performance characteristics are critical and require careful assembly. Temperature control at well-controlled sub-freezing temperatures may be necessary at certain stages of compounding.

At all times during compounding, environmental conditions, such as temperature, humidity, and so on, must be carefully monitored and controlled. Manufacturing parameters, such as the assay of the concentrate, pressure filling, in-line heating, and aging, et cetera, add considerable complexity to the compounding process.

It is important to remember that even the simplest type of DPI requires complex formulation development to ensure accurate and reproducible dose delivery.

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Errors in compounding have a high potential to adversely affect safety and effectiveness.

All of the factors I have mentioned in the previous slide need to be carefully controlled to ensure dosing reproducibility, performance, stability, and bioavailability where the concept of dosing reproducibility applies equally to the dose content uniformity and the particle size distribution.

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The complex formulation and container closure system require extensive manufacturing controls. Stringent

environmental controls are required for air cleanliness, humidity, and temperature.

Temporary exposure to high temperatures or humidity can disrupt the particle size distribution. In some cases, exposure to high temperature has resulted in recalls of commercial products.

Some sophisticated equipment required for assembly include crimpers, pressure fillers, a propellant pump, and precision product filler.

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Special formulation requirements and attributes of the container closure system necessitates specialized technical training for both production and quality assurance. Lack of proper training in manufacturing requirements may affect all aspects of product performance. Inadequate training in quality assurance will prevent detection of compounding errors.

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Examples of complex tests which are necessary to ensure product quality include: particle size distribution, moisture content, leak rate, leachables, and microbial limits.

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The control of particle size distribution is more critical for MDI and DPIs than most other conventional

dosage forms, and not solely determined by the size of the drug substance particles initially suspended in the formulation.

Changes in the particle size may lead to a decrease in efficacy and an increase in systemic exposure. It is critically dependent on formulation, valve, and the mouthpiece, and the inability to meet particle size distribution specifications has resulted in product recalls.

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The control of moisture content is most critical for MDI suspension formulations and for DPIs. Strict limits are needed to prevent changes in, for example, particle size distribution, morphic form, crystal growth, and aggregation.

The leak rate is required control because canister pressure directly influences the performance of the actuator and valve, and thus, the delivery of the proper dose to the patient. Leakage of the propellant may be great enough to influence the composition of the formulation and change the particle size distribution and/or the dose content uniformity.

Failure to meet leak rate specifications have resulted in recalls of commercial drug products.

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Leachables result when the liquid formulation extracts compounds from either elastomeric or plastic

components. Identification and quantitation of potential leachables are necessary.

A concentration profile of leachables in the formulation must be established for each drug product to prevent undisclosed changes in the container closure components.

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The testing of microbial content includes testing for total aerobic count, total yeast and mold count, and assured freedom from pathogens.

Additional testing is necessary to ensure the formulation does not support the growth of microorganisms, and the microbial quality is maintained throughout the expiration dating period.

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Because of the above complex and necessary criteria for compounding, MDI and DPI drug products clearly present demonstrable difficulties in this endeavor.

These difficulties would likely have an adverse effect on the safety and effectiveness of such drug products.

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Difficulties in compounding result from the following characteristics and requirements: MDIs and DPIs are sophisticated drug delivery systems that require

extensive development to ensure dosing accuracy and reproducibility.

Precise dosing must be achieved by accurate and reproducible delivery of both the mass and the particle size distribution of the active. A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility. Product-to-product uniformity is critical for dosing accuracy and is usually difficult to achieve.

Reproducible bioavailability of the compounded drug product is difficult to achieve. Compounding of MDI and DPI products is very complex. Sophisticated facilities and equipment are required to ensure the proper compounding of the drug product.

Specialized technical training is essential to ensure proper compounding, and sophisticated and difficult-to-perform testing is required to ensure potency and purity.

Thank you.

DR. JUHL: Thank you, Dr. Rogers.

