FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Thursday, June 23, 2016

1:00 p.m. to 5:08 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

**Meeting Roster**

**DESIGNATED FEDERAL OFFICER (Non-Voting)**

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Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

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Director of Clinical Pharmacy Services

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**Donna Wall, PharmD**

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Senior Vice President and Head of Regulatory Affairs

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**William Mixon, RPh, MS, FIACP**

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Former Owner

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**TEMPORARY MEMBERS (Voting)**

**Jeffrey Brent, MD, PhD**

*(Participation in DMPS discussion)*

Distinguished Clinical Professor of Medicine

University of Colorado School of Medicine and

Colorado School of Public Health

Denver, Colorado

C O N T E N T S

C O N T E N T S (continued)

know this is oftentimes a tough condition to treat.

DR. CAROME: Mike Carome. I voted no primarily because I think there's insufficient evidence that it's effective for the proposed use that we were asked to consider.

DR. WALL: Donna Wall. I voted yes for the reasons previously stated. Again, this is yes for topical use only.

DR. VENITZ: Thank you. We are almost done, but before we can really wrap it up, we're going to take a break. So I want to remind everybody on the committee not to talk about any of the topics that have been discussed as a committee. And let's all reconvene at 3:45 p.m. for our last session.

(Whereupon, at 3:35 p.m., a recess was taken.)

DR. VENITZ: Let's reconvene the meeting, please.

Before we begin the last session, I want to introduce our newest addition, a special government employee who will be part of our discussion. He is Dr. Jeffrey Brent, distinguished clinical professor

of medicine at the University of Colorado, and he will help us on the DMPS topic. Thank you.

We will now continue with the FDA presentation first. And I'm asking Dr. Suh, who is a clinical team leader in the Division of Hematology Products, to give us the lead.

**Presentation - Kathy Robie Suh**

DR. SUH: Good afternoon. My name is Kathy Robie Suh. I'm a clinical team leader in the Division of Hematology Products in the Office of Hematology and Oncology Products in CDER.

Today, I will present the assessment for dimercapto-1-propanesulfonic acid, which I will refer to as DMPS in this presentation. This slide shows the review team for this nomination. The DMPS nomination is for the use, treatment of heavy metal poisoning. The applicable routes of administration for the nomination are oral, and IV, and intramuscular injection.

The materials received for this nomination consisted of literature publications which were mostly anecdotal case reports and uncontrolled

series of cases of exposures to various heavy metals in patients who were treated with DMPS. The available information for the assessment was limited, but what was available was reviewed.

No product containing DMPS is marketed in the US. The available chemistry information for DMPS was obtained from the Heyl Scientific Product Monograph, which is a document that has information regarding a DMPS product that is marketed in Germany.

FDA does not have access to the information used to support the market approval of the European DMPS product.

DMPS is a chemically-synthesized small molecule. It is usually supplied as its sodium salt. It is non-hygroscopic and exists as the monohydrate.

DMPS sodium salt monohydrate has a molecular weight of 228.3 Daltons. The monohydrate is stable in the crystalline form. It's relatively stable in aqueous solution, but it's labile to oxidation.

The Heyl Monograph states DMPS is purified

by release from the lead salt. There are potential in-process impurities including lead, allyl bromide, allyl sulfonic acid, and 2,3-dibromopropane-1-sulfonic acid.

Potential heavy metal contamination can be monitored using USP compendial methods. However, as you know, in the U.S., compounding regulations do not require evidence of adherence to good manufacturing process requirements, so there's no assurance that the in-process levels of impurities do not exceed safe levels.

These next two slides summarize available animal and nonclinical information for DMPS, again, based on the German product monograph and also a 2009 World Health Organization document.

DMPS chelates heavy metals, but the mechanism of action is not fully characterized. It increases urinary elimination of arsenic and interferes with arsenic methylation.

For mercury, it promotes excretion and protects against mercury-induced renal damage by inhibiting mercury accumulation in renal proximal

and distal tubular cells.

Administered intravenously, it mainly distributes in plasma and kidneys and has an elimination half-life of about 20 to 60 minutes.

In nonclinical studies, DMPS has relatively low acute toxicity and relatively low chronic toxicity in dogs and rats. There's no evidence of adverse effects on cardiovascular, gastrointestinal, or renal systems. There are no data available on central nervous system or respiratory system effects.

DMPS is not mutagenic in the Ames test and it shows no reproductive toxicity or teratogenicity. These toxicity assessments do not address the potential toxicities of any potential impurities such as, for example, lead or allyl bromide, which is a known mutagen. There is no information available on carcinogenicity of DMPS.

This slide summarizes the safety information that we know. Exposure to DMPS is not without risk. There have been cases of serious skin reactions, including the case of Stevens-Johnson

syndrome in an 11-year-old boy and one death due to severe diffuse desquamation in a patient who received DMPS.

The most common reported adverse reactions are dermatologic reactions, nausea and vomiting, hypotension, increases in serum transaminases, transient bronchospasm, fever, and leukopenia. Most reported reactions have been typically mild or moderate in severity.

This slide summarizes the clinical evaluation of effectiveness. There are a number of publications of clinical experience with DMPS in the literature for various uses, including the uses listed here.

Most of the reports are uncontrolled investigations or anecdotal cases and are cases of treatment of various heavy metal exposures.

The literature reports do not include sufficient information to reliably evaluate the effectiveness of DMPS for treating heavy metal poisoning, though as mentioned earlier, the nonclinical studies clearly establish that DMPS can

chelate heavy metals. The reports of use in humans do not allow a conclusion of a clinical benefit of administration of DMPS to people.

Most of the studies described a single or group of persons with exposure to heavy metals who are given DMPS and show an increase in excretion with those metals.

Though symptoms are sometimes described, the symptoms are non-specific such as fatigue, memory loss, headache, and change in those symptoms, if it's documented, is not shown to correlate with degree of metal excretion.

