FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Pharmacy Compounding Advisory Committee

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P R O C E E D I N G S [8:30 a.m.]

Agenda Item: Call to Order

DR. JUHL: We will begin. Welcome to day two of the Pharmacy Advisory Committee -- Pharmacy Compounding Advisory Committee. We will continue on today with a review of drug products or drugs that have been nominated for inclusion on the pharmacy compounding bulks list.

I think we will go around the table and have everyone introduce themselves. We have a few new faces at the table. So, if we can start, Judy, with you.

MS. RIFFEE: Good morning. I am Judy Riffee. I am faculty, College of Nursing, University of Florida.

MS. LA FOLLETTE: Joan LaFollette, Bristol-Myers Squibb.

DR. SELLERS: Sarah Sellers, pharmacist, North Carolina.

MR. CATIZONE: Carmen Catizone, representing National Association of Boards of Pharmacy.

MS. HOPE: Rose-Ellen Hope, consumer rep.

MR. RUSHO: William Rusho, University of Utah.

MR. TRISSEL: Lawrence Trissel, the University of Texas, M.D. Anderson Cancer Center.

DR. JUHL: Randy Juhl, University of Pittsburgh, School of Pharmacy.

DR. CERNY: I am Igor Cerny, executive secretary.

DR. MC BURNEY: Elizabeth McBurney, dermatologist from Louisiana.

DR. RODRIGUEZ: Bill Rodriguez from Children's Hospital, National Medical Center in Washington, D.C. and George Washington University.

DR. ALLEN: Loyd Allen, International Journal of Pharmaceutical Compounding, the USP representative.

MS. OGRAM: Lana Ogram, co-chair, FDA.

DR. CHAMBERS: Wiley Chambers, deputy director, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products.

MS. AXELRAD: Jane Axelrad, associate director for policy in the Center for Drugs and co-chair of the Pharmacy Compounding Steering Committee.

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

DR. JUHL: Thank you.

Agenda Item: Mild Silver Protein

Our first drug this morning is mild silver protein. And Dr. Chambers will give a presentation on behalf of the Agency.

DR. CHAMBERS: Good morning.

My name is Wiley Chambers. I am an

ophthalmologist with the Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products. I am going to talk about mild silver protein.

Mild silver protein has been marketed in the past. It was developed prior to 1938 so that it came into effect or it was used prior to the enactment of the Food, Drug and Cosmetic Act of 1938. It was marketed under the names Argyrol and Protargol and came in a variety of different formulations, including formulations that were marketed as OTC products in a 10 percent solution, both in 15 and 30 ml containers, an Rx product that was 20 percent solution marketed with EDTA in a 1 milliliter dropperette.

While it was being marketed, and to my knowledge it is not currently marketed, it was marketed by Cooper Laboratories and when Cooper Laboratories sold all their products to IOLAB, IOLAB continued to market it for a period of time until IOLAB stopped marketing products and the product was not picked up following the marketing by IOLAB.

The indications that it was marketed under included the treatment of eye infections, preoperatively for eye surgery and as a dye as part of the preop surgical procedure.

There is no question it has been well-known

that silver ion is perfectly capable of killing microorganisms. It is also perfectly capable of killing cells and tissues. It was, therefore, considered to be a useful anti-infective agent as long as it was possible to kill the microorganisms without damaging the surrounding tissue.

One of the ways to make it a little bit safer so that it would not damage any of the surrounding tissue was to bind it in a protein complex and that was what the creation of mild silver protein was, was a binding of the silver ion in a mild -- in a protein complex. This made it less harmful to tissues, but, unfortunately, also made it less effective.

It has been studied in a number of different ways, including back in 1937, this slide shows a comparison of the concentration in the number of organisms surviving. Obviously, the fewer the number of organisms surviving, the more effective the product is. And this is a comparison of a number of different products that were available in 1937.

As can be seen on this slide, Argyrol was not one of the more affective products even in 1937. It was used fairly widely during that period of time and because it was continuing to be used, additional studies were done at different points in time. In 1986, another

comparison was published in the literature with a variety of different products. Again, the lower the number, the better off it is. And as you can see, mild silver protein with an MIC90 at 200 is far less effective than even thiomersal.

There are also clinical studies in which the product has been evaluated, published in the Archives of Ophthalmology was a comparison between an untreated eye and using mild silver protein, both before irrigating and after irrigating. As you can see, the results are very similar between untreated and treated and, in fact, if you do the wash afterward to wash the mild silver protein out, either in the controlled or uncontrolled, you increase the number of organisms that are found in the eye.

A number of investigators looking back in the literature did not understand why they were continuing to use mild silver protein at their institution and people in New York decided to put together a trial to find out what the true incidence was of endophthalmitis, which is the particular disease that they were trying to prevent.

Endophthalmitis is what destroys eyes. So, it is why we use prophylactic antimicrobials prior to surgery. They looked at a comparison between povidone-iodine, which was being touted as a product that

potentially should be used and silver protein, which was the standard at the time.

As you can see, the percentage of positive endophthalmitis cases was considerably lower when using povidone-iodine than it was with silver protein. From the side effect perspective -- this doesn't project, I think, quite as well as the handout did but there is the possibility of silver staining even with a single administration, although it is not particularly common to occur with a single administration of this. It is much more common after repeated administrations.

But as you can see in this picture, the slight gray, bluish gray area in the conjunctiva is the result of repeated administration of mild silver protein. This also does not project as well as the handout, but there is depositing in the lacrimal sac and that will trace then through the skin of a grayish area.

If you look on a slit lamp and look at the cornea itself, you can detect the deposition of the silver protein in the cornea. And if you look on electromicroscopy, look at the basement membrane, you can see the thick black line that is along there is not a normal process. That thick black line is the deposition of silver protein.

This is not the first time that this product

has been reviewed. As was discussed a couple of different times, the agency does not frequently completely rule out products at any point in time. We do periodically relook at products and that is what is being done here. There was an OTC review of this product between 1973 and 1979. At that time, the external OTC panel reviewed the data that was available. Some of the slides that I presented were presented at that time and the authors at that time had given me permission to go in and reuse those articles.

From a safety perspective, the panel concluded that there were not toxicity concerns as an OTC product, provided that everybody was warned of the potential deposition of silver. The efficacy to the best that they were able to determine was not supported in any way and they looked and were unable to find any data to support the efficacy. So, the overall conclusion was that it might be useful but it requires clinical studies to show that it was useful.

The literature review that I have done, as well as reviewing the Agency files have not found anything since this time to support the efficacy.

There are a number of alternatives that have been developed and this is a partial list of a number of the anti-infectives that are all currently approved and

are available to treat the same types of infections that mild silver protein was originally developed for.

Goodman and Gilman provided a summary of the efficacy and safety that they determined for mild silver protein and I have quoted just a couple of excerpts from the end of Goodman and Gilman's discussion on mild silver protein. They also did not conclude that there was any efficacy, but noted that these products -- and I will -- as listed within the book, "Fortunately, the colloidal silver preparations are now in a deserved oblivion." That was at least the conclusion that the textbook made.

I will be happy to take any questions.

DR. JUHL: Questions for Dr. Chambers?

DR. MC BURNEY: I have a question.

Dr. Chambers, are there any conditions in which you could consider using this silver preparation that these other preparations would not be effective?

DR. CHAMBERS: I am not aware of any conditions that the other products are not clearly more effective.

DR. RODRIGUEZ: Having grown up in another area of the world, did you come into the use of Argyrol for, quote, unquote, strep throat?

DR. CHAMBERS: For strep throat?

DR. RODRIGUEZ: That is right.

DR. CHAMBERS: I did not review anything other

than the eye indications.

DR. RODRIGUEZ: It used to be used as a painting solution on the tonsils to, quote, unquote, take care of strep throat with similar results.

DR. CHAMBERS: Thank you.

MR. TRISSEL: In looking at the two papers that you presented in here, there seems to be a conflict in the relative efficacy in relation to merthiolate or thiomersal. In one study it shows it is better. In the other study it shows it is much worse.

At least as you have characterized it, I would argue that the second study in 1986 actually compares -- is really a comparison of equivalent activity doses rather than one being better than another. But merthiolate and thiomersal are the same things, right?

By your characterization in one place it would be better and in the other place it would be worse. So, it would be conflicting information.

DR. CHAMBERS: I am sorry. Which are you referring to?

MR. TRISSEL: The 1937 article by Thompson, Isaacs, et cetera, merthiolate is worse by the comparison they have here, is the worst in the category, as I understand this table, right?

DR. CHAMBERS: Correct.

MR. TRISSEL: And Argyrol is the next to the worst.

DR. CHAMBERS: Correct.

MR. TRISSEL: In the next paper in 1986, thiomersal by your characterization is better because it is used in a lower dose, but -- and what I am saying is that I wouldn't characterize this second study in 1986. It is really a study of what doses are equally effective among these different agents.

DR. CHAMBERS: Correct. This is -- they are looking at slightly different avenues. They are looking at slightly different bugs. I mean, this is only a comparison of Neisseria on the 1986 slide, but the orders of magnitude that they are compared to other agents that we have available --

MR. TRISSEL: But it is just a dose equivalency and it doesn't necessarily mean one is superior to the other. You would have to take into account the relative toxicities as well.

DR. CHAMBERS: Absolutely and I would put much more weight on the clinical studies that were done afterwards than I would on the in vitro studies that were done earlier on.

MS. RUSHO: In the study by Isenberg, where the colonies actually increased, doesn't that indicate two

things; number one, the solution was not sterile and, number two, it was ineffective?

DR. CHAMBERS: When you wash the eye afterward and it was not well-known before the study was published, what you do is you potentially wash other areas of the eye that were not necessarily covered by the initial drops that you put in -- now, in the conjunctiva. So, that was probably what leads to the increased count. And everybody is trying to wash just the areas where they thought they had already cleansed, but as shown by the data, that is not necessarily the case. It leads to the conclusion that you should not be trying a wash after you attempt to go in and cleanse the area. That is probably the biggest message that that study shows.

MS. RIFFEE: I just have a comment. I appreciate Goodman and Gilman's comment about oblivion, but there is a silver -- a colloidal silver solution that is now being promoted in a non-prescription area among health food stores. I did a seminar and was presented a whole batch of literature on it.

So, just in case we think silver is not out of the picture, it looks like it is coming back in and this is for internal use. And I have none of that material with me, but just as a comment.

DR. CHAMBERS: I am not questioning that

products resurface multiple different times. And we discuss the products and what is known about them at the time. Absolutely.

Agenda Item: Open Public Hearing

DR. JUHL: No further questions or comments, let's move to the open public hearing on mild silver protein. We have two speakers listed; Gina Ford -- is Gina here? I don't see her here. Then Rosemary Jacobs. Rosemary, welcome.

MS. JACOBS: My name is Rosemary Jacobs. I am a private citizen. I am not sponsored by anybody. You will read rumors on the Internet that will tell you I am sponsored by the pharmaceutical associations, by the medical associations and by the government. That is not true. If it is true, they must be sending homeopathic checks because I haven't gotten any money from anybody.

Now, I have condition, which is called argyria, a-r-g-y-r-i-a. Argyria is gray skin caused by the ingestion of silver. Argyrol, which the doctor mentioned before, was sold in a Hispanic community in Florida until at least 1996. Argyrol was introduced into commerce in the United States by Dr. Alfred C. Barnes in Philadelphia in 1902. Argyrol was the best known brand of mild silver protein.