Are there questions for Dr. Rogers? Elizabeth.

Committee Discussion

DR. McBURNEY: Dr. Rogers, thank you for that presentation. I would like you to help me understand a little bit better about the delivery system.

To my way of thinking, there are actually two

components here. One is the compounding of the medication that is going to be delivered, and the second is the mechanical device that is going to be used to deliver that compounded medication.

When the pharmacy is carrying it out, the device that is used, those are not assembled by the pharmacist, those are the ones that all pre-packaged and used, are they not?

DR. ROGERS: Basically, pharmacists do not assemble or produce these devices. They don't obtain a formulation and don't create the drug product from pieces. In every case, these drug products are assembled and manufactured, and the formulation created in very secure manufacturing environments that are unavailable to all but very few drug companies.

It is very difficult even for a good drug company to make these devices with good and reproducible particle size distribution and dose content uniformity. So, that the concept of a pharmacist doing this is hard to understand.

DR. McBURNEY: Is there not now -- and I would turn to the pharmacists on our committee -- is there not now compounding pharmacists that are doing this presently?

MR. WELDER: Not that I know of.

DR. McBURNEY: Not at all, even with the dry powder?

MR. WELDER: Not that I know of.

DR. ROGERS: Even the simplest dry powder inhalers would require measurement and controls of the device and what was put in the device beyond that available.

MR. RUSHO: As far as the dry powder inhalers, there is another delivery system -- and I am blanking on the name of it -- for delivering of albuterol where the capsule is partially filled with albuterol and lactose, and you put it in the device and break the capsule, and it falls down on a screen. The patient tips her head back, and they can inhale that.

I have had one request prior to budesonide and fluticasone propionate being available to make one using triamcinolone. The problems that you just mentioned, particle size distribution and everything else, were things that I looked at, and I finally threw up my hands and said this is not possible.

But I think if the agency is considering this, we need to put that type of dosage form in there, because I can see that as being able to be compounded much more easily than the devices you have shown us today.

DR. ROGERS: Well, the device that you are talking about would strictly fall under the category of dry powder inhalers, single dose devices, so it would be covered.

MS. AXELRAD: I would just like to clarify

something that I think addresses Dr. McBurney's question.

The product that we are talking about here are combinations of drugs and devices, and they are regulated as drugs in the Center for Drug Evaluation and Research. New Drug Applications are submitted for these, and I think that there is -- as you saw from Dr. Rogers' presentation, there is an incredibly close interaction between the drug itself and the device in order to make sure that the dose that is delivered is the appropriate dose, and we do regulate them as drugs, so if there is any question about that, you know, that is why we are concerned about this, because we want to make sure that somebody doesn't think, oh, this is a simple thing, we can just take a drug and stick in a pre-packaged device and give it to a patient, and it will deliver the appropriate dose, you know, it is not a problem.

We think that these are so difficult and so complex, and there is such a direct connection to safety and efficacy of the product, that we think that they should be put on the list of Difficult to Compound products even though right now maybe nobody is compounding them, but we want to make sure that even in the future, that they know that we think that this is something that they shouldn't be getting into.

DR. ROGERS: As I mentioned in my talk, poor compounding of these types of drugs not only results in a

lack of efficacy, but increases systemic exposure, and that increases systemic side effects.

DR. JUHL: There were a couple of opinions offered through the nodding of heads, and I want to make that is available for the transcripts. The question was asked are compounding pharmacists doing this now, and both Tony and Loyd had nodding of heads, so I would like you to --

DR. ALLEN: I am not aware of anybody that is doing it at this point in time, but one I guess philosophical thing would be, let's say, five to 10 years from now, if technology develops to the point that it does become feasible, where you do have a manufacturer, let's just say, for example, that has an MDI without an active drug in it, but that manufacturer has gone through and tested half a dozen drugs for stability, uniformity, you know et cetera, and they elect to distribute the MDI without the active ingredient, and the pharmacist then could simply prepare a solution, not a suspension which most of your things were oriented towards, but rather a solution of a drug, sterile filtrate into the pressurized system with newer technology, that the compounding pharmacist could then come back to the committee to open that up if the technology develops that way in the future.