Most series lack controls, and where controls are used, the studies do not adequately establish baseline characteristics, do not control for factors such as effects of supportive care such as the hydration, removal from the source of exposure to heavy metals, for instance. Most of these studies do not include a clearly stated measure of treatment success.

There are no adequate scientific studies that demonstrate the effectiveness of DMPS as used

in drug products for the treatment of heavy metal poisoning or other uses.

There are FDA-approved drug products for treatment of heavy metal poisoning as listed in this slide. These drug products were approved on the basis of safety and efficacy data submitted to the Agency to support adequate labeling for the use of these agents for the treatment of toxicity due to the various heavy metals as indicated.

The drug products include calcium disodium versenate for lead, Chemet or succimer for lead, BAL for arsenic, gold, and mercury poisoning, Cuprimine, a penicillamine for Wilson's disease. It's also approved for cystinuria and active rheumatoid arthritis and trientine approved, a second line in Wilson's disease.

This slides summarizes the historical use of DMPS in compounding. At the 1998 meeting of the Pharmacy Compounding Advisory Committee, it was stated that compound dates to the mid-1980s.

In the literature, we find clinical use of DMPS mentioned as early as 1958. Just internet

searches, just looking at intended uses implied or asserted on those sites, seems to focus on two things: this very large representation of treatment of persons with presumed mercury toxicity due to mercury amalgam dental fillings. And also, there are some mention of treatment of persons with autistic disorders.

In conclusion, our review has found that DMPS is well-defined and can be identified consistently, but manufacture may leave residual impurities including lead, and we do not know the levels of these in compounded products.

Clinical investigation of use of DMPS has not been adequate to establish safety, and there's no clear evidence for clinical benefit of DMPS as currently used.

There are FDA-approved medications available for treating heavy metal poisonings. Historical use dates to the 1950s.

In conclusion, based on the information that we have, we recommend that DMPS not be included on the list of bulk drug substances that can be used

in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act. Thank you.

**Clarifying Questions from the Committee**

DR. VENITZ: Thank you, Dr. Suh.

Let me ask the first questions. The uncontrolled and anecdotal reports that you reviewed -- what was the preferred route of DMPS administration?

DR. SUH: In most of the administrations, the route was oral. We see a lot of oral administration in the mercury amalgam studies, but there also were parenteral administrations.

DR. VENITZ: Were they single-doses or were they repeat doses?

DR. SUH: Some were single-dose, and some were multiple dose. Many of the studies looked at administration of a dose and then urinary excretion of the heavy metal.

Maybe one thing to note is that even in cases where the agent was being given, the DMPS was being given to treat, let's say, mercury poisoning due to dental amalgams, even in studies where some

patients did not even have such amalgams, an increase in excretion was seen. So the efficacy of the treatment really has not been established in any of those controlled studies.

DR. VENITZ: Thank you. Then my second question; in the approved agents right now for lead, arsenic, and mercury poisoning, how were they approved? What clinical evidence did support their role?

DR. SUH: Well, the approvals date, I think -- our earliest approval is BAL, I think, which was approved back in 1945. And then there, I think, in 1953, we had versenate, calcium disodium.

DR. VENITZ: What they did actually look at clinically?

DR. SUH: There are studies that provide sufficient data to support the labeling of the product. And this both has to do with a demonstration of efficacy, as well as a demonstration of safety for the product as marketed.

DR. VENITZ: Was efficacy defined as

increased excretion of the heavy metals or did they look at clinical symptomatic?

DR. SUH: Excretion; excretion is measured.

DR. VENITZ: Okay. Thank you.

Any other questions? Dr. DiGiovanna, did you want to --

DR. DiGIOVANNA: Yes, John DiGiovanna. I'm not familiar with the management of this group of diseases, but are the approved medications useful for all of the heavy metals or is there an unmet need? Are there some toxicities that are not managed by the approved drugs?

DR. SUH: If you look at the literature, you'll certainly find -- now, I'm thinking about U.S. use and U.S. labeling. You find that some products are used for agents for treatment of toxicity of agents that they're not really approved for, if you will.

For instance, BAL is really the only product that is labeled, if you will, for arsenic poisoning. However, penicillamine, if you look at textbooks and reviews, recommendations and things

that are also used, we do find that penicillamine and succimer, for instance, are used for arsenic poisoning, though neither one of those had sufficient data to support labeling for those uses. However, those approved products have some quality assurance in the manufacture.

DR. VENITZ: Dr. Gulur?

DR. GULUR: Of the approved products that are FDA-approved, how many of them can be given intravenously?

DR. SUH: Intravenously, as labeled, if you want to speak to what we have labeled, the BAL is administered. It's an oil-based product, and it's administered by deep intramuscular administration. The others are oral products as labeled.

DR. GULUR: Do you see an indication, especially with, say, arsenic and mercury in a large dose toxicology or poisoning, where intravenous might offer an additional benefit to intramuscular?

DR. SUH: The intravenous administration -- well, let me just say, for BAL,

there is known -- it's an uncomfortable one, uncomfortable treatment that has to be given on a repeated base, so we certainly would welcome alternatives. And of course, alternatives would have their own set of adverse reactions or problems. But would an alternative be welcome? Certainly.

DR. VENITZ: Dr. Brent?

DR. BRENT: I wonder if I could speak to several of these points, and thank you for that nice overview.

You had mentioned that you didn't feel that there was sufficient efficacy data for DMPS and that we had other agents for which efficacy has been demonstrated.

The answer, the truth is that none of the agents, whether you're talking about the approved ones or DMPS, have ever shown efficacy in terms of outcome for metal poisoning.

What they have shown is efficacy in terms of enhancing metal excretion, and DMPS has shown that just as well as the other agents that are currently

approved.

To get to the question that was raised about intravenous, it's true we do not have now a water soluble intravenous chelator available for serious heavy metal poisoning.

