run into problems with adverse events and even seizures. This is the impression that these physicians have given me and these reports are consistent with the data that you have heard earlier from Dr. Hamm, showing marked intra and inter sample variability, as well as the presence of impurities and loss of potency over time of pharmacy compounded formulations.

The key directive of the Hippocratic oath is first do no harm and I believe that all of us as health care providers are concerned that any potential pharmaceutical agent for serious or life-threatening conditions in particular be developed as rapidly as possible, but at the same time maintaining accountability and responsibility and a concern for patient welfare.

It is difficult to credit adequate accountability and responsibility to the current situation in which thousands of patients receive variable

and undefined doses of fampridine without documentation or adequate assurance of safety and efficacy.

We recognize the desire of patients with seriously disabling conditions to have access to an agent that they believe offers some improvement of their condition and we recognize that Acorda finds itself in a position to offer a responsible alternative to the current situation.

With this in mind, Acorda has informed CDER that if fampridine is not placed on the list of allowable substances for compounding, Acorda would be willing to sponsor a long-term expanded access clinical study of our formulation of fampridine within the appropriate regulatory framework.

In such a study, which may require cost recovery, Acorda would provide its formulation of fampridine in an open label fashion to patients who would be deprived of pharmacy compounded fampridine. we would collect data related to safety of long-term administration and we would continue to sponsor this study while Acorda conducts additional Phase 2 and 3 studies in preparation for filing a new drug application or NDA.

If, however, the compounding of fampridine is allowed, we will be unable to offer such a program.

Acorda and Elan already have invested several years and many millions of dollars in research and development efforts to develop a safe, reliable form of fampridine in compliance with recognized drug development procedures.

If pharmacy compounded fampridine continues to be made available, we would not be able to justify the significant additional investment of time and resources that an expanded access study would require. Moreover, we would have to seriously review whether it would be economically feasible for us to continue clinical development of this compound. We believe that such an outcome would poorly serve the long-term interests of the patients and their health care providers, who deserve to have a therapy that can be prescribed with assurance of reliable dosing, appropriate indications for use and overall safety and efficacy.

Such assurance can only be obtained for this drug if it is developed under INDs and approved by FDA under an NDA.

Thank you. And I would be pleased to answer any questions you may have.

MR. CATIZONE: Dr. Cohen, if we can, can we return back to the Hippocratic Oath, in which you quoted your remarks and let me ask the question. Doesn't it seem logical that the patient that you talk about in the

study that is currently hospitalized, that the hospitalization was caused in some part to being stopped from the medication they were stabilized with and that the compounding pharmacist supplied a medication that was unavailable to that patient?

DR. COHEN: I am not sure I understand your question.

MR. CATIZONE: Any patient that is stabilized, particularly a patient with a severe illness, on a medication, and whose therapy is stopped immediately with no recourse of that patient to access that medication is going to have complications with their disease state. I can't believe that by the pharmacist compounding that medication alone, that was the sole reason for the hospitalization and the epileptic seizures.

DR. COHEN: There is no way in fact to demonstrate on an anecdotal basis that a given event is due to a drug or is not due to a drug. Obviously, we look at the population. We look at the trends and the patterns. My concern is an overall concern, not specifically keying off this patient, but rather on the overall experience in the data you have seen today, which demonstrates that the pharmacy compounded formulations of this drug are widely variable and if we put those in the hands of physicians to try to dose their patients

appropriately, we really have not given them any compass whatsoever with which to work with a compound that is known to have the potential for these sorts of effects.

So, whether or not in this particular case, the patient's status epilepticus was directly related to having been on the compounded drug for six months, my concern is a larger concern and that is that you have an absolutely uncontrolled situation out there, an undocumented situation where thousands of people have access to very variable and undocumented, non-GMP formulations of this drug. And this is a drug that needs to have as much information as we can put into the hands of physicians and the patients in order to make it a reasonable therapy and to mitigate the known risks.

MR. CATIZONE: So, I have an understanding of your closing comments then, is Acorda and Elan saying that unless there are economic incentives provided to the company to make this economically feasible for your two companies, you will not conduct extensive clinical trials to prove this medication is worthwhile and useful, but in a small clinical trial in which a limited number of patients were participating, that guarantee to provide the medication was not carried through or honored and at least the few patients were forced to use this inferior product because your company said they couldn't produce

it because of some sort of snafu in the transition.