It has caused many cases of argyria when taken

internally. I have ads that are -- I was born in New York in 1942. I have ads from medical journals that are older than I am in which Argyrol was fraudulently advertised as non-toxic. I have articles from medical journals warning doctors and pharmacists about the fraudulent ads.

Now, Argyrol was used for many purposes. There were many, many kinds of silver medicinals on the market. But remember, folks, there was a time we didn't have antibiotics. People were very sick. There wasn't much they could do. They were using all kinds of noxious substances to try and save people from these horrible diseases. Silver was one of them.

I know I don't have much time. So, I will be glad to answer questions privately later. I have a Web page, where I have got a lot of my information up, but I have got a lot more to put up. I have got citations from the medical literature, which I have been reading for about 30 years now.

I was given nose drops that contained silver by an eye, ear, nose and throat specialist in New York when I was a child. I was 11 years old. I was to take them intermittently as needed for allergies, which I did, and my skin turned gray. I am now splotched. I was originally a solid gray but in the late seventies, I was

dermabraded and then I went from solid gray to splotchy gray.

There are other people with argyria living today in the United States. Many people with argyria become reclusive and I am a mild case. I am not a timid person. If anything, I am obnoxious. I feel as though I am speaking for everybody.

Now, I believe, but I am not certain that the doctor that gave me the medicine was ignorant. He was a good person. He was a caring person. I also know he didn't make a cent when my mother bought the drug. The pharmacist, I believe, compounded it and I believe the pharmacist realized the danger and never warned my mother.

I know the companies that are advertised -- the drug companies that advertise silver drugs knew exactly what they were doing. They were lying to make a buck. Now, with Argyrol -- as I said, Argyrol was used for many things and there are three kinds of argyria, generalized or systemic, which I have, which covers large portions of the body, usually the face. There is localized argyria. Argyria has been caused by every form of silver used therapeutically.

It has also been caused by elemental silver. Then there is argyrosis, which is the silver deposits in

the eye. Argyrol has caused many, many documented cases of argyrosis. I think as the doctor pointed out, there was one case recently in Canada, where just one application of the drops to the eye have caused deposits in the eye. That is unusual. Usually, it requires repeated doses.

And also from reviewing the literature, it would look as though there is a very, very wide range of individual susceptibility to silver, to silver toxicity. I know that is for generalized argyria. I don't know if that would be true for the eyes, too, but I would just have to assume that probably it is.

Now, as you probably all know, silver nitrate was used in the eyes of neonates and according to the literature, it seemed very effective in stopping blindness, but it was only effective against the bacteria from gonorrhea, which they thought that the infant got from the mother when the infant passed through the birth canal or from the hands of the people taking care of it.

Argyrol was promoted for that use, too. In 1928, the Council of Pharmacy and Chemistry for the American Medical Association reviewed the literature and kept asking the company, please, give us your data. Give us the evidence. You are advertising it for this use. Show us that it works.

Well, they never got the data. They got something -- they got testimonials from maybe six different doctors. They found one of them. The others, they couldn't find and the one had to admit that, no, they weren't using Argyrol. They were using silver nitrate in the eyes of neonates, using it once, not repeatedly.

It didn't work in vitro. It didn't work in vivo. Now, today, there is also the danger if people are permitted to compound this for ophthalmic use, there is the very grave danger that it is also going to be used systemically, people are going to be drinking it. As was pointed out, if you will get on the Internet, if you will go to the health food stores, there are people all over taking what they call colloidal silver. Colloidal silver if you -- I have asked people -- when I first heard about colloidal silver, I was stunned.

I saw an article in a magazine and I thought I was going to read about people that looked like me. I didn't. I read that this is silver in your body, protects you from every bad thing known to man. And it doesn't hurt any good thing known to man and it doesn't hurt the host himself.

I was stunned. There were lists -- they give you lists of these 650 different diseases that it

prevents, including cancer. They are promoting it to prevent and cure breast cancer, which I have. You know, I tell them, excuse me, I have it. The nurse thought I was in cardiac arrest. You are telling me silver in your body prevents cancer. How can you say this?

Well, it works for me. Great. It goes on and on and on. I tell them -- the promoters have actually asked me -- I am not a scientist. I tell everybody I am not a scientist. They want me to do their toxicology studies for them. There is no animal model for argyria. You have to line up people who are going to agree to take the stuff to see how much causes argyria. Fine, guys. You have evidence that it prevents or cures a terrible illness, like cancer or AIDS. I bet you are going to have to turn people away. They will be volunteering to take the stuff.

But you don't have any evidence. Until you have the evidence, you can't do toxicology studies to get the people to sign up to agree for the studies. Okay. I did an estimate -- it is on my Web page. I think it is hysterical. I mean, you know, I can't believe that anybody would take an unregulated product -- you know, would take a risk with an unregulated product and want me to evaluate the risk for them. All I have done is gone through the literature and pulled out -- you know, if

somebody took a silver nitrate stick in the mouth, so many grams caused argyria and I gave both extremes. And I think in one example somebody used three grams and became argyric, another person used 24.

The same thing with fulvarphenamine(?) in all the different forms. There is this huge, huge wide range and I published it on my Web page for them to look at. The EPA also has done some studies or has something on their Web page about silver.

So, there are people that believe it, though. There are many people out there that actually believe that silver is beneficial for health and it is not toxic. You know why? Because it is natural. It can't hurt.

They are also using it to purify water. From what we can find, when I first found out about colloidal silver, the first thing I did was go to the promoters and say, please, please, guys, show me your evidence. If you can prove, you know, that it actually prevents serious illnesses, like cancer or AIDS, you know, I will go with you to FDA and present the evidence to them and say here, you have got to approve it.

If you have got evidence that you can help people and save lives, there is no government on earth that can stop you. Just give me the evidence. No evidence yet. I am still waiting.

But it is out there and the people believe it and they are using it to purify water. I have heard of cases where people like living in the Southwest instead of carrying, you know, a little bottle of the kind of supposedly purified water you buy in the store, they have their bottle of colloidal silver. They sell machines to make their own.

When I started -- I know lots and lots of dermatologists, who are experts on argyria. Nobody would speak to anybody but me. Now, I found out about this in 1995. Now I have got a lot of doctors and scientists, who are interested. Some of them are trying to test the products out there. What we are getting, we are getting just pure water or we are getting trace elements of silver. But when you think of people going around all day long out in the Southwest carrying a huge bottle of water that they think they have purified with silver, they are being exposed.

And there are also records of people with dairy herds using it in animals. They are using natural products now to cure their animals. The veterinary branch of FDA has told them that they can't do this. But milk, supposedly, is one of the primary sources of silver in the human diet. So that people could be being exposed from many areas. And for this reason, I just feel that

the idea, first of all, to use any form of silver in the eye, all the evidence that I have seen indicates first that it is not effective, second that it is dangerous and then there is the potential for abuse.

They hear all the hype and the promo, the false ads. They are going to take it systemically, somebody is. I just don't see any reason why it would be put on a bulk list for compounding. I also would like to ask something of the compounders about -- compounders are compounding colloidal silver. Pharmacists are selling colloidal silver and I would like to know -- I would -- please, is there anyone here, please show me your evidence that the product is beneficial and safe. That is all I want.

If I can see evidence that you have got a product that is beneficial and safe, I will support it. I will endorse it. However, without that evidence, please tell me why you are doing it. Are you ignorant, like my doctor was? Or are you quacks, like my pharmacist was?

Thank you. Are there any questions?

DR. JUHL: Thank you very much for coming to present to the committee.

Is there anyone else who would like to address the committee from the public, who hadn't contacted us

ahead of time?

[There was no response.]

Agenda Item: Discussion and Vote on Mild Silver Protein

Seeing none, we will move to discussion. Comments from the committee.

MR. TRISSEL: I wonder if I could be reminded by the Agency who sponsored this material and what was its -- I hesitate to say indication, but what was the proposed use in the community of this material because I am afraid I do not recall.

MS. AXELRAD: It was the International Academy of Compounding Pharmacists, I believe, was the nominator of the substance and I believe it was recommended for use and for the ophthalmic use as an antiseptic.

MR. TRISSEL: Was there any survey or discussion with the ophthalmology groups, whether there is any use of this -- well, obviously, someone is using it, but whether there is any recommended use of this in the ophthalmology community.

DR. CHAMBERS: I am an ophthalmologist. I have talked with a number of the people that presented at the OTC Advisory Committee. There was not any supported use at that time. There has not been any since then.

DR. ALLEN: I am not aware that it is used to

any extent anyplace, at least in compounding right now.

DR. JUHL: Are we ready for the question? Again, two options, simpler today. Option 1, we recommend that the mild silver protein be added to the bulks list. Option 2, we would recommend that mild silver protein not be on the bulks list.

All those in favor of Option 1, please raise your hands. Seeing none, all those in favor of Option 2 raise your hands. It is unanimous that we recommend that mild silver protein not be added to the bulks list.

Agenda Item: Monosodium Aspartate

Moving on to our next compound, monosodium aspartate, which was used in cardioplegia solution, we welcome Dr. Norman Stockbridge to the table and to make a presentation.

DR. STOCKBRIDGE: My name is Norman Stockbridge. I am a medical team leader in the Division of Cardio-Renal Drug Products. The review of monosodium aspartate for use in cardioplegia solutions was written by the division director, Raymond Lipicky. He is not available today because of health problems.

I would like to point out, however, that there are several people here, who might be able to help the committee with questions they may have about this product. In the audience today is Mr. John Brandon and

some of his associates from Central Add Mixture Pharmacy Services and, also, Dr. Gerald Buckberg from the Department of Surgery, UCLA Medical Center. He did much of the development work that I will speak to here.

Cardioplegia is an elective procedure designed to halt the mechanical activity of the heart to permit surgery to take place. The way in which cardiac contractility is controlled is through interference with the electrical activity of the heart.

The resting membrane potential of cardiac cells and other cells is determined by the ratio of the extracellular potassium to the intracellular potassium and raising the intracellular potassium in the bathing medium depolarizes the cell and interrupts the electrical and thereby the mechanical activity of the heart.

It is important for you to know that there have not been a series of controlled clinical trials that have resulted in the development of cardioplegia solutions. Instead they have evolved by and large through experience, both laboratory and clinical experience. There are a large number of factors that have evolved more or less simultaneously. Considerations about whether to use warm solutions or cold solutions, considerations about what the optimum pH ought to be, considerations about the calcium concentration, this has

often led to compromises.

One I have illustrated there is a compromise between the use of solutions that allow good visibility versus blood cardioplegia, which provides better preservation of cardiac function after surgery and in this case has led to solutions based on a combination of blood and crystalloid.

Aspartic acid is a non-essential amino acid by which it is meant that your body is capable of making its own. Aspartate is the anion component of aspartic acid. The body is capable of interconverting aspartate and glutamate and either of these can serve as carbon sources for energy production during anaerobic metabolism and this has been sort of the rationale for the development of use of this.

The experimental evidence that aspartate is good to use in cardioplegia comes from some animal studies that were performed. They showed that in an animal -- in a dog model, cardiac reprofusion model, that the amount of work that you get out of the heart as a function of the pump priming pressure was lowest with just blood cardioplegia, was intermediate in case of blood cardioplegia in which it was supplemented by a 26 millimolar concentration of glutamate and was much more nearly normal after cardioplegia in which 13 millimolar

glutamate and 13 millimolar aspartate were used.