In other words, if we say no today, is that no forever, or is it still open for new technology that may be

coming down the road?

MS. AXELRAD: They can come back and show that there is new technology that is significantly simpler than it is at this particular point in time for somebody to take a drug and put it into a device and make a safe and effective product.

MR. WELDER: I have I guess a need for clarification on your question, Bill. Would you ask again, because you said it included -- I was under the assumption we were talking about MDIs and dry powder inhalers as a multiple dose kind of thing.

MR. RUSHO: Well, what I was requested to compound was a triamcinolone capsule, a partial filled capsule filled with lactose as a vehicle in order to put in the device, so you could put it down there and break it, and the patient could inhale it.

That can be compounded right now. I don't know how much of it is being compounded. But when I looked at that, one of the things that I looked at was particle size distribution, and, number one, I didn't have the sieves in order to tell what particle size I had.

I went ahead and made one up just to look at it, and I looked at it under the microscope, and you could see a wide variation in particle side. Obviously, this was one of those areas where it was too complex for me to do it. I had

to go back to the physician, and I said, you know, we can't do it, I am sorry.

MR. WELDER: And your comment was that procedure would be included in this as Difficult to Compound?

DR. ROGERS: That is an example of a single dose dry powder inhaler, and that would be covered under exemption of dry powder inhalers.

MR. WELDER: So, we would --

MS. AXELRAD: You would not be able to do it under this. We are suggesting that that type of a thing would not be permitted, that it would be placed on the Difficult to Compound list. That is the proposal.

MR. WELDER: I would ask that that would be reconsidered for a single inhalation kind of thing. As Loyd said, you know, the technology is changing, but the particle size would be critical, of course, I realize that, but if you had a prescription for something that was an inhaled powder, and it didn't involve a complicated device and sealing that device, I don't think that should fall in the same category as what we were talking about the metered dose inhalers.

DR. JUHL: I guess the question I am asking is how could we ensure that an accurate dose would be delivered in such a single dose preparation.

MR. WELDER: I am not sure, because I have not

done this, but if you had an exact amount, say, 2 milligrams of a substance, and the whole inhalation was done at one time, you could be assured that it was delivered into the body. Now, particle size is something else, but I think this falls into a different category than what I am taking as the metered dose inhalers and dry powder inhalers. That is all I am saying.

DR. JUHL: And yet the purpose of the dose being inhaled is to get it into the lung. Whether you had 2 milligrams or not doesn't really tell you whether it gets into the lungs. As Bill had pointed out, if you had a micronized particle, then, you would assume that some portion of that 2 milligrams gets to the lung, and if you have just regular powder, most of it would be deposited in the throat.

MR. WELDER: That happens in the manufactured products also.

DR. JUHL: It does indeed, but they do have an estimate in the clinical trials how much gets in and how much is effective.

MR. RUSHO: Just the triamcinolone dry powder, there was a wide variation in particle size, and that was supposed to be a micronized particle. Mixing becomes a problem at that point, too, because you can't mix that in a mortar and pestle. You know, your lactose has to be of a

set particle size, too, and then you have the problem of weighing this out, and you are doing a partial filled capsule, not a full capsule.

You have to weigh each and every one of those capsules out. It becomes -- you know, I have no problem saying it is too complex for a pharmacist to compound.

DR. ROGERS: Under the best of circumstances, with a light microscope, you might be able to estimate a particle size distribution of the powder under the conditions of examination under the microscope, but the conditions of inhalation are different than that, and you are not going to get the same particle size distribution in the aerosol or in the inhaled powder that you will see in a microscope.