This is a really serious deficit. Now, most of the times for metal poisoning, we can get by with oral chelators. We can sometimes give BAL, but BAL, as you mentioned, is very difficult drug to give. It has a high side effect profile.

It cannot be given intravenously. It's a deep, painful injection. It's in peanut oil. People can be allergic to it. And it's a very inadequate agent. We also have very little experience with it. It's been used, but there's very little experience with it.

DMPS is a good intravenous chelator in terms of enhancing metal excretion. So in that sense, it does fulfill a niche that is currently not filled.

Patients who have serious arsenic or mercury poisoning in the acute phase, which is a time when you want to treat them, can have significant amount

of gastroenteritis, and it can be very hard to actually get them to take an oral medication.

There is this niche in terms of an intravenous chelator that DMPS will definitely fill. All that being said, I'm very sympathetic to your observation that so much of the use of DMPS in this country today, as compounded, is for things like treating people with dental amalgams and treating autism, for which there's no evidence of any efficacy. But in terms of serious heavy metal poisoning, it does potentially, as an intravenous preparation, fulfill a very important niche.

DR. SUH: I should say that this nomination came in for all routes of administration and was evaluated as such. And the other point I would make is that in saying that DMPS has not been shown safe and effective, I am not saying that it is not safe and effective.

We do though, I guess, also have to be cognizant that, at least, as in the German monograph cited that being as it's purified from a lead-containing source itself. In the compounding

arena, we have no knowledge of what the levels of those residual impurities from manufacture might be.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: In veterinary medicine, they use an injectable arsenical to treat heartworm disease in dogs. And we are frequently presented with unintentional self-administration by a student or a veterinarian, and they have become intoxicated with arsenic.

In years past, we have researched heavy metal chelators for treatment of those incidents, and we commonly came across a German product, which was available from a company in Houston, Heyltex. And that was listed as the internationally recommended drug of choice for arsenical and mercury poisoning.

Is that product still available? Does that represent an alternative to patients in acute need of heavy metal chelation for mercury or arsenic? And what would be the options there?

DR. VENITZ: Do you want to answer?

DR. SUH: Others may know, but to my knowledge, that European product is still available. And I think when we look at global, worldwide, what might be the preferred drug being marketed in Europe, that very well could be. But I know that if you look in some others, you, again, get -- well, from the U.S. perspective, you get a different first-line, if you will, recommendation.

In terms of availability, we've talked some about getting things under IND, so I don't particularly want to rehash those routes. Being able to obtain that product under an appropriate IND setting for emergent use is possible.

DR. VENITZ: Dr. Brent?

DR. BRENT: Yes, you do bring up a good point, and the product is the European by Heyl as a manufacturer.

With regard to this issue about potential lead contamination, Heyl actually has a certificate of analysis that they provide. And there's not much lead in it. It's about 4 micrograms associated with a 2-gram dose.

So lead poisoning would not really be a significant issue, particularly since you really only need to use this drug for a very short period of time where you'll get people over the acute phase, and then they can be transitioned to an oral agent. So I don't think the lead contamination issue is a significant issue.

DR. VENITZ: Thank you. Any final question for Dr. Suh?

(No response.)

DR. VENITZ: Thank you, Dr. Suh.

Then we have our nominator. Third time is a charm. Dr. Anderson is going to nominate.

**Presentation - Paul Anderson**

DR. ANDERSON: Thank you. So many, many of the points I'm going to make have been discussed, so I'll go through this reasonably quickly.

Under efficacy, I did want to bring up a severe case of mass acute poisoning where DMPS was used and was life-saving. That was in 2003 in Maine, and it was a felonious poisoning of some people at a church. Sixteen people were poisoned

and transported to ER.

Cary Medical Center was the first place that they went where they were exhibiting all of the signs of acute arsenic poisoning. We were able to contact, first, Dr. Karen Simone, who was involved in the triaging and assessment of the drugs to be used. She's currently the president of the American Academy of Clinical Toxicology.

They took the sickest people over to Eastern Maine Medical Center, and they were put on the standard BAL therapy because as was mentioned earlier, BAL is the only one with the on-label arsenic indication.

Knowing, as was mentioned, the painfulness of that approach -- the treatment protocol is Q4 hours for two days, and then you decrease after that in the acute phase.

The worst patients got the BAL right away, and the BAL was failing according to the toxicologist. So the medical resident got a hold of Dr. Simone. She called a group of toxicologists, including Dr. Michael Kosnett, and

they recommended to start DMPS.

Dr. Kosnett also sent us a note -- neither of these doctors could be here to bring this, but they sent notes for me to present, so this is his.

"Thank you for bringing this to my attention." He read the FDA review brief and believes it's incorrect in several instances. And he believes that, in toxicology, there is a clear need for DMPS and would like it to be available.

At the time, in 2003, Dr. Kosnett was aware of a compounding pharmacy in California which was actively producing injectable parenteral DMPS and so they were called after hours and were able to get the product because it was already in production.

It should be of note, when considering emergency use in an acute arsenic poisoning, for instance, that if a compounding pharmacy had to make product from base raw material, it takes a minimum of 16 days to get the material produced into a parenteral form. So that would be outside the window of use for an acute poisoning.

Fifteen out of the 16 were treated with IV DMPS. For reasons that I could not unearth in the investigation, the one patient who was not was the only patient who died out of the acute group.

There were no adverse events reported and the Attorney General is on record as confirming it was arsenic poisoning that was done. Essentially, the person laced the coffee with a large, large amount of arsenic.

We also sought counsel from UCSF and the Vancouver Poison Control Centers, and obviously the caveat that every poisoning is unique in individual. They also recommend the intravenous route over the BAL, Q4 hours, and then decreasing the dose for a couple of reasons.

One is their feeling is that the IV use of DMPS would be a faster and more efficacious way of getting the arsenic out of the body and also, it's also much more tolerated by the patient, pain-wise, et cetera.