Through such experiments, there have been a large number of -- well, there have been developed a number of different cardioplegia solutions for use in different phases of the cardioplegia procedure. There are several solutions that have been developed for use during induction; that is, getting the heart to stop initially. I will point out that aspartate and glutamate now appear in one of those.

There is a different solution that has been developed for use during the bulk of the cardiac surgical procedure. Sodium aspartate and glutamate do not appear in that solution because clinical experience has shown that you get substantial vasodilation in the presence of prolonged exposure to glutamate and aspartate. But it reappears during warm profusion in the warm profusion solution.

There are no national formulary specifications for aspartate. There are, however, specifications for glutamate and what I have done here is shown the specs for glutamate alongside comparable specs for the sodium aspartate that is available for one of the large Japanese bulk chemistry chemical suppliers. And it shows they have, I think, done a reasonable job at matching comparable specs for glutamate.

The clinical experience that supports the use of glutamate and aspartate, as I say, does not include controlled trials. There have been two theories reported and the first of them, compared 800 cases using a blood cardioplegia solution containing glutamate and aspartate and 2,500 other consecutive cases where only crystalloid cardioplegia was used. Appreciating the fact there are many differences between these settings, they demonstrated less morbidity in the case of the blood cardioplegia containing aspartate and glutamate.

In addition, there is another uncontrolled series from Dr. Buckberg in which a very low total mortality rate was reported among 1,400 cases in four clinical centers.

Summarizing a little bit about safety, aspartic acid is a natural amino acid. Plasma levels are on the order of 30 micromolar. The total circulating level of amino acids, a normal person is on the order of about 3 millimolar and as I alluded to before, it is appreciated that high levels of aspartate and glutamate during the maintenance phase leads to peripheral vasodilation. So, that is appreciated.

Other than that, there are no known safety concerns. We summarized the data as follows: The use of aspartate is supported by clinical experience, if not

clinical trials. There are no unappreciated safety concerns evident from the literature. There appears to be no good use for the potassium salt of aspartate because its use would make the potassium level higher than is the target level for use in these solutions.

We believe that sodium aspartate should be approved for pharmacy compounding.

I will take any questions that you have.

DR. JUHL: Questions for Dr. Stockbridge.

DR. MC BURNEY: Dr. Stockbridge, I have a comment and then I have a question.

This particular compound has the distinction of being the first one that the FDA suggests approval for that we have been reviewing in the last two days. My question is in reviewing the safety data that you presented to us, that there were no problems with this whatsoever. There were no accounts of any -- no side effects from use.

DR. STOCKBRIDGE: As I said, use during -- prolonged use during the maintenance phase of cardioplegia has an evident side effect. Perhaps Dr. Buckberg will speak to this issue. I think there is a real problem with taking a multifactorial cardioplegia and attributing whatever adverse events that you see to any one of them, to any part of this.

Dr. Buckberg, would you say a word on this?

DR. JUHL: We need to have you at a microphone, please.

If you could identify yourself and your affiliation, please, Dr. Buckberg.

DR. BUCKBERG: Dr. Gerald Buckberg from UCLA Medical Center, Department of Cardiothoracic Surgery.

We have not encountered problems with the use of glutamate and aspartate during the maintenance phase of the operation. Usually the body is cooled down and sometimes if you give too much of the drug at that point, you can have dilatation of vessels, but we don't use it at that point. We only use it during the phase at the beginning of the operation, when the cardioplegia solution is given warm at the end of the operation.

The reason we do that is we have found that when we looked at this in animals that were sick -- and we did all of our experiments and not in healthy animals, basically animals that were made injured, as you saw in that slide that Dr. Stockbridge showed, and we found that if you just use our standard approach, that the recovery was not as good as if you added certain amino acids. It turns out that part of the problem that occurs after animals or patients have ischemia -- and I think it is all related to the fact the animal studies precede the

use of the drug clinically -- is that the heart becomes depleted of certain key precursors of the Kreb's cycle, which is the cycle that allows oxygen to be utilized.

Not only is the glutamate aspartate useful during ischemia, that is, when we have the aortic clamp, but, more importantly, when the heart has to use oxygen after the operation, if you deplete the heart of certain key Kreb's cycle intermediates, it is the capacity to produce energy is reduced.

So, the real working of this is not necessarily during the time we are working surgically, but we are replenishing things that can be depleted before the operation and also things that can be given during the period of reprofusion to allow the heart to start up better.

So, with that, we have reserved the use for those two times in the operation and it has been very effective and other people in the United States and Europe have supported this approach that we have used.

DR. MC BURNEY: My concern is certainly not in the use that you have described, but in making available for bulk compounding, are there any other situations in which it could be used, in which there could be a toxic effect? Because by putting it on the list, it opens it up completely.

DR. BUCKBERG: No. In fact, I don't believe that is a problem for toxic effect and I think the effect that we are describing is a transient on by bypass. But other people have potentially used this solution with intravenous administration. For example, if you look at intravenous amino acid solutions that will frequently have glutamate and aspartate in it. So, when we had it approved, we had it approved because it was an approved compound but not for a specific cardiac use.

So, I don't think there would be any problems that I could imagine where it would -- where this drug would cause a clinical problem.

DR. RODRIGUEZ: Dr. Buckberg, would it be correct to say that this is more or less a general use across the country in people who perform the type of surgery you perform?

DR. BUCKBERG: I think it is used by many people around the country. For example, the study that you saw Dr. Stockbridge talk about was the Cleveland Clinic and Dr. Loop and they have been using this routinely for about eight or ten years since we introduced it. They use it in 4,000 patients a year just in that clinic and there are many people around the world that use this, both in the United States and internationally. Several different companies have

produced the drug outside of the United States because of its documented benefit.

MS. HOPE: I have a question for either of you and also the FDA. This is a very specialized use. Can you envision any reason to compound this out of a hospital pharmacy setting?

And to the FDA, could the committee restrict this to hospital pharmacy compounding only?

DR. BUCKBERG: I would think somebody from the pharmaceutical company would probably be better able to answer that than I could.

MR. TRISSEL: Actually, maybe I can -- in our Texas medical center, where we have 43 medically-related institutions -- and we are the largest medical center in the world -- well, I am from Texas -- at the St. Luke's Heart Center -- I think there is another name for that -- when Denton Cooley performs and all that -- they do get their cardioplegia solutions compounded by an outside contractor, which is licensed as a retail pharmacy in Texas.

DR. ALLEN: Just to follow-up on that, and, in addition, you know, every compounded product that we are looking at, not only this one, but pharmacists just don't go out and compound. These are all under a prescription from a physician. It is the physician that initiates

this. Pharmacists just don't go out and compound them and sell them. You know, it is all based upon the prescription from the physician.

DR. SELLERS: I believe that Elizabeth raised the issue about other uses for this bulk substance, other than cardioplegia solutions. I wonder if in the open hearing are we going to be hearing from Mr. Brandon?

I would like to ask the question then if this substance is being used in any other product for any other indications --

DR. JUHL: I believe, Dr. Buckberg, for the record, you are here on behalf of Central Add Mixture Pharmacy Services, in addition to your --

DR. BUCKBERG: Yes.

DR. JUHL: Good. Thank you.

Agenda Item: Open Public Hearing

MR. BRANDON: I am John Brandon, vice president of operations for Central Add Mixture Pharmacy Services.

This is the only use that I have seen for monosodium aspartate or glutamate and it is because we compound as an out source company for hospitals. Many of these hospitals that we spoke of here order these by prescription through our company.

As far as I know, there is no other indication, other than, you know, the Japanese restaurants use it

everyday, I guess, in cooking their meals. But I don't have any other indication for this.

DR. SELLERS: So, it is not being used for TPN solutions?

MR. BRANDON: I have never seen it used in a TPN solution.

DR. BUCKBERG: I don't know what these concentrations are, but I think that the TPN solution sometimes will have glutamate and aspartate as part of them. When we first came to Washington to get it as a -- I forget what it was called, some type of drug that was -- had a smaller usage, it was taken right out of the fact it was used in TPN in essentially the quantities we are talking about.

Another area it potentially may be used, separated from the cardioplegia solution is some groups in Europe, Stockholm, have used this as an intravenous support solution; that is, instead of giving someone after the operation dextrose in water as we normally do, they would use a support solution of glucose, insulin, potassium and amino acids and it has worked essentially the same way we found it worked in the cardioplegia solution. We have done some work on that.

DR. SELLERS: I have a concern as the result of an article I read in the International Compounding

Journal about the bulk compounding of TPN solutions from bulk active materials. That is the background for the question.

If we put it on the list, will we be restricting it to use in cardioplegia solutions?

DR. JUHL: I believe not.

Dr. Rodriguez.

DR. RODRIGUEZ: I have heard about the use of this preparation on TPN. I heard about the use in cardioplegia and I would like to hear more about the sterility checks. Essentially we are talking about -- the first one, we are talking about IV preparations and I think that -- I am sure that has all been taken care of; otherwise, we would have heard about it, but I just wanted for the record to hear about the sterility maintenance.

MR. BRANDON: I also have an associate with me that is responsible for our QA for our company and can probably go through better detail if you have questions about the sterility checks and how we prepare the monosodium aspartate and glutamate.

I would say that that is one reason we are in this business, because, I guess, in 1992, when the ASHP and other organizations started looking at how compounding was done in hospitals -- I won't go into the

stories of things I have seen from customers, who do this, who have given this over to us to prepare. We go through a lot of steps that a little more restricted than what your typical hospital pharmacy does and that is why they are more than happy to give this up to us to compound.

You know, there are not necessarily, I guess, in that case, the sterility checks were being done, even in the hospital. So, if you allow this to only go on in hospitals, which I think you will have to do with all of the heart surgeries going on now, I mean, I would want this product used on me and I would hope we would approve this so we can, you know, continue to get the good -- you know, the product sterile.

Helen Chang is our QA director and could go into any details, I guess, about how we prepare it and what the steps are that we go through to ensure the sterility.

DR. STOCKBRIDGE: I would just like to note that the sterility issue has to do with the whole cardioplegia solution product and it isn't specific to the aspartate component.

MR. TRISSEL: This would seem like a likely candidate for USP to look at as a monograph product, wouldn't you say, Loyd?

DR. ALLEN: Yes. Basically, everything that would go on the bulk drug substances, USP will look at developing monographs.

DR. JUHL: And there are already standards for sterility for the preparation of IV add mixture kinds of products.

Other questions?

[There was no response.]

Well, thank you, Mr. Brandon, Dr. Buckberg. We will assume that was the open public hearing from your perspective. Did you have the opportunity to say everything you needed to say? Okay.

Are there others? We have moved to the open public hearing section. Are there others of the public, who would like to address the committee, who have not previously said they would like to do so?

Agenda Item: Discussion and Vote on Monosodium Aspartate

Seeing none, we will move on to committee discussion. Are there further comments or questions that the committee has?

DR. SELLERS: I would just like to state for the record that I am still uncomfortable with approving sterile products without establishing how those products are going to be regulated. It sounds ideal to have them

produced in a facility that is using very good QA procedures. However, that is not the case in all pharmacies across the country. When we approve these substances that are being used for IV use or for cardioplegia solutions, I am just very hesitant to put them on the list.