You have to ensure that the device correctly creates a particle size distribution in the 1 to 5 micron range, and it is technically impossible. You can't show the reproducible particle size distribution except under the most extreme testing conditions in a laboratory.

DR. JUHL: And a particle size distribution doesn't ensure delivery. It depends upon the air flow and all the other factors that go into that, too.

DR. ROGERS: That is true.

DR. JUHL: You use particle size distribution as a quality assurance.

DR. ROGERS: That is true. We test it under

specific conditions and assumed reproducibility.

DR. JUHL: Garnet.

DR. PECK: What you have just heard is a significant comment about lactose as one component. That is difficult to get in a reduced particle size necessary for inhalation therapy, and manufacturers are working very hard at making appropriate lactose for these particular capsules.

The particle size distribution is paramount to its success because you have to dilute out the drug, and the drug is going to have a distribution. Micronization does not guarantee a narrow particle size distribution, and you may have to go through cutting to give you the appropriate particle size for an inhalation product of this nature as a capsule.

This is a Fison [?] technique for putting the capsule in an appropriate unit that pinches the unit and you inhale it. You have to consider also that the patient is the one that is bringing in the material. It is not a pressurized device. So, if you do not have appropriate particle size distribution of both the diluent and the active, you may have problems with dosing for that particular patient because you are relying on a patient who is ill or affected by something, and they are the ones that are the driving force.

So, you have to have a very ideal dosage form.

When you get into pressurized systems, and about aerosols, aerosol products, the container is an integral part of the drug delivery system, and too many people forget this. It is not like a capsule or a tablet goes into a bottle. We are delivering the whole thing, the package and the product for therapy.

So there are many integral parts and what was reviewed here was excellent in terms of the components of the valve assembly. Various different materials of construction are used in there, and so one has to be careful about all these parts.

There was noted particular polymers and also rubber is within that system, and other things. So, it is extremely complex, the containment of what we are trying to deliver. But these little units -- and I can see a possible need for delivering a few capsules -- but the components and their size are crucial.

DR. ROGERS: Another crucial factor is the interaction of all the components with each other, the liquid phase, solid phase, container closure components, they all interact and there is a large potential for problems in those interactions that can affect the dosing and particle size.

DR. JUHL: How does one achieve, would achieve sterility or how do they do it commercially in the

spinhealer [?] kind of thing, the contents of the capsule? Obviously, Bill, in your example, you would have need to have some assurance of --

MR. RUSHO: In my example, there would not have been sterility.

DR. JUHL: I know, but I wondered how it is done commercially and is it possible.

DR. PECK: You can sterilize dry powders with a number of different techniques to fill appropriately, but it would have to be sterile.

DR. JUHL: Are capsules considered sterile?

DR. PECK: Well, no, that is a fallacy, but I think there is a little fuzziness here in terms of that capsule.

DR. JUHL: Other questions or comments on this topic?

MS. LaFOLLETTE: I would just like to make the comment, with all the information that we have heard, which was wonderful to hear, this is a single dose or multi-dose inhalers. These are products that really require in-process testing, qualitative or quality assurance protocols, I just don't see cuts it here. I mean there are too many things that can go wrong with, you know, I mean the valve delivery, the calibration of that. I mean these are things beyond the scope of compounding pharmacy.

DR. ROGERS: Even batch-to-batch variation in valves is a serious problem.

DR. JUHL: I see a hand being raised in the audience, and although we don't usually allow comment from the audience, if it is on this particular topic, I would be happy to entertain a brief comment.

If you would identify yourself.

DR. ADAMS: My name is Wallace Adams, and I am with the Food and Drug Administration, CDER.

I would like to comment on the issue of the MDIs and the DPIs just briefly. The Center has spent a lot of effort in concerning itself with determination of bioequivalence of metered dose inhalers and dry powder inhalers, and the recommendations which we have involve both in vitro and in vivo testing.