As was mentioned earlier, there is a large amount of peanut oil in the injection, and not

everybody can handle that.

The other thing that the poison control were clear on is that the side effect profile are lower with DMPS than BAL.

The other thing, as was mentioned just a few minutes ago, is in many cases, especially in arsenic poisoning where there's a great deal of nausea and vomiting going on, the oral products that are available may not be appropriate for use in the acute stage.

With regard to safety, as was mentioned in the first setting, a lot of the data -- and in fact, all of the data that we could unearth really comes from European sources because that's where the drug began, as the Heyl monograph was mentioned but others as well.

Looking at human safety using the FAERS data system we looked at, there were two cases that came up. Of interest, the first case was a moderate adverse event of a hypotensive crisis when the physician gave the DMPS intravenously too rapidly which later I'll bring up.

This is a drug that I've used in clinical practice a fair amount; that is, one of the administration cautions is there's a definite administration rate that is supposed to be used. The patient recovered.

In the second case, the association of DMPS administration and the patient's death in my, and my most people who have read the case, opinion are not correlative because the patient injected themselves with elemental mercury.

Complicating that as a method of suicide, he received the inappropriate treatment of diphenhydramine and was sent home, which is an unusual treatment for elemental mercury injection.

Then 10 days later, he went to the ED after he had had a DMPS treatment, and he died of mercury deposition throughout the body which would've come from the mercury injection most likely.

These are the citations. Again, all are European, but they look at human use of unithiol and its use as an antidote in a number of instances of poisoning.

This is an American pharmacy that is ISO 9001 compliant, and so their adverse event reporting system is ISO 9001 compliant and follows GMP.

Since 1999, there's been 10,000 plus orders. Patients receiving it are estimated because of the dose size versus the dose administration so quite a large number of DMPS at just this one pharmacy and there are a number of compounding pharmacies that do produce DMPS.

They're approximating doses at around 67,000. The complaints received through their ISO 9001 compliance system to-date have been zero and that was the one pharmacy I could get clear data from.

Now, alternatives were brought up, and the discussion I'm about to give has already been really given so I'll just give it very briefly, but I'd want to put a point on it.

Versenate, the only metal that is not a label indication as far as poisoning with versenate is really arsenic and then mercury. Chemet is an

oral, as you know, substance, and it does not have a label indication for arsenic either. It is also going to be oral and probably not appropriate in acute toxicity.

We talked a lot about BAL. And the major issue with BAL is the volume of inert oil that's being given; that's peanut oil. The pain, the frequency, and in the case, at least in 2003, where they started with that, is both the product they could get and the standard of care, they had to abandon it for non-efficacious use.

Penicillamine and syprine don't have an arsenic indication either. With mercury, there's maybe possibly a little bit of crossover, but arsenic and mercury are really excluded from most of these.

As was brought up, there were the U.S. label indications. But if the experience, at least in that one very bad acute poisoning, was of note, it probably is true that DMPS is preferable in acute arsenic poisoning.

I've done many thousands of parenteral

administrations with DMPS over the last 20 years. We have not had any serious life-threatening or high-grade adverse events during that time.

I discontinued the use of BAL and penicillamine mostly due to oral intolerance with penicillamine and pain, and patient compliance with BAL. Also, occasionally, there's difficulties in sourcing drug.

So again, it's extremely safe when ordered, monitored, and managed by a qualified physician. And as was brought up a little bit earlier, another one of the substances, having it available through 503A would assure that it was only filled through qualified physicians.

The other thing that I think becomes of note is if it is going to be used in an emergency, and the product has to be synthesized from base product, it would not be able to be synthesized in enough time to deal with the emergency. Thank you.

**Clarifying Questions from the Committee**

DR. VENITZ: Thank you, Dr. Anderson.

Any comments or questions? Mr. Mixon?

MR. MIXON: Thank you. First of all, I'd like to just say how fortunate we are to have Dr. Brent here. I just finished looking through your 50-page CV. I'm very impressed; clinical emeritus professor of toxicology.

My question is for Dr. Anderson. I'd like to get a little more clarification on why you think it would take 16 days for a compounding pharmacist to produce this preparation. That's just not true. We can have it done in a matter of hours if we had the pure active ingredient.

DR. ANDERSON: I will defer the answer to that to the pharmacist who will be commenting in the public session.

MR. MIXON: Okay. I just didn't want the --

DR. ANDERSON: Yes.

MR. MIXON: -- the committee to have the wrong impression about that.

DR. ANDERSON: Thank you.

DR. VENITZ: Dr. Carome?

DR. CAROME: In the numbers you gave on your

personal use, Dr. Anderson, you said 5,000 doses or 5,000 patients you used --

DR. ANDERSON: Doses.

DR. CAROME: Doses.

DR. ANDERSON: Doses, yes.

DR. CAROME: What number of patients would that translate into approximately?

DR. ANDERSON: At this point in the day, I don't have the reverse math written down. It is over a 20-year period, though. So it's a series as was mentioned earlier, and so there's some division involved there.

DR. CAROME: With those, are the majority of those -- was that for acute arsenic or mercury poisoning or did you also use it for some of the other indications that we see being used like autism and concerns about amalgam-related mercury?

DR. ANDERSON: I see. Yes. So that's a very excellent question which I should've prefaced with. I've never used DMPS or any other chelator for things like any of those instances.

In the beginning, I was in practice in an

area where there were still arsenical pesticides available and being used, and we had a lot of exposures to deal with. So really, it was that exposure, yes.

DR. CAROME: If you could go to your slide 13, if someone could put it up? So these are numbers from one pharmacy alone?

DR. ANDERSON: Correct.

DR. CAROME: I guess you probably don't know this. Do you think this will be an extraordinary high incidence of arsenic and mercury poisoning to be making this much?

What is the incidence? Do we know the incidence roughly in the U.S. of arsenic and mercury poisoning?