DR. COHEN: I think that is an interesting interpretation of the events, but it does not accurately reflect what my statement was meant to convey. You know, we are talking about a drug for which there are intonations of efficacy. As Dr. Bever told you and as you have seen elsewhere, there is still to date not a single large, well-controlled study that gives conclusive evidence of efficacy. So, to begin with, although personally I do believe that the drug has efficacy and is a useful clinical compound, that still remains to be proved, whether I believe it or not, whether you believe it or not.

Secondly, it is a compound with demonstrable potential for serious toxicity and putting those two elements together tells me that if we are going to do this responsibly, we need to go through the process of controlled clinical trials, dosing studies, so that we know what we are doing and with a formulation that is a controllable formulation, that gives reliable plasma levels. To me, that boils down very simply. In terms of the intonation that we left patients high and dry, I reject that information.

You know, we are a small company and we are doing our very best to do a good job of bringing this

compound to the clinic for our patient populations. At the end of the day, that is why we are here. In terms of economic feasibility, we live in a world of real economic constraints. I don't think I have to tell anyone here what it costs to develop a drug in an appropriate fashion. What I am saying is that if compounded 4-AP is out there on a widespread basis, where we have basically uncontrolled formulation and wide access to it, it will make i t much more difficult for us to convince our investors that they ought to invest in us to carry out this program because I answer questions from them everyday about why are you developing this drug in the right way when you have got all this stuff out there that people can just get and no one is investing in clinical trials out there.

DR. JUHL: There are a number of fallacies in what you are going through here and I want to pick them one at a time.

Are you saying to us that you are unable to mount an economic effort to conduct the trials without the revenue stream that you would have from an expanded access program?

DR. COHEN: No. What I am saying is that we are proposing to make an expanded access program available and --

DR. JUHL: I understand that and I appreciate that. I really do --

DR. COHEN: And within that expanded access program, we certainly aren't going to make any money off that. In fact, we have concluded that even with cost recovery, we are going to have to invest significantly additionally to carry out that program. So, that is an issue of actually doing a study that we otherwise would not be required to do and would not choose to do. We would do it because we recognize that the patients out there do need an alternative and they do need a drug that is better controlled and better defined.

So, we are willing to do that. We are not going to make a dime off that nor can we, frankly, under the regulations. We are going to invest additionally to do that study.

DR. JUHL: Here is the part that I don't understand. If you do the study and get the drug approved, then that is an NDA'd product for which pharmacy compounding would not be allowed. So, how does that adversely effect your economics when you get into the market?

DR. COHEN: I have to say that I am not aware of -- if we get an approval, I am not aware that the pharmacy compounded would be -- compounding would be

disallowed at that point under the current regulations.

DR. JUHL: Under Section 127, the pharmacist cannot make copies of a commercially available product.

MS. AXELRAD: Excuse me. That is not strictly speaking correct. They cannot compound regularly or an inordinate amount --

DR. JUHL: Unless there is a significant medical need.

MS. AXELRAD: -- copies of a commercially available product and we have yet to define what it means to be regularly or an inordinate amount. Certainly, some compounding of commercially available products would be allowed under our regulations. In fact, don't forget that one of the criteria for the bulk drug substance that you can use in pharmacy compounding is that if it is the subject of an FDA approved application, then you can use it to compound.

DR. JUHL: There has to be a valid medical need above and beyond just changing a milligram or two. I mean, the discussion in Congress I thought was rather clear to prevent that.

MS. AXELRAD: They don't specifically use the words "medical need." There are issues associated with what level of need there is that we will be addressing in the general regulations.

DR. COHEN: So, what I understand about the situation is that it is not cut and dried. There is uncertainty. There is nothing in my experience that scares away investors faster than uncertainty. We rely on investors to allow us to continue our programs. We are not a revenue generating company as yet. We are an R&D company, research and development. So, all the R&D that we do is funded by the good will of the investors, who believe that we are developing important products that ultimately will make it to market.

That introduces more difficulty for us to the extent that there is more uncertainty. However, let me say that that is still not my chief concern. I mention it because it is a real concern and we will have to seriously review what -- how to move forward, where we choose to put our investment dollars if that uncertainty continues to exist. But that is not my chief concern. My chief concern is that we truly have a situation with a compound that in my view and our view ought not to be compounded because what we have seen is that these compounded formulations are nowhere near as reliable as they need to be to ensure a standard of safety, a reasonable standard of safety for our patients and dosing.

We have a formulation that we believe is much

superior in those regards and we are willing to make it available and, in fact, we are willing to invest additionally of our time and resources to make it available in the case where there were no compounding of 4-AP.

DR. JUHL: I appreciate the GMP produced drug is going to be better than a compounded drug. The question is is a compounded drug better than no drug at all?