We have seen a lot of aspects, as Brian Rogers has talked about this morning, about the critical nature of the formulation, the materials that go into the product, and in addition to that, there are in vitro tests.

From a bioequivalence standpoint, we do not believe that in vitro testing only is adequate to assure these equivalence of two products, and that is to say the particle size distribution can be the same, the lactose particle size distribution can be the same, but as was mentioned, these products are combinations of formulation

and device, and it is critical that not only the formulation be well controlled, but there is the formulation-device interaction.

So, in the case of a solution formulation MDI, not only must the concentration of the drug in the solution, and the concentration of the various inactive ingredients be controlled, but the characteristics of the metering device are critical, and many firms make these metering valves, and they would greatly impact the performance of the product.

They would the particle size distribution, and this has direct relevance to the bioavailability. I thought it was interesting to hear questions or comment about taking a Ventalin rotocap product or rotohaler product and filling a different capsule other than Ventalin capsule intended for the purpose, and using that same device.

My suspicion would be that the bioavailability could be drastically altered by using a formulation compounded in the pharmacy, and used in that product. Even if you knew what the particle size distribution is, I am not sure that you would know what the particle size distribution of the drug in the innovator product is, and even knowing that, it is not the particle size distribution determined by microscopy that is critical so much as aerodynamic particle size distribution determine by the cascade impactor. This is not equipment which is available in the pharmacy.

This does require, as Brian had indicated, sophisticated equipment in a well-controlled laboratory.

So, there are many aspects to these products, these combinations of device and formulation which are critical to the performance of the product, and I think that we have to be aware, as the discussion has been going this morning, that these are very complex devices and that in vitro data alone is not adequate to assure bioequivalence of the products, but rather we only know that through in vivo testing, comparative testing.

Thank you.

DR. JUHL: Thank you.

Are there other comments or questions on the topic?

MR. TRISSEL: I will be brief. As I understand this, it does not include pump sprays nor nebulizers or any of those kind of other inhalation devices, am I correct?

DR. ROGERS: That is true, as being considered at this point.

DR. JUHL: I see the International Academy of Compounding Pharmacists is represented. Are there comments that you have on this topic?

Would you come to the microphone, please, and identify yourself.

MS. CAPPS: Thank you, Mr. Chairman. My name is

Shelley Capps. I am with the International Academy of Compounding Pharmacists. We have requested, and will present tomorrow. We do have comments concerning all of these. We are concerned about the definition, that it is so broad that it would include some significant compounded medications, however, there is no compounding being done currently of the product that has been described here this morning.

DR. JUHL: Thank you.

MS. CAPPS: Thank you.

DR. JUHL: I assume then that we are ready for the question, referring to your handout again.

Question No. 2. Do you agree that the class of metered dose inhalers, as described, should be included on the list of drug products that may not be compounded because they are difficult to compound properly?

Those that agree, would you please signify by raising your hand?

[Show of hands.]

DR. JUHL: No opposed.

That is unanimous. The committee agrees with that recommendation.

No. 3. Do you agree that the class of dry powdered inhalers, as described, should be included on the list of drug products that may not be compounded because

they are difficult to compound properly?

All those that agree with that recommendation, please raise your hands.

[Show of hands.]

DR. JUHL: That, too, is unanimous.

We will reconvene at ten minutes after 1:00.

[Whereupon, at 11:50 a.m., the proceedings were recessed, to be resumed at 1:10 p.m.]

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

[1:30 p.m.]

DR. JUHL: Let us resume.

Next on our agenda is the open public hearing. I apologize to our speakers, we are half an hour behind schedule. We won't penalize any of the speakers for out tardiness, but we will assume the full amount of time as necessary for the open public hearing.

We have four speakers who have asked for time and we will see if all are here.

First is Jana Nestlerode who is representing herself to discuss DMPS, if you would like to step to the podium. She has asked for 13 minutes worth of time.