However, I see the need to have them there. I understand that we are going to get to this, but it is still very uncomfortable for me to go ahead and list it when I know that it is being used for these indications.

MS. OGRAM: I think it is extremely important to assure the sterility of these types of solutions. And there have been problems in the past. I remember a case back in the nineties in which here were two deaths related to non-sterile cardioplegia solutions. This is an issue that the Agency is going to look at very closely when we get to the demonstrably difficult to compound drugs.

So, we definitely welcome your input on controls.

DR. JUHL: But as was pointed out, this is bigger than just this particular compound because something that already has the USP monograph or is part of an NDA product could be used now and the same concern for sterility exists there as well.

Other comments?

[There was no response.]

Are we ready for the question?

Option 1, we recommend that sodium aspartate be recommended for inclusion on the bulks list. Option 2, we recommend that it not be included on the bulks list.

All those favoring Option 1, please raise your hands. I see that as being unanimous.

So, we will recommend that that sodium aspartate be added to the bulks list.

Thank you, Dr. Stockbridge.

Well, we are scheduled for a break now, but I see no reason to do that while we are on a roll.

MS. AXELRAD: Our people are here and ready for the next one.

Agenda Item: Cyclandelate

DR. JUHL: So, we will move to cyclandelate and betahistine. These are a couple of compounds with a bit different nature to the problem and the issues. Dr. John Feeney will make a presentation on behalf of the Agency.

And we welcome Dr. Sid Gilman back to the table as an expert consultant.

DR. FEENEY: Let me start by saying that the Division of Neuropharm is involved with cyclandelate because we are the primary reviewing division for all

migraine drugs. Additionally, I will be summarizing some information on diabetic retinopathy and that was assembled by Dr. Stockbridge from another division.

So, the first drug I am talking about today is cyclandelate. Cyclandelate acts as a calcium channel blocker and, as such, as a vasodilator and may also act to protect cells from hypoxic injury. It is being proposed for compounding in two conditions; migraine prophylaxis and as a treatment for diabetic retinopathy.

Before proceeding, it is probably worth summarizing the rather extensive regulatory history of cyclandelate in this country. At one time it was approved for marketing in the U.S. under the trade name Cyclospasmol and it was labeled for two indications; first, as a treatment for intermittent claudication(?) and second as a treatment for cognitive dysfunction in Alzheimer's disease.

It was approved prior to 1962 at a time when the Food, Drug and Cosmetic Act required only proof of safety and not efficacy for marketing approval. Then in 1962, when the act was amended to provide the drugs required evidence of efficacy, it went through subsequent reviews and appeals and ultimately the Commissioner issued a final order in 1996, which withdrew approval of the NDA because of lack of substantial evidence of

effectiveness for those particular labeling claims already mentioned.

It has continued to be marketed in other countries however. Cyclandelate exists as a white amorphous powder. It is an ester of mandelic acid and trimethylcyclohexanol and it is a mixture of 4 steroisomers. The chemical properties are considered well-characterized.

First, cyclandelate is proposed for migraine prophylaxis. Let me say a few words about migraine. Migraine is basically a predisposition to bad, throbbing headaches. Treatment for migraine can be categorized into two groups. First are the PRN medications taken for individual attacks on the PRN basis. This group would include mild analgesics, anti-nausea medications, ergotz and sumatriptan-like drugs. The second group includes prophylactic medications that are taken on a regular basis in the hope of decreasing the frequency and severity of migraine attacks over a period of months.

And it is into this category that cyclandelate would fall. In this country, beta blockers, valproic acid and sanserd(?) are approved for migraine prophylaxis. Tricyclics, other calcium channel blockers and enseds(?) are also frequently used off label for migraine prophylaxis.

There are five controlled trials in the literature reporting on the use of cyclandelate in migraine. I would like to talk mainly about the first three here. The first two are both reports from Italy and are active control trials, comparing cyclandelate to, in the first, another calcium channel blocker, flunarizine, which is used frequently in Europe, but not available in this country.

Then in the second trial, cyclandelate was compared to a serotonin antagonist, pizotifen, again, used widely in Europe, but not available in the U.S. Both of the first two trials had a similar design. One month of placebo treatment, after which patients were randomized onto one agent or the other for three months. Both trials were small with roughly 20 to 30 patients per treatment arm.

In the first study published on cyclandelate in migraine, there was progressive improvement in all of the headache parameters for both drugs compared to the placebo period, as you can see here. While flunarizine was significantly more effective than cyclandelate, cyclandelate patients had a 40 percent reduction in a total monthly pain index.

The authors concluded that cyclandelate was a useful alternative based on these results. In the second

study, by the end of the third month, there was a 77 percent reduction in attack frequency for cyclandelate and a 31 percent reduction in frequency for the pizotifen-treated patients.

The authors conclude that cyclandelate has now become the drug of first choice for migraine prophylaxis in their clinic. Both of those trials used a dose of 800 milligrams bid. In both trials, mild gastric complaints were the most common adverse events and across both trials there was only one withdrawal from cyclandelate and that was for GI complaints.

The third trial was larger and included a placebo arm. The Diener trial, published in 1996, entered 214 patients. It had three treatment arms, cyclandelate at a dose of 600 bid, propranolol at a dose of 120 milligrams per day, and the placebo group. The treatment period lasted for four months.

The protocol defined a responder as someone with a 50 percent reduction in seizure frequency. The percent of responders shown here was 37 percent for cyclandelate, 42 percent for propranolol and 31 percent for the placebo group. So, on this measure, neither drug was statistically better than placebo.

However, on migraine duration, each drug was statistically better than placebo with cyclandelate

performing about the same as propranolol. The authors concluded that cyclandelate and propranolol were equally effective medications in migraine.

Of the other two studies, that I won't go into detail on, one was limited by small size. There were only 25 patients entered. The other was an active controlled trial comparing cyclandelate 800 bid to propranolol, 160 milligrams a day and in that comparison, cyclandelate seemed to outperform propranolol.

Cyclandelate is also being proposed for the treatment of diabetic retinopathy. To my knowledge, there are no other drugs approved for this indication in the U.S. There are only two reports of cyclandelate on this in the literature. The last one was published in 1987. I should say that both of these are from the same center and include some of the same authors.

In the first study, 24 diabetic patients without any evidence of retinopathology were treated with either placebo or cyclandelate, 400 qid, for three months. Every month, fluorescein angiograms were performed. This graph represents the average amount of fluorescein leakage out of the retinal vessels for each group by month.

This is thought to be a marker for the development of diabetic retinopathy. As you can see, at

the third month, there was a separation in favor of cyclandelate.

This is the second study here. Twenty-six patients were treated for 12 months at the same institution. Again, this shows the leakage at six month intervals. If you look at month 6 and month 12, there doesn't appear to be any big difference. It is only if you change from baseline that you see the trend in favor of the cyclandelate eyes, but, again, this is only statistically different for one side and not the other side.

So, based on these two reports, we would think that the evidence for an effective cyclandelate in preventing diabetic retinopathy is considered weak at this time.

A few words about the safety of cyclandelate. It appeared to be well-tolerated, based on the five reports in migraine. Adverse events were not reported for the two reports in diabetic retinopathy. Additionally, we went through an extensive list of 97 abstracts, referencing cyclandelate from 1960 to the present and there were no serious adverse events related to cyclandelate obvious from any of those reports.

Since it was marketed in the U.S., we looked at the spontaneous reporting system that we have internally

at the FDA. Between 1971 and 1996, there were only 34 reports for cyclandelate. No concerning pattern of adverse events arose from that. Remember it was approved in a fairly elderly population, a lot of them with cerebral vascular disease. So, you will find individual reports of MIs. There is one sudden death, but, again, there is no alarming pattern coming out of that.

And that is it.

DR. JUHL: Let's have questions on cyclandelate and do that now before we go to betahistine.

DR. SELLERS: What would be the contraindications for use of this product in either of the two indications?

DR. FEENEY: I can't really think of any contraindications. I suppose somebody who was prone to hypotension or vasovagal reactions, you wouldn't want to give them a calcium channel blocker. Other than that, I can't really think of anything.

DR. RODRIGUEZ: With the prevalence of its use in, quote, unquote, preventing diabetic retinopathy for which the only alternative treatment, quote, unquote, is good glycemic control, which many of the diabetics don't do.

DR. FEENEY: I have no information on its use at all. Again, there are only these two small reports in

the literature. I don't know if Dr. Stockbridge -- I guess we just have no idea.

DR. GILMAN: I can comment on that. There is no very good treatment for or prevention for diabetic retinopathy. It proceeds apace. If diabetic patients do very carefully control their blood sugar levels, then both the diabetic neuropathy and peripheral neuropathy do not progress at as fast a rate as if these people do not watch their glucose levels. This has been very carefully documented in a study that was centered in the Mayo Clinic.

So, good glucose control is absolutely key in these complications. There is no other medication that I know of that is effective for the control of this disease -- of this disorder. It is part of diabetes.

DR. SELLERS: We need to speak about the chemistry of this compound because of the 4 stereoisomers. There is no evidence to suggest which of the diastereomers(?) are responsible for the calcium channel blocking effects and whether they vary in their therapeutic effectiveness and whether any other diastereomers are responsible for any adverse effects. The effects of the drug that I have in my notes are decreased calcium induced contraction of smooth muscle, which is typical for calcium channel blocker, decreased

platelet aggregation by thrombin and also decrease in adenosine, either release or responsiveness, as well as decreased provote(?) 5HT(?) release from platelets.

I don't know whether any of those actions are specific to 1 diastereomer or another, whether we need to be concerned about that with this drug that is proposed for chronic treatment.

DR. FEENEY: It is certainly a very good question. I don't know of any chemistry on the formulations that were used in any of these studies and I don't know of any work specific to which stereoisomer was associated with particular adverse events.

DR. GILMAN: May I comment on that question? I think I need to make a couple of remarks, just to put this into perspective. I will comment on the pathogenesis of migraine along the way because the bottom line in this is that the primary effect of the -- the effect that is thought to be primary from some of the anti-migrant prophylactic agents is, in fact, not the mechanism by which they work. So, I will try to explain that.

First, you need to understand that we know a lot about migraine now. There have been a lot of advances in the field and it is now known to be a hereditary disorder, transmitted as an autosomal dominant

trait. There are familial migraine disorders that have chromosomal localization.

For the usual ones, there may be multiple sites. It is not clear that they are on the same chromosome as the one family that is described. The disorder does result from a change in the caliber of blood vessels during the course of the attack with a decrease of flow initially that spreads in a wave across the cerebral cortex, that is due to a phenomenon called spreading depression.

It has now been shown with pet studies at UCLA, showing a moving wave with depolarization at the cortical level. That is a secondary phenomenon, though. The primary phenomenon takes place in the brain stem and has to do with the raf-a(?) nucleus and the serotonin receptors and transmitters. The early events in migraine is release of serotonin from platelets, as a matter of fact. That is part of what happens in the periphery, but also in the brain stem.

The next set of events have to do with the transmission of information to neurons that control blood vessel caliber out of the brain stem from the trigeminal nerve and an inflammatory response that occurs at the junction of the nerves and the blood vessels.