DR. ANDERSON: Yes. Because I'm not connected to and don't have the background data from this pharmacy, I really can't speak to that at the moment. I can only speak to what my practice has been. Yes, sorry.

MS. DAVIDSON: I did research that before this meeting, and the most recent data I could find

was 2010. There were 927 arsenic exposures in the U.S., no statistics on mortality.

DR. VENITZ: Dr. Brent?

DR. BRENT: You were referring to poison center data. Poison center data generally reflects far more exposures, or even possible exposures, or non-exposures than really serious exposures.

I had an opportunity to mine a database that we use, which is called the Toxicology Investigators Consortium -- it's a big consortium with almost all practicing toxicologists across the country -- to see their use of DMPS

The consortium started in 2010. Since 2010, not a single medical toxicologist has found a reason to use DMPS in this country, the reason being that we would reserve it for really high quality acute arsenic or mercury poisoning, which is rare, which is very rare.

As we can see here, there's probably a lot of illegitimate use of it, and I recognize that as a concern. And that is a big concern. I was listening a little while ago when you were

talking in the presentation that was given, I believe, by Dr. Jarow.

I gleaned from that, that while we can advise for routes of administration, we cannot advise approval for indications. But I think even the routes of administration issue is a big one because a lot of it is being given orally and there's no real legitimate oral need for it.

I think one suggestion to get around this problem would be to only allow intravenous use of the medication and probably would be even better, if possible -- and I notice this was the American College of Medical Toxicology's recommendation as well -- to allow it to be used for intravenous in-hospital use. And I think that would cut down a huge amount of the illegitimate use that we see.

DR. VENITZ: Thank you, Dr. Brent.

Any other? Dr. Davidson?

MS. DAVIDSON: I just had one comment on the availability of the alternatives. Being, again, in a veterinary institution, I'm constantly looking for chelators because our patients ingest all kinds

of heavy metals all the time.

Calcium versenate is gone. It is not available. It can be compounded, I believe, because it does have a monograph. BAL is currently available but is frequently on the short supply list. And penicillamine right now is available for $25,000 for a bottle of a hundred tablets.

So it does leave many practitioners with no alternative, except some sort of compounded preparation. In this case, it would be calcium versenate or maybe the DMPS.

DR. VENITZ: Dr. Dohm?

DR. DOHM: I just want to comment that the committee can certainly recommend limitations outside of route of administrations such as hospitalization use. But it's unclear that we would be ever be able to enforce such a limitation or put that limitation on the substance because it's so downstream from the compounder.

So the compounder doesn't need to know necessarily whether or not the drug will be used in a hospital setting or otherwise for purposes of

compounding the drug.

Although that can be a recommendation as to the limitation, it's clear that we would be able to do much about it, just so you know.

Then the other point I'd like to make is that with respect to intravenous formulation alone, it's my understanding -- and please correct me if I'm wrong -- some of these other uses such as for autism is also IV.

DR. VENITZ: Dr. Gulur?

DR. GULUR: This is just a clarification on what you had asked. So if we were to say in-hospital use, that cannot be enforced, but intravenous can be enforced?

DR. DOHM: We can limit the route of administration so we can limit the compounder to IV. But as I said, I believe that the autism use -- and I'm not sure about the dental amalgam -- is also IV.

DR. VENITZ: Any final comments to Dr. Anderson's presentation?

DR. DiGIOVANNA: I have one.

DR. VENITZ: I'm sorry. Go ahead.

DR. DiGIOVANNA: It's my understanding that the discussion we had earlier about different types of INDs is that the single-patient emergency IND that is one that could be enacted within a short period of time, 24 or 48 hours, would be one that would be applicable for a rare event that would occur a few times a year in the U.S. and might be managed in a tertiary care center would be an appropriate way of fulfilling the need for that rare situation.

DR. VENITZ: Mr. Mixon?

MR. MIXON: If we'd limit the drug to that extent, it just simply won't be available, period. I mean IND or not, compassionate use or not, it won't be available. I just want to echo what Gigi said. Remember, we have drug shortages all the time. And when this drug is going to be needed, it's going to be needed now, not three weeks from now, and that's where the compounder can really come to the table and help the patient, if it's available.

DR. VENITZ: Last comment. Dr. Jungman?

MS. JUNGMAN: I actually just want to understand Mr. Mixon's comment. So what would it be that would make it unavailable? In my understanding, you said that, if it's not available sort of for the broad spectrum of uses, then there wouldn't be a case for continuing to keep it available for this kind of acute toxicity use. Or what would be the reason that it would become unavailable if we had to kind of go through that emergency IND step?

MR. MIXON: If the committee votes to add it to the do not compound list, then that's the end of it. If the committee votes for it to be available, whether it's only intravenous or intravenous for use in hospitals, then presumably, our chemical manufacturers will continue to produce it, and stock it, and make it available. So the availability would be there.

Does that answer your, Elizabeth? I'm not sure.

MS. JUNGMAN: I guess. Thank you.

**Open Public Hearing**

DR. VENITZ: Dr. Anderson, I think that concludes your presentation. Thank you very much.

Let's then move on to our final open public hearing. Let me read into the record the OPH statement.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the product and, if known, its direct competitors.

For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging or

other expenses in conjunction with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, that will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them. With that said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when

recognized by the chair. Thank you for your cooperation.

So I'm now asking our last open public hearing speaker to come to the podium or the microphone and present.

MR. McGUFF: All right. Thank you very much. My name is Ronald M. McGuff; call me Ron. I am the owner of McGuff Compounding Pharmacy Services, Incorporated in Santa Ana, California. We've been in business for 17 years. We compound with bulk drug substances. We create sterile and non-sterile drug products.

I have some background information based on some of the questions that have been asked. The Heyl product is available in the United States. It just returned. It is being compounded now by compounders.

I need to go back to the first part, which says I do have a financial relationship with this product, and I paid for my own way to get here.