Open Public Hearing

MS. NESTLERODE: I have handed out a packet of my information including my remarks today. I don't normally read my remarks, but with 13 minutes I think I had better.

Thank you for the opportunity to address this committee today. I have waited a long time to do this.

My name is Jane Nestlerode. I am a Professor of Criminal Justice at West Chester University in West Chester, Pennsylvania. Before I retired to teaching, I worked in federal and county governments. I know that in that capacity, you are generally overworked and underpaid.

As a government employee, I know the role of

entertaining viewpoints and inputs from other people and that you do so with patience and indulgence, but today I hope you don't feel that you have to indulge me. I hope that you will hear me.

I was also an Assistant District Attorney in the Delaware County District Attorney's Office for many years, and I prosecuted a lot of violent individuals. I knew that every time I spoke to the jury, what I said mattered. By my performance, a murdered could go free, to kill again, or he could be locked up where he couldn't hurt anyone. I was acutely aware of my responsibilities in that role.

But those responsibilities pale in comparison to the purpose for which I am here today. This may very well be the most important thing that I do in my entire life. Dimercapto propane sulfonate (DMPS) is devastating the lives of too many patients, and this committee has the power to stop it. I consider this matter urgent. Today, I traveled here to ask you to withdraw your recommendation of this drug for inclusion on the List of Bulk Drug Substances That May Be Compounded by Pharmacists. I made the trip here because it matters.

I am a DMPS survivor. A single injection of DMPS almost took my life. I went to a doctor recommended by my dentist for treatment of mild and asymptomatic hypothyroidism. This doctor ordered a complete blood workup

and determined that I had healthy liver, kidney, and immune functions.

Because I had dental amalgams, he wanted to test my urine for mercury. He told me that he would first have to inject me with a harmless substance which would make the mercury show up. I allowed him to inject me, and within minutes of the injection, I became acutely ill. I spent the next 13 months trying to recover.

I suffered from debilitating physical, cognitive, and psychological symptoms, consistent with metal poisoning. My symptoms included nausea to the point where I had to carry a basin and a towel in my car. I had gnawing stomach pains, throbbing headaches, joint pain, blurred vision, sometimes uncontrollable and embarrassing diarrhea, numbness of the extremities, chest pains, labored breathing, extreme fatigue, the kind of fatigue that made walking to the mailbox an enormous effort.

In addition, I suffered an inability to concentrate, short term memory loss to the point where I couldn't remember where I worked. One morning I struggled to find some clue as to where I worked, so that I knew where to go.

I experienced severe depression where I would sob for hours and sometimes days, and I had suicidal ideations. There were two occasions when I sat with a loaded gun to my

head debating whether to pull the trigger.

I also suffered frightening psychotic episodes. At one point my real doctor considered institutionalization.

Prior to this injection I had robust health. I worked out rigorously several times each week and held down a full time job. I was one of those annoying people who woke up happy and energetic every day. I had no history of depression or mental illness.

But after the injection of DMPS, I longed for death. Sleep was my only respite, but the pain would keep me awake. I listened to audio tapes to take my mind off the pain that I could drift off to sleep, but as soon as I woke up, the tears would start because I was back in the hell that my life had become.

I was horrified when I later learned that the substance that had been injected into me was an unapproved metal chelator (DMPS), with very serious adverse effects. It never occurred to me that any doctor would use an unapproved drug on me.

I was not told it was unapproved, nor was I informed of possible adverse effects. The Commonwealth of Pennsylvania has since instituted disciplinary action against this doctor for improper use of injectable drugs, including DMPS. A copy of a recent Philadelphia newspaper article about this is attached. I am also instituting my

own legal action.

Neither the doctor who injected me, or the several legitimate doctors from whom I subsequently sought help, knew how to help me. If fact, none of the other doctors had ever heard of this drug. The occupational health physician with the University of Pennsylvania had to do research to learn about it, and still had no idea how to treat me. For months I lived in despair, not knowing if I would ever recover. In the end, it was a chemist who saved my life.