I give you all this because we now know that

some of the drugs that are effective in migraine, such as proproranolol and the other beta blockers, do not work by means by means of beta blockade at all. In fact, they are serotonin agents. They stabilize serotonin receptors and neurons in the brain stem.

It is not clear how cyclandelate works, but I strongly suspect that it may have a serotonin effect and that may be the basis for its effectiveness. In the treatment of acute migraine attacks, sumatriptans are actually quite specific serotonin agents. They go into 5HT1 site and that is they are effective.

Probably some of the longer term -- the prophylactic agents work in a similar fashion, as far as we know. So, that is a long-winded way to answer your question. It is not entirely clear which of those multiple actions may be responsible for the effect. The question is whether there is an effect and is the drug safe and do we need another migraine drug when there are already approved and others that are used off label?

I think the best response to that is, yes, we do need another drug for the following reason. The abortive agents are actually pretty good. Most of the triptans are excellent and some of them can be delivered by a nasal spray, Maxide(?), for example, which is really very good, very fast. It is expensive but it works very

well.

For prophylaxis, though, we have an embarrassment. We have several drugs, most of which at best give you 30, 40, 50 percent improvement with frequency, severity, duration of migraine attacks. This is anecdotal from my personal experience, but I think most neurologists will tell you that, those who see migraine headache patients.

In addition, the degree to which each patient will respond to each medication is variable. Some people respond wonderfully well to amitriptyline, for example; others to propranolol or other beta blockers. I like to use tinorman(?) because that has very few side effects.

But we sometimes go from one drug to the next, usually starting with a beta blocker and it may be the second beta blocker you try that is effective, oddly enough, in a particular patient. So, having a larger armamentarium is in the patient's best interest as long as these are safe drugs that you are speaking of, and this one seems to be.

I agree with Dr. Feeney. I don't think that there is any real contraindication, except a person subject to postural hypertension, for example. In that case, maybe it would not be advisable. But then beta blockers are usually not advisable in those sorts of

people either.

MR. RUSHO: In the preparatory material, it talks about three asymmetric centers on the molecule and you have already mentioned the four isomers. It further mentions that this is an ester of mandelic acid reacting with 3,3,5 trimethylcyclohexanol and it talks about the different shifts in transisomers of that cyclohexanol as far as toxicity, with the transisomer having twice the toxicity.

Now, is there any guarantee or anything to indicate that we are going to get the one that has reacted with the sisisomer(?) or are we going to get a mixture of this when we buy chemicals. The question actually gets back to the question Dr. Peck asked yesterday about the purity of the compounds we are using.

If we can't be assured of the quality of these chemicals -- and I am sure that that is not going to appear on a C of A(?), as far as the different isomers, I am uncomfortable with this one because we could be doing more harm than good to our patients.

DR. JUHL: Now, let me try and address that.

Were this drug or a similar situation to be added to the bulks list, we would actually be embarking on a process of setting standards and we wouldn't be doing it but we would initiate that process. The USP has

agreed to develop monographs for anything that we put on or the Agency puts onto the list. There would, obviously, be a time lag between when the drug was listed and when the monograph appeared, but that monograph would then contain those kinds of specifications as to what exactly the mixture of isomers is and perhaps even the method of synthesis to get there.

That would be made available to those using the product. It won't happen immediately but that is a process that would occur, I think, to ensure uniformity.

DR. RODRIGUEZ: We were given a print to review in which two things immediately came out to me after I was looking an done of them was the -- somebody who may have, quote, unquote, vasoclusive -- in other words, severe cardiovascular type or somebody who has glaucoma.

Now, both of those conditions may not be known to the person. So, I assume that all these warnings will be forthcoming if we were to approve this preparation because, yes, they are printed, but when the thing is done in the compounding, those two conditions many times are very silent.

Again, somebody who would take the medication should at least take the responsibility of knowing or be informed that those two conditions are very important contraindications for the use of the drug.

DR. JUHL: Well, that would rely entirely upon the physician writing the prescription to do that.

DR. SELLERS: The other issue with this may be drug interactions as well. If there is no formal labeling for the drug, what are we going to do about drug interactions?

DR. JUHL: I think that is true of any compounded off label prescription products, but this one we have a better situation in that the drug has been on the market, was on the market, has the safety database to go along. So, there are some clues. Obviously, it won't be updated for new drugs, but that is a problem.

Other questions for Dr. Feeney?

[There was no response.]

We are going to split the open public hearing and do cyclandelate now and have a separate session for betahistine when we get to that. Gina Ford has asked to speak at this one.

Gina is the executive director for the International Academy of Compounding Pharmacists.

MS. FORD: Good morning. I am Gina Ford, executive director, International Academy of Compounding Pharmacists. I am a compounding pharmacist myself.

I don't have much to add. That was a very good job as far as description and what the possible uses are

for cyclandelate. I would just like to, again, bring us down to the level of the physician and the patient and where the compounding pharmacist fits in on that.

We often times call ourselves problem solvers and when that patient is in that physician's office every other week because the latest medication for migraine headaches isn't working and that patient can't go to work, guess who they call? They call the pharmacist and through working with those two people, that pharmacist and physician and the patient figure out maybe what might be the best medication for that particular patient.

If that patient goes back to work on cyclandelate, then that particular compound has been effective for that particular patient. As far as what you are concerned with, as far as contraindications and what kind of information is going to be available, I think Dr. Juhl said it best. We do have a history on this since it was a manufactured product. It was not removed because it was ineffective, simply because it was not ever proven effective.

We, I think I told you yesterday, are developing a program as far as adverse drug events. Part of that program will be to write for each one of these substances that is put on this list what we call a patient advisory leaflet that would list all those types

of things on a one page format. That is not a great in-depth history on the drug, but at least that is something that would be handed to the patient and also advise with the physician as well. So, just to touch on a few things.

DR. JUHL: Do you have any indication from the commercial sources for this product as to the mixture of isomers that are available?

MS. FORD: No, sir, I don't. I looked at the C of A and it is not indicated on there, but I am sure we could find out if that was available from the supplier all the way down to the repackager if we could pass that information along.

DR. JUHL: I think that would be useful not only to find out what is available, but to investigate what was used in the trials that were quoted earlier.

Questions or comments?

[There was no response.]

Agenda Item: Discussion and Vote on Cyclandelate

Let's move to committee discussion with the intention of taking a vote on this before we break. Are there other comments from the group?

MR. CATIZONE: Mr. Chair, in accordance with the criteria we are using and the FDA has established in

regard to safety, efficacy and historic use, I think this product meets those criteria favorably and I believe the report from the FDA experts indicate that the product does have a usefulness and is safe. So, I would urge the committee members to include it on the list.

DR. JUHL: Are we ready for the question?

Option 1, we recommend that cyclandelate be added to the bulk compounding list. Option 2, we recommend that it not be added to the list.

All those favoring Option 1, please raise your hand. Eight voting for Option 1.

For Option 2, please raise your hand. Three. Eight to three, the committee will recommend that cyclandelate be added to the list and the previous suggestion that we do some work to find out about the isomers or not we, but I would strongly ask the academy to do that. I think it would be useful information to pass on to pharmacists and patients.

We will now take a break and reconvene at 20 after.

[Brief recess.]

DR. JUHL: We will reconvene and continue on with betahistine. Dr. Feeney.

Agenda Item: Betahistine Dihydrochloride

DR. FEENEY: The next drug is betahistine.

Betahistine is a histamine analogue and through its action on H1 receptors, it is also a vasodilator, like cyclandelate. It is being proposed for compounding for the vertigo associated with Meniere's disease. Like cyclandelate, betahistine has an extensive regulatory history in the U.S. At one time, betahistine was actually approved for marketing in the U.S., labeled for use in Meniere's syndrome.

Betahistine under the trade name CERC(?), was the subject of NDA 14-241, approved in the 1960s for marketing. The commercial sponsor was UniMed. In 1970, the Commissioner of FDA withdrew approval of the NDA after the discovery that the submission contained unsubstantiated information about some patients in the efficacy studies upon which approval was based.

Betahistine has continued to be marketed in other countries however. It is available commercially as a crystalline powder with a melting point of 148 degrees. Structurally, it is very similar to naturally-occurring histamine. Its chemical properties are considered well-characterized.

It is proposed for the vertigo associated with Meniere's disease. Meniere's disease causes a triad of symptoms, tinitus, vertigo and stepwise hearing loss. The attacks of vertigo can last from minutes to hours and

can recur regularly for patients. While of unknown etiology, its pathophysiology is believed to be related to swelling of the indolymphatic sac in the inner ear.

Between 10 to 30 percent of cases can be bilateral and, obviously, hearing loss is a concern for those patients. It has a variable course and spontaneous remission is not unusual after a few years.

This fact makes evaluation of therapies difficult. While there are no interventions to prevent the hearing loss, numerous medications are proposed to treat the tinitis and vertigo. Surgical procedures have also been proposed to include endolymphatic drainage and section of the vestibular nerve.

In this country, only antivert or meclazine is labeled as possibly effective in the treatment of vertigo. Other histamines and anticholinergics are indicated for the treatment of motion sickness but are used off label to treat vertigo. Betahistine, although taken off the market in the U.S., has wide use throughout the rest of the world in the treatment of vertigo. Its mode of action is believed to be related either to local vasodilitation in the inner ear or alternatively to direct action on the vestibular nuclei in the brain stem.

Between 1970, when it was taken off the market, and 1985, there are at least three positive placebo

controlled crossover trials of betahistine for vertigo found in the literature. Each of these is small and enrolled only 20 to 30 patients. Outcome variables included frequency, severity and duration of attacks of vertigo, as well as patient global assessments.

The first two trials enrolled only patients with Meniere's disease. The third included patients with and without Meniere's disease, but over half of the patients did have Meniere's.

The active treatment periods were between 6 and 16 weeks long in the three studies here, followed by crossovers of equal duration. Again, in each of these small studies, betahistine seems to outperform placebo on at least one measure.

Since 1985,, betahistine seems to have found an established place in the literature, so that only active controlled trials are found after that time. These are two active control trials with the calcium channel blocker, flunarizine, which again is available in Europe but not the U.S.

Note that both of these included patients with and without Meniere's disease. In one, published in 1991, betahistine at a dose of 16 milligrams tid was found to be superior to flunarizine at a dose of 10 milligrams a day. In the other, published in 1988,

betahistine at a dose of 8 milligrams tid was inferior to flunarizine at the same dose.

Newer interests in alternative medications are reflected in these two recent active controlled trials, one with ginkgo and one with a botanical called vertigoheel. Both of these studies demonstrated equivalence of betahistine in the comparitor drug. This is not a controlled trial, but this report from Finland serves as the largest single center experience reported in the literature. At a dose of 8 milligrams tid, the majority of patients treated had favorable results with few side effects.

It is worth noting in many of the reviews, the beliefs of others, who have performed the reviews. These conclusions that you see here seem to echo a theme in the literature and that is that betahistine seems to provide benefit for the vertigo of Meniere's disease.

Now, a few words about the safety. While the safety profile that emerges from the literature seems favorable, there are several situations where you would want to use precaution. As a histamine analogue, betahistine has the potential to aggravate peptic ulcer disease. It also has the potential to aggravate asthma and there is at least one report of that happening in the literature.

Obviously, concomitant use with antihistamines should be avoided. So, in conclusion, there is some evidence for the effectiveness and safety profile seems acceptable.

DR. JUHL: Questions for Dr. Feeney?