The FDA has indicated in its brief to you and at this meeting, the FDA has indicated a vote

by this committee against inclusion to the approved bulk drug substance list will not restrict access to DMPS.

FDA indicates a physician or a hospital that needs DMPS will be able to obtain this drug through the expanded-access or intermediate-sized access IND process.

This may not be true. Let me explain. One of the most difficult activities of a compounding pharmacy performs is to locate raw material manufacturers that are willing to sell very small quantities of active pharmaceutical ingredients and comply with the regulatory overhead that is part of compounding pharmacy today.

The economic reward for these manufacturers is very small, and there is the added potential for regulatory review and product liability lawsuits. Please understand, there will be no access to any drug if a raw material or API is not available.

Simply put, if the API is not available to the manufacturer, no drug will be available to use in an IND.

The 15 persons in the Maine poisoning, who were just talked about here, were poisoned and survived. They were very fortunate because we had the DMPS on hand and available when this emergency occurred.

The current system requires the physician to write a prescription for an identified patient to obtain the drug. This works. This system works very well.

Today, under the current system, DMPS API is available. If the FDA does not include DMPS on the approved list, the API is deemed not to be safe and not to be effective for compounding. This obviously is not good news to the DMPS manufacturer. This alone may cause the manufacturer to leave the U.S. market.

A bit about Heyl. Heyl is the only company that we have been able to locate that manufactures DMPS that meets all the requirements for the FDA. We've looked high and low at alternative sources, and we cannot find one, so we are dependent upon one manufacturer for DMPS.

But the FDA tells us to replace the current prescription system with the expanded access or the intermediate-sized IND process. I believe the additional bureaucratic overhead will keep many physicians away, as they are already overloaded with work. This will lead to an even smaller market for DMPS.

The DMPS API manufacturer has to balance the FDA statement of not safe and not effective, smaller purchases in an IND market, higher cost, and greater liability to the economic particulars of staying in the market.

I believe based, on my experience with Heyl and 17 years of working with suppliers, that the sole API manufacturer will want to reduce their liability and simply exit the market.

The reward is not equal to the risk. Again, there will be no access to any drug if the raw material or the API is not available. It makes sense to keep the status quo. It works.

Additionally, there's no guarantee that a manufacturer, physician group, or physician will

apply for an IND of any type, no guarantees to that. If there is no active IND, DMPS will not be available. There will not be a market to sell to, simple as that, so the DMPS in the United States will not be available.

So how long will it take to get DMPS to a physician to treat a patient if another arsenic poisoning exists? Unfortunately, I disagree with Bill here. When you compound a sterile drug, just the act of proving that it's sterile takes 14 days. By the time you understand there's a need for production, and if you can get it in production on day 1, you bring it out, you put in quarantine, you wait for 14 days until you get the sterility test back.

Then on the 16th day, you go ahead and deliver. This does not take into effect or account the time of getting an emergency IND together, the time of getting DMPS from Europe through customs, which is an interesting thing all by itself, to us to compound. This is merely the time it takes to compound a sterile drug, 16 days.

For acute poisoning, 16 days may be too late. Patients will probably die and for no good reason. FDA has not reported a single death directly attributable to DMPS in 47 years of record keeping. The system, as it stands now, works. The status quo works. No harm will be done if you vote to include DMPS to the approved list.

(Pause.)

MR. McGUFF: A vote against inclusion is a vote to potentially remove DMPS API from U.S. soil, significantly increase the time to obtain sterile DMPS in case of another poisoning, take away a readily available tool for physicians to improve patient healthcare, and it adds bureaucratic burden to physicians when none is needed.

In addition, just one other quick comment, the CDC recognizes that arsenic poisoning could be used as a terrorist agent. We've kind of shown that in Maine, that 16 people ingested arsenic poisoning. I believe that would relate today to a terrorist attack.

So thank you for your time.

DR. VENITZ: Thank you. Are there any questions or comments by the committee? Mr. Mixon?

MR. MIXON: I just want to clarify. Thanks, Ron, for letting us know about the sources of this. I just assumed that PCCA and others had it. My comment about we could have it available in hours of course assumes we have the active ingredient on hand, so Ron just added valuable information about that.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. I'm just a little confused what the status quo is. When you get someone acutely intoxicated with arsenic or mercury, are you making IV preparations of DMPS and waiting 14 days for sterility test? Or are you making it and then using it? Are you not using sterile -- so I'm completely confused by the status quo.

MR. McGUFF: No problem. No problem. I understand the question is about is it available currently and how is it available, if it is currently available.

We get enough prescriptions, and this is how it works. We receive a prescription from a physician, and we compound for that prescription. Under 503A, they allow us to anticipate those prescriptions.

It's anticipatory compounding. We do keep a supply of DMPS on hand all the time in anticipation of those prescriptions that we're going to receive. It is on hand, and it is from the Heyl raw material.

DR. CAROME: Just to follow up, how many prescriptions are you filling a week, say, or a month?

MR. McGUFF: The information that you saw was from my pharmacy.

DR. CAROME: So you have an epidemic of arsenic poisoning, or you're using it for other things?

MR. McGUFF: We respond to prescriptions from the physicians.

DR. DiGIOVANNA: That was sort of my question, but can you give me a little bit more

about the demographics? I believe was that 5,000 prescriptions or what geographic area?

MR. McGUFF: The McGuff Compounding Pharmacy -- I'm sorry. The geographic area we ship to -- we have licensing in every state that requires licensing; 49 out of 50 states require licensing. The territories and protectorates, we also are allowed to ship to.

Basically, we're allowed under California law, which is where we're located. We can ship to any US licensed physician within the United States.

Yes. Sorry.

DR. GULUR: He's my boss. So what age group are you dispensing the majority of your prescriptions to?

MR. McGUFF: I beg your pardon?

DR. GULUR: How old are the patients?