DR. BEHRMAN: Dr. Juhl, could I make a comment because some of what we are debating right now is very common to life-threatening diseases, where there aren't good therapies and there are new therapies coming along and maybe people have access and maybe people don't. It is something the Agency struggles with a lot. Unfortunately, it is not uncommon to see circumstances where people are left without supplies and that is something that the Agency is becoming better at trying to prevent. But, obviously, it doesn't always work.

But the issue before us that concerns the Agency is not what is economically feasible for a particular company or -- well, in particular, that, but rather is something that may or may not be provided to the public safe. In other words, as Dr. Woodcock discussed yesterday, when we think about access, any kind

of access, one of the first concerns we have is that the safety of the patients is being protected.

So, for us, it is a question of should this substance be on the compounding list or not. That has to be answered before we can then turn to how to develop it safely and by whom and also ensure that during that process, there is access for those who need it. But they are really two separate questions and the ability to -- or at least it doesn't so much influence our decision about whether to make it available, that other mechanisms aren't available if we believe it is not safe.

So, for us, the real issue, is it safe, can it go on a compounding list or not. If we answer the question that, no, it can't be compounded, then we have to tackle the question of how can we get it developed and how can we make sure that there is appropriate access.

DR. JUHL: The different quirk here is that unlike other compounds that are being developed and are new, you don't have a few thousand patients that are already on it. This is the issue here. We have patients who are already on it, who we have to be concerned about.

Unfortunately, I mean, I understand the Agency doesn't deal with economics, but in order to mount the effort that would be required to provide the entire country with this drug, there has to be some confidence

in -- at least from my perspective -- in the company to be able to do that. The only example of performance we have here is was unable to get drug for 23, 29 patients, one of whom ended up in status in the hospital.

So, I want to be sure that --

DR. COHEN: If I could comment on that?

DR. JUHL: Let me finish, please.

I want to be sure that if this committee recommends that they ought not be put there, just as our discussions this morning, that there is a place for patients to turn and they won't get caught up in what you described as a year's worth of bureaucracy to transfer papers and the patients didn't come first in that situation.

DR. BEHRMAN: Well, I think to a certain extent then it is our responsibility to assure you that -- and this is something we are very familiar with and good at -- that we will represent you in those negotiations with the company and satisfy ourselves that the distribution program, to the best of our ability, obviously, because as Dr. Woodcock mentioned, we can't force any company, but we are fortunate that we hear an assurance that, in fact, such a program would be developed, but that you trust us because we are committed to doing that, to making sure that entry criteria, inclusive criteria, are

reasonable and that the people who need the access are the ones that get the access and get it in the safe manner.

DR. SELLERS: I am trying to understand what you are describing, Dr. Juhl. If the company was no longer to obtain the drug that was being manufactured, wouldn't obtaining it from a compounding pharmacy be a better choice than cutting off the drugs altogether?

DR. JUHL: Well, I think that is one of the questions.

DR. SELLERS: Right. And I feel like we are implying that they did the wrong thing by providing a compounded product, but they didn't necessarily know at the time that they were providing a product that wasn't of the same standard as what the patients were getting.

DR. JUHL: Yes. There was no alternative at that point.

DR. COHEN: Actually, if I could add to that because that really was along the lines of what I wanted to say. You know, we are all learning as we go along. It is a development program. So, we continue to learn. At the time -- I am sensitive to your concern and certainly retrospectively how one might interpret the fact that you have this group of patients, who were on drug and then the company cut them off and they went to

compound and then we have these problems.

I think the reality is more subtle and more complicated than that in meaningful ways. If we had -- I think if we had had the understanding a year ago that we have now, after having the benefit of studied the circumstance more, having become more aware of the compounding issues and looked into it in more detail, having taken the time to interview physicians in more detail and bringing ourselves down the learning curve, we might well have had a greater sense of urgency amid all of the priorities that one has in the company even as we were transferring this whole portfolio, which does take time.

I would also say that that was a one off event. We are talking about a business alliance, which occurred once in which Acorda entered into an alliance with Elan and consequently there had to be some time to transfer information and documentation. That is a one off. At present and for the foreseeable future, Acorda has the exclusive license to all of Elan's technology related to this drug and to -- and the exclusive license to develop it for multiple sclerosis and spinal cord injury.

So, we do not anticipate a repeat similar event in which there will be any lengthy interruption of the chain of command, as it were, or chain of activity. So,

that is an issue that is behind us. I think moving forward what we are saying is we have spent a good deal of time over the last few months studying this, discussing it with Elan in great depth and concluding that we needed to offer to do a large expanded access study.