Dr. Rodriguez.

DR. RODRIGUEZ: Since this disease is not only relenting, in other words, they are almost undulating, but also we assume it is going to lifelong, the question is a lot -- we should have a lot of information on really prolonged use of this medication and the question is these trials that you gave us, how long were the uses of the betahistine?

DR. FEENEY: I think the longest treatment period was on the order of several months. I actually can't recall from that one large single center experience in Finland how long the average duration was.

DR. JUHL: How long was the drug on the market and do you have an idea what the patterns of use were when it was marketed?

DR. FEENEY: Well, in the U.S., it was on the market up until 1970. I think it was approved maybe five or six years earlier. I think in the world I think there are people that have probably taken it for at least a year if not a couple of years. And I should say that a

lot of people do have spontaneous remissions with Meniere's disease. So, when you say life long treatment, I honestly can't give you an idea of how many people would continue with symptoms for their whole lives.

DR. JUHL: Other questions for Dr. Feeney?

Agenda Item: Open Public Hearing

Let us move to the open public hearing session of this compound. Gina Ford, again.

MS. FORD: Not much to add on this one. As far as the uses I think was discussed properly and the way that it is being used. Looking at sales data and interviewing pharmacists, there are probably right now in this country about 300 patients on this medication, the compounded medication. However, pharmacists report that they do have a number of patients that will seek to get this treatment out of this country either from Canada or Mexico. So, if we could show that the committee had recommended it, they would probably stay here and get the substance here.

DR. JUHL: Thank you.

Agenda Item: Discussion and Vote on Betahistine Dihydrochloride

Moving to committee discussion, are there comments or questions amongst the committee members?

Sarah.

DR. SELLERS: The substances are histamine analogue. Are there any concerns for compounding procedures would be a potential problem with compounding?

DR. ALLEN: Well, obviously, with anything that there is a potential problem, adequate care, you know, should be taken. Use of gloves, mask, no person that has allergic or asthmatic tendencies should use it. But that is pretty well common procedure.

DR. JUHL: Other comments or questions?

[There was no response.]

Then we will call the question.

Option 1 will be that the committee recommends betahistine be listed on the bulks compound list. Option 2 will be to recommend that it not be listed. I have had a request for roll call votes here on in, rather than raising of hands. So, we will begin with that end of the table. Judy.

MS. RIFFEE: Yes.

DR. SELLERS: For listing.

MR. CATIZONE: Yes.

MS. HOPE: Yes.

MR. RUSHO: Yes.

DR. PECK: Yes.

MR. TRISSEL: I am assuming we are voting "yes" for No. 1. Yes for No. 1.

DR. JUHL: The chair votes "yes."

DR. MC BURNEY: Yes.

DR. RODRIGUEZ: Yes.

DR. ALLEN: Yes.

DR. JUHL: It is unanimous as I recall.

We will recommend that betahistine be added to the bulks compounding list.

It is now 10:30. Anybody want to argue about anything. We are scheduled to resume at 1 o'clock and we are going to move that up to 12:30 in an attempt to kind of hasten the afternoon, but we do then have two hours and I am sorry, committee members, we are unable to move that up any farther because people who we have scheduled to speak are elsewhere and are scheduled to be here at 1 o'clock and we have had no luck in reaching them.

Given the difficulty with which it was to schedule this in the first place, I am not surprised by that. So, we will make every effort we can to be somewhat efficient, but let's be back here by 12:30.

[Whereupon, at 10:30 a.m., the meeting recessed, to reconvene at 12:40 p.m., Friday, May 7, 1999.]

A F T E R N O O N S E S S I O N [12:40 p.m.]

DR. JUHL: We will commence our afternoon session, but we do have some new people at the table. I would like to have them introduce themselves. The FDA staffers that weren't here this morning, if you could introduce yourselves to the group, please.

DR. CHRISTIAN: I am Dr. Michelle Christian. I am the director of the Cancer Therapy Evaluation Program at the National Cancer Institute.

MS. MC CABE: I am Mary McCabe and I am director of the Office of Clinical Research Promotion at the National Cancer Institute.

DR. MALOZOWSKI: I am Saul Malozowski. I am a medical officer at the Division of Endocrine and Metabolic Drug Products at the FDA.

DR. DeLAP: I am Bob DeLap from Office of Drug Evaluation 5, back from yesterday.

MR. GIDDES: I am Ken Giddes. I am the patient rep. I am a Stage 4 lung cancer survivor.

DR. JUHL: Ken, welcome to the committee. Ken is on the oncology committee but is now a member of our committee for this afternoon's discussion.

Agenda Item: Hydrazine Sulfate

Now, we have three speakers today to address us on the topic of hydrazine sulfate and first is Dr.

Malozowski from the Agency.

MS. AXELRAD: Maybe I could just say a little about presentation.

DR. JUHL: Yes, if you want to give us some background.

MS. AXELRAD: Not only do we have people from the Review Division here to speak, Dr. Malozowski, but we also have Dr. Charles Loprinzi from the Mayo Clinic, who is one of the principal investigators on the NCI studies of hydrazine, who has taped a presentation. He was in town and he was not able to be here today in person. So, we taped a presentation from him that we will be showing after Dr. Malozowski's presentation.

Dr. Loprinzi will also be available by telephone hook-up. We need to get him on the phone because he will be available also to answer questions from the committee and then, of course, we have representatives from the National Cancer Institute, who will also be speaking.

DR. MALOZOWSKI: I am Dr. Malozowski. You know me because I just introduced myself. I was told that this group was very small and I was happy because I thought that I feel like at home. The only difference that probably you will be listening to me because at home, I have problems with that.

Okay. Today I have to talk about hydrazine sulfate and I will give you some background and this will be a short introduction to leave Dr. Loprinzi and the people from NCI that will relate to you what happened with this particular compound.

This is the formula of hydrazine sulfate and it is a chemical compound that is derived from rocket fuel and is known to inhibit gluconeogenesis in animals. It has been used since the mid 1970s in attempts to improve survival or provide other benefits in patients with diverse cancers.

The claims that were listed during this period include improvement in survival, weight gain, improved well being, that the drug was well tolerated when given to patients with cancer, that the side effects were well characterized and that these side effects were mild in nature.

I think that the paper that brought hydrazine to the forefront was this one that was published by Dr. Gold in Oncology, 1975. In discussing this paper, I think it is important to state that this was an open label study; therefore, was not randomized, was not controlled. Patients with different conditions were treated with the compound.

Another important issue to state, that from the

initial 158 patients that Dr. Gold treated, he only report on 84 of these patients. That means 53 percent of the total patients treated. And he claims that the compound is efficacious and also has a benign safety profile.

Although he does not account for all excluded patients, we don't know whether the patients that were excluded is 84, responded or did not respond to a treatment. I think the best paper really that follow that one was the one that was published in the Journal of Clinical Oncology in 1980 and this was a well-designed study, was randomized with placebo and received either hydrazine and placebo, as you can see in the third bullet. Sixty-five patients with known small cell lung cancer were treated and the findings are listed in the last three bullets.

They also report improvements in caloric intake and albumin levels in the hydrazine-treated group and this is a very important finding because the study was well-designed. But also it states that there were not changes in survival, body weight or objective tumor responses. And recall that these were claims that were made before regarding these compounds, that this compound was able to induce weight gains, survival and these kind of things.

Therefore, when the first study, well-designed, was done, the only thing that was shown to be positive was the improvement in caloric intake that is very important for a patient with cancer and also the levels of albumin that is a surrogate indicator for nutrition.

As I stated in the last bullet, also when he look at a subset of patients, he notice that this patient that has less advance tumor staging have improvement in survival and in the paper, I think that he advances the hypothesis that this particular group of patients should be looked into with these compounds because these are the patients that probably could benefit the most for this particular intervention.

As a result of the study, I believe, the NCI sponsored three randomized clinical trials and overall, 600 patients approximately were randomized to receive hydrazine or placebo and the endpoints in replications to the claims that were made in the past by Dr. Gold and the literature and the last paper I just review were also survival, weight and quality of life.

From this supported research, three papers were published consecutively in the Journal of Clinical Oncology and here you have the reference and the authors. As you can see in the second bullet, Dr. Loprinzi was the principal investigator in two of these studies.

In conclusion, none of the studies achieved the desired outcome. Therefore, none of these studies were able to replicate what was seen in the previous studies and no replication of favorable outcomes in the subset of patients with less advanced tumors, as suggested before was found. Therefore, the patients that before were seen to benefit from this therapy were not -- who did not improve while receiving hydrazine sulfate.

What other things were found? Patients receiving placebo had better albumin levels and quality of life outcomes than those receiving hydrazine. Therefore, this is in contrast to what was found in the previous paper. Hydrazine was shown to induce sensory and motor neuropathy and hydrazine patients had increased deterioration of physical functioning, fatigue and cancer related symptoms.

One of the studies by Dr. Loprinzi was terminated prematurely due to increased mortality or the trend to increased mortality in the hydrazine-treated group. The lack of beneficial responses to hydrazines were seen in patients on and off chemotherapy and regardless of receiving any other medications.

This slide, I think you have to take with a grain of salt because I listed here what I call additional safety considerations and I listed that

hydrazine has been shown to induce tumors in animal studies, that occupational exposure to hydrazine has been linked to increased cancer rate in humans and other adverse reactions were reported also, linked to hydrazine and I listed them and I am telling you that you should take this with a grain of salt because this is the information we can find in the literature. We never review a new drug application for this particular compound. Therefore, we never were able to assess this safety profile in a manner that is rigorous.

Therefore, the information I am sharing with you is the information that is in the public domain. We were never able to address this issue ourself.

As a result of the outcome of these studies, the negative result in patients with diverse cancers receiving hydrazine in any of these well-controlled studies that the NCI supported, I think that probably that was the reason, although I am not sure, that NCI discontinue funding for studies with hydrazine sulfate for these indications. At least, this was my understanding.

In closing, as a consequence of the results of the well-controlled studies with hydrazine showing lack of efficacy, because none of the well-controlled studies was able to show that there is improvement in any of the

outcomes, also as a result of their reduction of life expectancy, the worsening of quality of life and increased toxicity in subjects receiving hydrazine, the Division of Endocrine and Metabolic Drug Products stopped granting compassionate INDs for the use of hydrazine in patients with cancer.

That is it.

DR. JUHL: Thank you.

Any questions of clarification?

If not, we will move on to our next speaker, who will be brought to us via video tape. Dr. Charles Loprinzi, as you heard, was the principal investigator on two of the three NCI-sponsored trials of hydrazine sulfate and is professor and chair of medical oncology at the Mayo Clinic.

As I say, we have him on video tape and later we will have him on the telephone.

DR. LOPRINZI: I am a medical oncologist in Rochester, Minnesota, currently the chair of the Division of Medical Oncology there. I am also coordinator of a cancer control studies for the North Central Cancer Treatment Group. That is a group that has been involved with a number of studies, 50 to 75 studies over the last ten years or so, looking at ways to prevent cancer, ways of treating symptoms related to cancer therapy.

I got involved with the hydrazine sulfate study several years ago because I have had interest in our area related to the potential properties it might have had for preventing -- for helping appetite problems, weight loss in patients with advanced cancer. There was a trial that stimulated our interest conducted by Dr. Chlebowski and published in the Journal of Clinical Oncology, along with an editorial that reported positive results in a subset of patients with lung cancer, who received chemotherapy and hydrazine sulfate.