MR. McGUFF: I don't recall. Excuse me. I am not involved in the prescription receipt process. We have pharmacists that when we receive prescriptions, if we don't have enough information relating to other drugs that the patient is taking,

allergies and things of that nature, we will call the physician back and ask about that.

Typically, physicians don't indicate what the treatment is actually for. It's just they're looking for this particular drug.

DR. GULUR: Is the age group difficult to determine from the prescription, the age of the patient, perhaps by dose, the dose that you are dispensing?

MR. McGUFF: As a gut feeling, I would say we don't -- we do get birth dates so we have the data. Have we extrapolated that from the data? We have not, but we can certainly do so if you'd like to, if you'd like us to do that.

DR. GULUR: Thank you.

DR. VENITZ: Last question. Dr. Davidson?

MS. DAVIDSON: I'd like to follow up on that just a little bit. The medical toxicologist recommended -- they recognize an appropriate use of DMPS, and they recommended in their letter monitoring of physicians by appropriate state regulatory agencies.

I would like the committee to consider that if we try to change prescribing practices by limiting supply, have we really changed prescribing practices? I would suggest that, not with just this drug but if we're really concerned about inappropriate prescribing, I would mention pain gels as another possible example of that, that we focus on getting the appropriate regulatory agencies to consider appropriate actions for those prescribers and not cut off supplies of drugs to needy patients.

I realize that is entirely out of the purview of this committee and the FDA, but I would suggest that as a place to start instead of cutting off supply for people that really need it.

MR. McGUFF: Thank you.

**Committee Discussion and Vote**

DR. VENITZ: Thank you for your presentation.

That concludes the open public hearing portion of this meeting, and we won't take any further comments from the audience.

Now, we're moving on the committee's discussion and vote. We already had a lively discussion, but I'm opening the floor for any comments, discussion items. Dr. Pham?

DR. PHAM: I just wanted to give a little context also in use in pediatrics and actually ask this of Dr. Brent because I believe BAL does not have any pediatric indication, or information, or sort of dosing data. So I think that only oral options are available.

However, there is oral. There's data on oral dosing of DMPS in children. It's not IV, but with a lot of things with pediatrics, we have to extrapolate. So just any sense of place in therapy for pediatric poisoning?

DR. VENITZ: Dr. Brent?

DR. BRENT: Certainly, we see significant heavy metal poisoning in pediatrics in lead encephalopathy, for example, which is an absolute medical emergency that mandates IV therapy where we don't have IV agents really available. So there is a very important role there, yes, totally agree.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome, again. As you know, I don't get to vote on this one because 1999 Public Citizen opposed including this product on the bulk drug list with concerns that it was being -- the compounding of it was being abused.

I am pretty much convinced that there is a narrow need for this drug for patients with acute severe arsenic or mercury poisoning and that the drug is -- there's data to support its use in that narrow thing.

I remain concerned that there's a tremendous amount of abuse and misuse of this drug when it's compounded. But I think there is a narrow appropriate use, and doctors should have access to it in that case.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: Yes. I think, basically, I was going to say something very similar here that we have to acknowledge that the majority of the use here is not in these acute toxicity situations.

So I'm just kind of thinking through this

supply problem because what I hear us struggling with is, should we encourage a use for which there is very little evidence of effectiveness in order to maintain a level of supply for the very limited use that we -- and I think that's -- I don't really actually know how to resolve that.

How do you convince a manufacturer to continue to maintain supply without allowing kind of broad uses that are not supportable? But I think that is -- certainly, I wanted to kind of at least make it explicit what I think we're kind of talking about.

DR. VENITZ: Dr. Brent?

DR. BRENT: Your point is exactly right. And that's I think what we're all struggling with here.

To me, the best way of dealing with this -- and I realize we can't police this necessarily -- but at least to express the spirit of the way it should be done would be to have it available for in-hospital intravenous use.

Nobody is going to be admitting people to

hospitals to treat their autism with chelating agents or to treat their dental amalgams with chelating agents.

Will people expand outside of that? Well, yes, I suppose they do to some degree at their own risk. But I think that's the best we can do here to try to encourage legitimate use and discourage illegitimate use.

DR. VENITZ: Mr. Mixon?

MR. MIXON: Dr. Brent, when your patient population needs this drug, where is it obtained from, do you know? Is your hospital able to compound it?

DR. BRENT: Medical toxicologists are all aware that when we need it, if we need it, that we go to McGuff because they're the ones that have the pharmaceutical-grade preparation available. They can get it very quickly from them.

DR. VENITZ: Last question. Dr. Jungman?

MS. JUNGMAN: I think I hear your point. I think realistically, if we put this on the 503A bulks list, there's a big market here, and it will

continue.

I think that the idea that we sort of count on folks to say, "Well, this committee thought that, really, it should only be used in hospital use so we're not going to compound it outside of that setting," I think is unrealistic. If it's on the list, it's on the list. It's legal for people to do it.

DR. VENITZ: Very last --

DR. DiGIOVANNA: Sorry. If we were to be able to put it on for only in-hospital use, would that include infusion centers, which are pretty widely available?

DR. VENITZ: Very, very last --

MR. MIXON: I'll make it brief. If we say it's available only for in-hospital use, I will submit that Mr. McGuff will not be able to provide it on a timely basis because he won't have the demand for it to keep it available ahead of time.

I'm not speaking for him. I'm just speculating, but I bet you that'll be the outcome.

DR. VENITZ: Let me proceed with the vote

because we're already behind schedule.

DR. BRENT: I'm sorry. Can we make this vote contingent upon the requirement for in-hospital intravenous use?

DR. VENITZ: I was going to read -- this is your first vote, so the vote is yes, no, or abstain, but then I'm going to go around the table, and you can add any comments like any additional restrictions that you'd like on the record. But the vote is you have three buttons to push basically.

Let me just read the whole preliminaries again since we do have Dr. Brent joining us.

If you vote no, you are recommending FDA not place the bulk drug substance on the 503A bulks list. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes a subject of an applicable USP or NF monograph or a component of an FDA-approved drug.