Heyltex, a subsidiary of Heyl in Germany, is the primary manufacturer of DMPS in this country. In its scientific monograph, Heyltex cautions: "DMPS should be administered parenterally only if oral administration is not possible."

Yet, with the inclusion of DMPS on the list, most complementary/alternative medicine practitioners are using this drug by infusion and injection.

I actually support certain aspects of alternative medicine. But as with any group of professionals, there are good and bad influences. I believe that those advocating DMPS are setting back the alternative health care movement by decades, and giving a bad name to competent and compassionate practitioners in the field. The issue of whether amalgams cause chronic mercury poisoning is quite irrelevant to this matter. This is about detoxification if

and when such poisoning does occur.

At a prior meeting of this committee, someone said that it was doubtful that doctors would be pulling patients in off the street to test them for mercury. Well, they are not yanking them in by the collar yet, but it is close.

You see, mercury is considered a "root" in the alternative practitioners' lexicon, it causes anything and everything. Patients are being injected with DMPS for such diverse medical conditions as headaches, sinus infections, eczema, depression, hypothyroidism, Lyme's disease, and even carpal tunnel syndrome.

In what has become a very lucrative and callous cottage industry, these practitioners are convincing even well patients that they are poisoned by their dental amalgams, and must undergo amalgam replacement and DMPS detoxification programs.

When patients are injured by these programs, they are often abandoned because these physicians simply don't know what to do. It is not just quackery; it is the practice of experimental medicine on unsuspecting and uninformed patients on a growing scale, and patients are paying not only large sums of money for essentially worthless medical care, but they are sometimes suffering debilitating adverse effects.

I believe that this practice violates the spirit,

if not the letter, of the Act which requires a prescription for an identified patient. My sense is that the Act was designed to give physicians certain latitude in treating unique patients, not adopting a protocol for every patient in the practice.

As I learned more, I was alarmed at the number of patients who health had been adversely affected by DMPS. Like me, none of them had been told that DMPS was an experimental drug, none had been asked to sign informed consent forms, and none were warned of possible side effects. They had been blindsided, just like I had.

Because I felt I had to do something to warn patients of the dangers no one was talking about, I recently started a web site. It is www.dmpsbackfire.com. I first learned all I could about this drug by speaking with researchers, toxicologists, and biochemists. Those individuals have no financial interest in this drug and were appalled at its use for the treatment of chronic metal poisoning.

At the site, I not only inform patients of what I learn about the dangers of DMPS, but I also offer to post patient reports of adverse effects. A summary is attached which includes in from about two dozen patients who received this drug in oral or parenteral form.

When I first started learning about this drug, I

was so naive. I thought all doctors, researchers, and pharmacists told the truth. I thought we were all on the same page and shared the same goal of patient health. I am no longer as naive.

You are probably all aware that alternative medical practitioners view the FDA with, if not disdain, then fear. I have read that fewer than 1 percent of all adverse reactions to medications are reported to this agency. Alternative medical practitioners are probably the least likely to do so. The last thing they want is FDA scrutiny.

And so I have found what I call a conspiracy of silence regarding the adverse effects of this particular drug. Indeed, the president of a large compounding pharmacy wrote to me at the web site and said, "Shame on you for suggesting your readers use Medwatch."

He went on to tell me to, "get my facts straight," that DMPS is now approved by the FDA and that the DMPS challenge test is "backed by our federal government."

A researcher told me that she had never never heard of an adverse reaction to DMPS. I believed her until I communicated with one of her patients. He suffered severe adverse effects from her infusions of DMPS and had been very vocal to her in his complaints. He left her clinic and never returned, and no one from the clinic ever asked why.

I attended a conference at which a doctor claimed to never have heard of an adverse reaction to DMPS. It was becoming a tiresome refrain. Later, I was given a copy of a letter this same physician had written on behalf of a patient who had become disabled from a single injection of DMPS.