We, therefore, decided to replicate that to -- this really wasn't advanced for patients. Dr. Chlebowski, when he set up his trial, did state that this subset analysis was exploratory. We talked to the National Cancer Institute about doing this particular trial. Around the same time, we also decided to look at another aspect -- a different trial looking at a different disease population, those were our patients with colon cancer as opposed to lung cancer in the first trial and also look at patients who were not receiving concomitant chemotherapy.

So, we did the two trials, we went to NCI and said we would like to do those and NCI at the same time told us they would like us to do those and, therefore, we developed those trials together with NCI.

The trials were designed and conducted in a joint manner with a number of people. I was the leader of that aspect, designed the first trial with lung cancer and the second with colon cancer with concomitant chemotherapy, both designed in a prospective manner, placebo controlled, double blinded, so neither the patient nor the physician knew or the nurse knew, which medication that each person was getting, whether that medication was actually hydrazine sulfate or the placebo.

There were hundreds of patients on these trials. It was designed in an optimistic manner to learn whether this medication would provide benefit for patients with cancer. The results of the trials -- there were really three trials that were all published in the Journal of Clinical Oncology. We did two trials with another trial conducted by another cooperative oncology group, the CALGB, initials associated with that treated group. Dr. Costi, Michael Costi from Scripps, was the primary author on that trial.

His trial was very similar to ours, to our lung trial, which were both designed after the Chlebowski UCLA trial, which had the subset analysis, where the subset analysis looked positive. All three of the trials were done and none of them showed any suggestion of benefit for hydrazine sulfate. They were -- there was no

evidence of survival benefit. In the Costi trial, there was some suggestion of increased toxicity with neuropathy, problems with tingling, nerve dysfunction. And there was a suggestion of decreased quality of life in their trial, but nothing that they utilized to measure quality of life.

In our trial, looking at lung cancer patients, there were trends for a decreased survival and trends for increased -- for decreased time to progression, although we did not pick up any toxicity or quality of life difference in the two arms of our trial.

For our trial looking at colon cancer patients, again, these patients were not receiving the chemotherapy, we saw trends for decreased survival and decrease of quality of life in this trial, but no evidence of toxicity.

Our colon trial was stopped a bit early because of the negative results from the other ones, after meeting with NCI and other members of our group for that. The P value for survival was actually -- well, some people might call it a significant P value, P equals .05, as I recall or .04 -- we didn't feel comfortable in saying this was a significant survival loss or increase in survival because it was an interim analysis and had we seen the results the other way on interim analysis, we

wouldn't have called it positive.

How were the results of this study handled or interpreted by the medical oncology community? As I mentioned before, all three of the trials were published in the Journal for Clinical Oncology and also with an editorial. The title of the editorial written in that particular issue of the journal was something akin tot he following, "Three Stakes in the Heart of Hydrazine, but Unorthodox Therapies, like Vampires, Always Rise Again." And sure enough, that has happened again and again with this particular compound.

There is a separate issue of -- the Journal of Clinical Oncology has another publication called Classic Papers and Current Promise, where they take the best papers over the last five to ten years in a particular subject area and republish those and allow the authors to make other comments on what has happened since that time.

They did that for colon cancer a little bit ago and in those -- of the colon cancer papers they chose, they ended up choosing this hydrazine sulfate paper as being one of the best colon cancer papers over the last several years and republished that.

They then awhile ago looked at lung cancer, a separate guest editor, and, again, chosen for this special publication was the hydrazine sulfate study we

did on lung cancer. More recently, they are developing a separate publication on supportive care in oncology and they -- again, a separate editor chose one of the two trials to be published again, indicating to me that these trials are something that have been felt to be papers that have shown what the truth is.

Actually, it surprised me somewhat because they were negative trials and didn't write up a big thing with them. They just mentioned the facts, but that is what has happened with them. So, the oncology community has bought into the fact that these trials have demonstrated that there is no suggestion of benefit.

There have been uprisings since these trials were published and actually before our trials were published by the advocates of hydrazine sulfate. This led to a number of -- well, this led to the Congress asking the General Accounting Office to audit these studies, to look to see if there was something going on that discredited hydrazine sulfate when there shouldn't have been.

The GAO set this audit up. They spent a lot of time. They provided a report looking at this thing. The end answer for what the GAO thought, I think, was nicely summarized in the title of the report, which reads, "Contrary to Allegation, NIH Hydrazine Sulfate Studies

Were Not Flawed." So, that is the bottom line. In looking at the details of the GAO report, there are some things where they talk about that some of the reporting wasn't done as quickly as they thought it would be.

My own bias, I disagree with them on that aspect. It is hard to report things early, ahead of time, in double blind trials. So, I would have some -- take some issue with what they came up with there. But the bottom line was that they did not feel the studies were flawed after a large investigation.

One of the issues that has arisen a number of times with regard to the hydrazine sulfate studies is the issue of potential incompatibility with tranquilizers, to alcohol and that sort of thing. The proponents of hydrazine sulfate have claimed on and off that this is something that made the NCI-supported studies at risk for not telling the truth.

The GAO audit and others that have looked at it, the NCI and we looked at it initially, there are no good data to demonstrate that there is a bad interaction between tranquilizers, alcohol and hydrazine sulfate, number one.

Number two, when our trial at the request of some of the proponents of hydrazine sulfate did exclude alcohol use, we could not disallow the use of anti-medics

or nausea medication for these people who were getting chemotherapy that caused a lot of nausea and vomiting. When we started the trial, the main anti-medics or anti-nausea medications that were being utilized were tranquilizing type medications, but this was well-known by Dr. Gold and his colleagues. He read the study. He provided correspondence saying that the thought they were good studies at that time.

Of interest, the first study that was done by Dr. Chlebowski also when people went back and looked utilized tranquilizers as anti-medics, the right sort of thing to do. This is the study that was felt to be, quote, positive, end quote. Dr. Chlebowski actually said it is a subset analysis and you can't depend on it.

Also, Dr. Chlebowski did not disallow or allowed people to drink alcohol on the study. There are no data to demonstrate how much they did or didn't drink. The alcohol was not excluded from their trial. Nonetheless, we did exclude it.

When we went back and looked at our trial results, based on whether people had received tranquilizers or not because it was actually an interesting thing that halfway through our trial, the new anti-medics became available, which are much better at preventing nausea and don't cause the drowsiness that the

other drugs have. So that about half or a third of our population was in each group that got the tranquilizers versus those who didn't.

When we went back and analyzed the data that we had on toxicity and survival and quality of life based on those separations, there was no suggestion of any benefit. So, the bottom line is despite the allegations of the tranquilizers inhibiting hydrazine sulfate's activity, number one, there are no good data to suggest that and when you look at the data with or without, it is not there.

Number three, if you look at the positive study, they allowed tranquilizers and alcohol. One of the questions that has come up repetitively is how is it that up to 70 to 80 percent of patients on the Phase 2 or on controlled clinical trials have stated between the physician and/or the patient, that the hydrazine sulfate was helpful for them because that is a pretty large number of people claiming benefit.

I have done a lot of thinking about that. It turns out that if we go back to a number of our other trials looking at appetite stimulus, a population that is quite similar to the population that gets hydrazine sulfate because the appetite problems are such that they are related to advanced cancer, that these trials were

before we studied medications versus a placebo and then looked in the placebo population, double blinded trials, so people don't know whether they are getting placebo or active drug, looked in the placebo population and look at what percentage of patients think that the medication they are getting is helping their appetite, the answer is that somewhere around 35 to 40 percent of people think this placebo is helping their appetite. What is helping their appetite, whether it is all psychological or there are other things are going on and we are seeing the chemotherapy also, which was helping their appetite or some other -- their pain is better controlled and, therefore, helping their appetite, there are a number of things that relate to that.

But, therefore, you can get 35 to 40 percent of the patients whose appetite alone has benefited. Other patients, it might be that their pain is better. Well, you could easily get 10, 15 percent of people who say their pain is better. They might also be getting chemotherapy or radiation that is helping their pain or other pain medications or the pains vary from time to time anyway. So, there might be another explanation for it, other than just the hydrazine sulfate medication.

You can get a few other people who have better -- decrease in their nausea, a few other people who are

sleeping better, a few other people who have decreased itching. It is easy to understand how you can get 70 to 80 percent of the people who are claiming benefit from a medication.

It is interesting that if you take the opposite situation -- and we saw this with vitamin E with one of our trials, we were looking at vitamin E to prevent hot flashes -- the toxicity, if you look at a lot of Phase 2 trials of vitamin E, there is a fair amount of toxicity, 10, 15, 20 percent of people get toxicity from vitamin E. However, if you do placebo controlled trials, the exact number of patients, 15, 20 percent claim some toxicities from the placebo as what they get in vitamin E. That is what you get doing the placebo controlled trials.

That is the explanation that I can give for why there is this subjective benefit seen in 60, 70, 80 percent of the patients who are receiving hydrazine sulfate in the Phase 2 trials.

Let me summarize the things with hydrazine sulfate. It has been investigated much more than many other compounds. The end results of the investigation are that there is no convincing evidence that it causes an improvement in appetite, an improvement in survival, an improvement in quality of life for patients or an improvement in any other symptom.

There is some suggestion that it can cause some toxicity and all medications can cause some toxicity. But the bottom line is there just isn't any suggestion of benefit for hydrazine sulfate.

DR. JUHL: We now are going to have to take a five minute break while we take care of the technicalities of getting Dr. Loprinzi on the phone. So, we will take five minutes and as soon as we get him, we will come back on line.

[Brief recess.]

DR. JUHL: Dr. Loprinzi, are you with us?

DR. LOPRINZI: I am here.

DR. JUHL: Good. Welcome to the committee. We have so far heard a presentation from Dr. Malozowski. We have viewed your video tape and now Mary McCabe from NCI will have a presentation of about ten minutes in length and then we would like to be able to ask you some questions about the studies.

DR. LOPRINZI: Sounds good to me. I am always happy to hear from Mary.

DR. JUHL: Great.

MS. MC CABE: Thank you very much for the opportunity to really give you a summary and to give you some details of some of the data about the NCI's evaluation of hydrazine sulfate. You have already heard

both from Chuck Loprinzi and the FDA the overview and the results of the studies. What I would like to do is give you some specific data so that you could actually see why the conclusions were drawn that were already presented and discussed.

You have already heard about Dr. Chlebowski's study and really the study that piqued the interest of the National Cancer Institute in looking further and soliciting cooperative groups, multi-institutional mechanisms that the NCI has to do randomized Phase 3 studies and this was a small randomized exploratory study, but it piqued our interest because non-small cell lung cancer is a devastating disease and anything that could be helpful, especially in the area of survival, was really very important to us.

So, based on this study where patients were given a standard regimen of chemotherapy that is listed here and randomized to either hydrazine or placebo, and as was already discussed, the overall survival did not improve when you looked at this study in total. However, the subset of what is considered good performance status patients, those that on a performance scale of 0 to 4, those that were 0 to 1 were those that seemed to benefit [illegible] evaluation of hydrazine sulfate. You have already heard

began the mechanism that we use at the Cancer Therapy Evaluation Program at NCI to begin to solicit those cooperative groups interested in conducting Phase 3 randomized trials. As Dr. Loprinzi already described to you, both the North Central Cancer Treatment Group and the Cancer and Leukemia Group B, both cooperative groups, sent in concepts that then were discussed and reviewed and then approved by the National Cancer Institute for conduct, which includes scientific review, as well as safety and ethical issues as well.