In order to perform the voting process, please press the button, yes, no, or, abstain,

three times on your microphone. You will have approximately 15 seconds to vote.

After you've made your selection, the light will continue to flash. Let me know if there's any problems. So go ahead and vote.

(Vote taken.)

DR. HONG: For DMPS, we have 7 yeses, 4 nos, and zero abstain.

DR. VENITZ: Now, let's go around the table. And Dr. Brent, let's go ahead and start with you.

DR. BRENT: I believe I've already expressed my beliefs here of what would be the appropriate way of using this drug. There's a lot of illegitimate use in this country. We want to discourage that.

We do want this to be available where it is necessary, and sometimes it is necessary. To me, the best way to attain that would be to have it available as an intravenous preparation for in-hospital use. I realize that could still be misused, but I think that's the best we can do.

DR. VENITZ: So no, you voted to not put it

on the list?

DR. BRENT: I voted not to support the --

DR. VENITZ: So we have the correct the official records. You meant to vote in favor of putting it on the list, which is not what it currently rates. That's all right.

The actual vote is going to be --

DR. BRENT: My actual vote was to be yes.

DR. VENITZ: Right. So it would be 8, 3. It would be 8 yes, 3 no.

Dr. DiGiovanna?

DR. DiGIOVANNA: This is one of the more difficult challenges. And from a philosophical perspective, the fact that a drug can be abused but is also necessary in certain circumstances -- I don't believe it should not be available in life-saving circumstances because other people may choose to abuse it.

However, the difficulty here is that it may not be available if it's needed. And unfortunately, in a world that we are living in, it very well may be needed on a very short-term basis

and a very emotionally-impacting basis. So I think for those individuals who need it, it should be available, and I certainly would limit it to in-hospital intravenous use if that is in any way possible.

DR. GULUR: Padma Gulur. I voted no. I feel very strongly that it's needed as an intravenous preparation having personally had to use it once. It has an extremely important role to play in severe arsenic poisoning, and it's the only intravenous formulation that we have available.

However, I voted no because what I heard here was that the incidence of mercury and arsenic poisoning of that severity is really low. There's very few people who are exposed to that.

It's true we are all under the terror -- we feel the fact that people can take advantage of the situation and poison the country. But in the meantime, we also heard that to go through this route, which is to rely on the compounding pharmacies to provide this, we would have to make sure that they could use it for other purposes so

it was economically viable for them.

It seems to me that the right way to do this is this needs to have another avenue, that if there is a drug that is that needed by this country, the only way to get it is to also make it available for potential abuse.

It does not seem to be the right way to do things and I would hope that there are other avenues that can be followed for these drugs to be legitimately used for the purpose that they are needed for.

As rightly pointed out, intravenous use, hospital would be a great restriction, but if it cannot be assured, then we are putting another larger population at risk by putting it on the list.

DR. VENITZ: Jurgen Venitz. I voted yes. Just two comments to support that. Number one, we had not only testimony today but also background submissions that, I think, very strongly argued in favor of keeping it on the 503A list.

Number two, in response to something, I

think, Dr. Day mentioned, I think implicitly or not or explicitly or not, we do consider alternative treatments, both the availability and the comparative efficacy, if you like.

This is one of those cases where that definitely went into my decision-making. I would also strongly encourage the IV-use only. Everything else, I don't think we can enforce. But I do think we can make sure that it still can be sterilely compounded.

MS. DAVIDSON: I voted yes and quickly just would limit it to IV use in-hospital as has been stated. And I also wanted to make a comment that it wouldn't need to be made in anticipation at risk of losing money.

USP 797 does have a provision for emergency release of product prior to testing results within certain parameters, so it is certainly possible to make this within the hour that Mr. Mixon mentioned.

MR. HUMPHREY: William Humphrey. I voted yes. I believe the toxicologists that there is a clear indication for this drug in acute

life-threatening heavy metal toxicity. And I also would recommend that it be used intravenously in hospitals.

DR. HOAG: Steve Hoag. I voted yes. This was a very difficult decision, but I figured the risk-to-benefit ratio was in favor of keeping it on the list.

MS. JUNGMAN: Elizabeth Jungman. I voted no for many of the same reasons as Dr. Gulur. I am very concerned about the acute toxicity situation that has been discussed quite a bit here, but the vast majority of the use is a use for which I didn't see a lot of support and was just uncomfortable exposing that significant majority of patients, given where the data is on that.

DR. PHAM: Katherine Pham. I voted yes even though every fiber of my being wanted to abstain, but I don't believe in abstaining.

I didn't have time to make this comment in previous discussion, but I did research a little bit further. There had been a nomination for this to go on the essential medicines list in the World

Health Organization back in 2010 and went through a pretty decent independent clinician review that brought it up for nomination there.

They ultimately decided that DMPS would not be included due to insufficient evidence, and I think that was back in 2011. Although that made me feel like I should say no, at the end of the day, it goes back to the criteria that we're all charged with looking at, which is whether or not there are alternative therapies available and there is not in this route. So I kept it very practical, and I said that it should be available only as IV.

DR. VAIDA: Allen Vaida. I voted no for all the reasons that Dr. Gulur has already made.

DR. WALL: Donna Wall. I said yes because of the severity of the poisoning. We really need to have that kind of product. We know it's being misused, but then we keep opioids on the formularies and use them, and they're being misused too.

The key is to having the medical communities step up and make sure that they are working with

folks and that drugs are being used appropriately, and if they're not, to sing out loud.

**Adjournment**

DR. VENITZ: Okay. Thank you. That doesn't just conclude our vote, it also concludes the meeting.

I want to thank everybody for what turned out to be a very lively and productive meeting. I hope you all have a safe trip home, and we'll see each other again in November, I believe.

Thank you.

(Whereupon, at 5:08 p.m., the afternoon session was adjourned.)