We are quite capable of doing that study and Elan is quite capable of supplying sufficient drug for that study. As with anything, it is a matter of timing, intent, planning and then execution. I think looking back over the last year is not going -- I would submit to you that that is not instructive for learning what we are capable and willing to do in the future because it really was a one off situation of transfer of responsibility for the project.

DR. BEVER: I apologize. I don't know whether you take comments from the audience.

DR. JUHL: We usually don't, but go ahead.

DR. BEVER: I just want to clarify that we are talking about a group of patients who were in a clinical trial. They were not in a compassionate use program or anything like that. There was never, as was intimated earlier, any promise to these patients that there would be ongoing availability of this drug. It always, with Elan and Athena and Acorda was sort of extending bits at

a time. And as you know, the consent form that patients were signing basically says that this sponsor has the right to terminate the trial at any time for any reason and patients were told that.

I mean, I was concerned about that from the beginning and tried to make that clear to the patients that this was a research study and it could be terminated. I mean, that was something that we just dealt with. We tried to deal with it as best as we could and looking back on it, it probably wasn't the best way of doing it, but we know more now.

DR. JUHL: Perhaps it is just one of my pet peeves, but having served on several IRBs, that is one of the things we always put in the consent form as to what happens when the study is done.

MS. LA FOLLETTE: I would just like to make a comment. If Acorda is successfully continuing with their IND studies and then successfully file an NDA -- at our training session yesterday, 90 percent of ADRs that are reported are from companies and that is a benefit if a product goes commercial, that you will actually have a history and you will have information, which we haven't been able to really nail down with pharmacy compounding, how adverse reactions are going to be reported or if they will.

MR. TRISSEL: What is the time span of your development plan now? How many years more in development do you anticipate? It sounds like you are pretty early on.

DR. COHEN: You know, I am quite hesitant to go on record predicting what the length of the development program will be. I think we all understand the vagaries of clinical development.

MR. TRISSEL: It is not a year.

DR. COHEN: Well, you know, it is not a year, but I don't think it is five years. I don't think it is ten years, but, you know, at the end of the day, we don't know until we get into the clinic further. We have done a couple of Phase 2 studies. We are going to be doing more Phase 2 studies this year.

If those go well, then our plan is to get into pivotal studies next year. I say this emphasizing that this is our current plan and it will entirely depend on the actual results of the studies that we see, which is why we are doing the studies, of course, to begin with.

MR. TRISSEL: As it applies to the expanded access program that you are offering, apart from the patients that are going to be on your clinical trials, how many patients do you anticipate that you will have to supply with drug during this time frame from the next two

to five years, two to ten years in terms of thousands? How many patients do you think you are really talking about?

DR. COHEN: Here, again, you know, I am reluctant to speculate on what we are talking about. I will tell you that we are capable and prepared to supply as many patients as we believe are out there. I will tell you that it would be many thousands, many thousands of patients, as far as we know, who are out there. We would be prepared to supply them, those who are taking compounded fampridine.

MR. TRISSEL: And you would be ready to start this in what length of time, do you think?

DR. COHEN: Well, again, I think -- as I indicated, we are going to look to see what the outcome is of this panel's deliberations, of the FDA's deliberations, because truly at the end of the day if the compounded drug is allowed to be -- or if the drug is allowed to continue to be compounded, we really will not be able to do the study. We just will not be able to muster up the investment in us that we need to do the study. It is just a fact.

MR. TRISSEL: But if we don't have a time frame for when you can begin delivering that, then we --

DR. COHEN: We could begin delivering it as

soon as six months.

MR. TRISSEL: As soon as six months.

DR. COHEN: That is, you know, give or take, but that is a reasonable time frame. If you wanted to say by the end of this year, I don't think we would be far off.

DR. LIEBMAN: When the patients who were told to get their medicine compounded because the study could no longer supply it, were they instructed that this is a very sensitive kind of drug and you need to go to a pharmacy, who is skilled in doing that or was the issue of find the cheapest guy around, such that, you know, it doesn't matter. Price is the issue.

DR. COHEN: That is just an area that we have never been involved with. Maybe Dr. Bever might want to comment on that.

DR. LIEBMAN: Dr. Bever, I don't mean to beat on you. If you were referring a patient of yours to another physician, would you say here are a list of four physicians. Call and get the cheapest one or would you say these are people I know are qualitative and I would strongly recommend these people because they are good at what they do?

DR. COHEN: I should point out that the two samples that were analyzed by Elan that Dr. Hamm