During the discussions and the design and the process of back and forth in developing a protocol, we included discussions with Dr. Joe Gold, who is one of the early investigators in a chief component of this product, discussions about the design of the study, as Dr. Loprinzi said; also, encouraged him to send data to us about concomitant medicines and his concern about their having impact on the activity of the drug while it is being used in the study. We even provided him with hydrazine sulfate that we were going to be using so that he was comfortable that these studies would be well conducted.

As Dr. Loprinzi said, that they have correspondence from him, as well as I think Dr. Costi does, that he was pleased with the study designs at the

beginning of these trials.

The overhead just gives you a chronology of how these studies were begun and the time period over which they were conducted and then finally published in the Journal of Clinical Oncology in 1994.

The first study, the CALGB study, was designed -- it was the first one that was begun to be a confirmatory trial, as you have already heard, to really confirm what was exploratory and the results of Dr. Chlebowski's study. These were 266 patients, performance status 0 to 1. Those seemed to be the patients that had benefited in the preliminary study.

They were treated with a regimen, two of the same three drugs that were used in Dr. Chlebowski's study and, again, randomized between hydrazine and placebo. These are some of the figures showing the results of this trial. We looked at response rate, both complete responses with total shrinkage of tumor and there is really no difference between the patients who received hydrazine and those who received placebo.

The partial response, having at least a 50 percent decrease in tumor, again, no difference between the two arms. If you look at the survival, the survival is measured in medium survival. You can see that there is no difference in either arms as well.

Quality of life, as Dr. Loprinzi already mentioned, was significantly worse with hydrazine, specifically in the areas of neuropathy, both motor and sensory.

This next study is one of the studies that Dr. Loprinzi was the principal investigator for. This is a study also in unresectable non-small cell lung cancer with 237 evaluable patients, again, a very similar standard chemotherapy regimen. Instead of using vinblastine, known as Velban, a BP16 was used in this study and patients received either hydrazine and placebo.

As Dr. Loprinzi mentioned that the North Central Group was very sensitive to wanting to be able to give hydrazine sulfate the best opportunity for evaluation and even though the data did not preclude and would not have, I think, justified necessarily and absolutely excluding these concurrent medications, they felt that they would try to give hydrazine its best chance and really address the requests and some of the concerns of proponents of this compound.

So, in both this lung cancer study and then a colorectal study that I will show you, they did exclude these, except for, as Dr. Loprinzi mentioned, the anti-medics, the anti-nausea drugs that really were not only necessary but really allowed for an ethical study because

of the cisplatin, which causes quite a bit of nausea and vomiting and these patients required it.

When we went back and looked at the anti-medics, for the most part, they were only given for about 48 hours right around the period of the chemotherapy and they were not given continually throughout the period that the patient was on study.

This overhead shows the study results for this North Central study in lung cancer. Again, no difference in response between hydrazine and placebo and no difference in survival, again, measured in months. No difference in quality of life and no difference in toxicity, except some central nervous system toxicity, dizziness and headaches.

This is the third study, also conducted by the North Central Group. When they began discussing the study, we thought it was interesting and valuable to do because these patients would not be receiving chemotherapy. So, again, a very important evaluation of hydrazine as what its potential was in benefiting patients and improving the survival with very serious and fatal illness.

There were 127 patients, performance status 0 to 1, as well as 2, and, again, the treatment schema because there was no chemotherapy was a randomization

between hydrazine and placebo. Again, these concomitant medications were excluded and as part of the discussion that took place between Dr. Gold and the head of that cooperative group, North Central.

Again, the third negative study with no benefit being seen for using hydrazine sulfate, there is no difference in survival between the hydrazine arm and the placebo arm and there was a worsening of quality of life, as measured using quality of life measurements both in this study, as well as the North Central study that are standardized quality of life instruments we use routinely in our cancer clinical trials specifically in Phase 3 studies. So, these were standardized instruments that we use routinely and really have quite a bit of confidence in the results.

This is just a summary conclusion that you have already seen before, that after over 600 patients were treated on three randomized Phase 3 trials, that we did not see any benefit in survival, nutritional status or quality of life and at the end of these studies, we asked the FDA to close the IND.

One other comment just on the third North Central -- the third study in colorectal cancer, as Dr. Loprinzi said, this study was closed early. There had been an interim analysis planned at about I think it was

150 patients, unless something untoward was seen, and there were a higher number of deaths in one arm than we expected. So, that is when the North Central Group took a look at the data, met with the National Cancer Institute and we didn't see any reason to continue with the study, not only because there was no chance that hydrazine, even if we accrued to the total number of patients, could be better than or equal to, but also we had the results from the other two trials and felt that we shouldn't continue the study.

The physicians in the North Central Group then went to their patients that were still continuing on hydrazine and offered them the option of either staying or coming off the hydrazine sulfate at that time.

I think I will stop here so we can have some discussion and answer your questions.

DR. JUHL: Thank you.

We will proceed with questions from the committee and if you could identify the speaker to whom you want the question directed, if you have a particular favorite, and because we have a series of hook-ups to get to Dr. Loprinzi, make sure that you are close to your microphone so that we can communicate well.

Judy.

MS. RIFFEE: Ms. McCabe, I wonder if you could

give us just a few specifics with regard to the instrument that measures quality of life, just a few of the things that you are looking at.

MS. MC CABE: Yes. There were a number of different instruments used. One is called the FLIC, the functional living -- I can't remember exactly, but it is a cancer specific instrument, and as well as one of the -- and Dr. Loprinzi can talk about the one specifically that they used and one is a European instrument from their cooperative group, which has a stable group of questions that has to do with both physical, psychological and social functioning and the ERTC(?), the European instrument also had a lung cancer module with it. So that you really not only can assess general questions about the cancer, but you also then assess issues of symptoms related to that particular disease. They have modules that are added to them.

They have been very carefully tested both for validity and reliability and are used virtually internationally in the cancer community and they are cancer specific instruments.

MS. RIFFEE: Thank you.

DR. JUHL: Any other questions?

Are we questioned out?

Well, seeing none, we will try and accelerate

our schedule. We have a break scheduled at 2:45, which we aren't going to take. We have an open public hearing for which we have no scheduled speakers, but I will ask if there are those members of the public present, who would like to address us, who haven't notified us prior to this.

Agenda Item: Discussion and Vote on Hydrazine Sulfate

Seeing none of those, let's move on to the discussion and vote on hydrazine. I would ask for comments, questions for discussion among committee members.

DR. MC BURNEY: I would like to ask a question of the FDA. I understood from the presentations that there will no longer be any INDs given or no longer being given for hydrazine sulfate so that it will not be available at all if it is not on the bulk list.

MS. AXELRAD: That is correct.

DR. JUHL: Unless someone develops some new information, which would lead you to --

MS. AXELRAD: Right. Or if someone decided that they wanted to study it further for something.

MR. TRISSEL: I just actually wanted to reiterate a comment I made at our last meeting, that for most of everything that we have had to deal with, we deal

with an absence of information, inadequate studies. We are trying to do the best we can. Here we have a compound for which we have really good information and I would encourage the members of the committee to act on that really good information.

DR. JUHL: Mr. Giddes, as a consumer representative member of the advisory committee and a patient yourself, any words of wisdom you would like to remind us of?

MR. GIDDES: Well, I have a database about three or four hundred people that I call and this drug has come up several times. What bothers me -- I didn't know that much until I got into reading the books, but they had a 70 percent cure rate according to a lot of these people and looking at -- being in the finance business, I did the percentages and figured the 70 percent is not correct.

Is there anything that the FDA is going to be doing to discourage this to get onto the Web sites where these people pick it up because I had a couple of people say they will give up chemo and radiation and use this drug. I think this is wrong because they are looking at the 70 percent success rate and like myself, I had like 30 percent chance I would be talking to you today. You know, you go by the percentages and they look out for

hope and they pick up a lot of this information on the Internet and I try to tell them, I said, well, go for your medical oncologist's advice first and then look at this second if you need to.

Is there any comment on that?

DR. JUHL: Jane or Bob, do you want to address that?

MS. AXELRAD: Well, the Agency -- it is sort of a very timely question because the Agency is very much involved in looking at sales of drugs on the Internet, both legitimate, you know, approved drugs, as well as unapproved drugs. I attended a meeting I think it was last week that Carmen was also attending, of a number of federal agencies who were looking into the issue. It crosses boundaries of regulatory agencies. It involves the Federal Trade Commission, the Justice Department, Customs, Drug Enforcement Administration. And we are trying to figure out how to address these issues.

There are a number of products like this that are promoted on the Internet that raise very difficult enforcement questions and we are trying to figure out what the agencies can do about that.

DR. JUHL: This is a very difficult issue, given that we live in a country where you can say what you want to say pretty much. I think the best way to

counteract this is through good information and the Internet is a way that people can find out lots of things and I think we do need to look to the Agency or to the FTC, whoever regulates the bad things that are said, but the converse is to provide people with information. That is what the cry is for is information.

I think that is perhaps not necessarily within the Agency but within the medical community, one of the things that we need to do more of.

Are there other comments or questions?

[There was no response.]

Are we ready for the question? We will proceed then. Option 1, that we recommend hydrazine sulfate be added to the bulk compounding list. Option 2, we recommend that it not be added to the bulk compounding list.

Starting with Judy Riffee.

MS. RIFFEE: Are we doing -- I am sorry. I lost the thought.

DR. JUHL: Option 1 would be to list it. Yes. Option 2 would be not to list it. No. Take your pick.

MS. RIFFEE: Do not list it.

DR. SELLERS: Not list it.

MR. CATIZONE: Not list.

MS. HOPE: Do not list.

MR. RUSHO: Do not list.

DR. PECK: Do not list.

MR. TRISSEL: Do not list.

DR. JUHL: Do not list.

DR. MC BURNEY: Do not list. Option 2.

DR. RODRIGUEZ: Do not list.

DR. ALLEN: Do not list.

MR. GIDDES: Do not list.

DR. JUHL: Unanimous, 12-0 vote to recommend that hydrazine sulfate not be listed on the bulk compounding list.

I would like to thank our participants. Dr. Loprinzi, thank you for joining us by phone and also thank you for making the video tape.

DR. LOPRINZI: You are welcome. Thank you for having me participate.

DR. JUHL: Ms. McCabe, thank you for making the trip over. We appreciate that.

That concludes -- and Dr. Christian, too, thank you for being here -- that concludes our agenda. I again would like to thank the Agency staff for their preparations in getting us ready and thank you to the committee for your attentive -- your preparation and it has been a pleasure to struggle with you together.

Our next meeting is scheduled for the end of

September and unless there are other things that need to be addressed -- Jane, do you have any parting comments?.

MS. AXELRAD: No. I just wanted to thank the committee for its efforts over the past few days. I think that we had deferred these drugs to this meeting, I think that these were much more difficult issues that we had to address and we appreciate the thoughtful consideration that the committee gave to the presentations and we appreciate all of your work. Thank you.

DR. JUHL: We are adjourned.

[Whereupon, at 1:32 p.m., the meeting was concluded.]