In that letter, he actually coined the term "backfire" with regard to this drug. A vice president of a prominent midwestern laboratory told me off the record that I would never find an expert to testify about the dangers of DMPS in my potential malpractice lawsuit because those in the alternative health field would never testify against a colleague. It is indeed a conspiracy of silence.

It is clear to me that the motive behind the advocacy of DMPS is not patient health. It is profits. It is estimated that 180 million Americans have amalgam fillings. With mercury as a possible cause of just about any minor or major medical condition, the potential market is huge. One doctor confided to me that he had increased his profits by 300 percent in one year by DMPS therapy to his repertoire. Another physician stated that he has increased his yearly income into seven digits thanks to the new DMPS protocols.

The protocols do tell the tale. The typical one involves intravenous administration of DMPS to just about

any patient who walks in the door. Indeed, the doctor who injected me refused to treat a patient because he declined a DMPS challenge test.

Because DMPS oxidizes quickly, it is a free radical generator, so doctors require patients to return in a few days for intravenous vitamin C. Because DMPS will also deplete essential minerals, the patient must return a third time for intravenous mineral replacement.

This trio of IV's is repeated for weeks, months, sometimes years. For each of these individual intravenous treatments, patients are charged from $100 to $300. I have patients telling me that they have spent tens of thousands of dollars for these protocols, and only one has ever told me that he thought his health had benefitted from it. The physician profits are simply enormous.

It is quite interesting that the protocol for use of DMPS is by infusion or injection. I have heard that the preparation of the powder for parenteral use is quite tricky. It must be done under nitrogen and the ampule must be topped with nitrogen.

To avoid contamination, the DMPS cannot come into contact with metal during processing, and the ampule cannot have a metal cap. I am sure a scientist could explain to me how a metal needle is then used to inject this drug.

Besides the summary of patient reports, I have

attached a June 27th, 2000 report from a Canadian toxicologist, Dr. Albert Nantel. This report documents the adverse effects of DMPS that he witnessed from its oral administration to 33 patients being treated for acute arsenic poisoning.

Dr. Nantel observed eight patients suffering from erythema multiforme, four of whom required hospitalization. Two were released after several days of intravenous cortisone, but as of the date of the report, two were still hospitalized with Stevens-Johnson syndrome.

One patient suffered bullous lesions of the upper extremities, and the other suffered severe ulcerations of all mucous membranes. For the adverse effects from DMPS, ten patients, or 30 percent, required medical intervention, and four, 12 percent, required hospitalization.

I have also been told that at least two cases of Stevens-Johnson syndrome from the administration of DMPS were reported in London, England in the late 1980's. It is my hope that the FDA will investigate this allegation as part of its review of this drug.

Because they were not accessible from the FDA web site, I have included with my information three letters sent in opposition to the inclusion of DMPS on the list. Two are mine, the other is from Dr. Steven Marcus, a toxicologist, who is the Executive Director of the New Jersey Poison

Information and Education System. Dr. Marcus refers to the inclusion of DMPS on this list as a "terrible injustice" to the consumers and the patients of this country."

I have come to know that this drug is very dangerous. Its availability to qualified toxicologists in cases of acute poisoning by means of an investigative New Drug Application is appropriate. Its inclusion on the list is not. I say this not only because I believe DMPS to be an unusually dangerous drug, but because chemists and toxicologists have told me that DMSA, dimercaptosuccinic acid, a drug already approved by the FDA, is comparably effective and much safer.

DMPS is simply not necessary in an effective program of detoxification for properly diagnosed chronic metal poisoning and it carries substantial risks of adverse effects. But, of course, there is a problem with DMSA. It is used in oral form, and there is not much profit for the physician.

This Tuesday night, night before last, I was asked to telephone a young woman I will call Jennifer. She was suffering from what I now refer to as a DMPS backfire. We spoke for four and a half hours, and her story was heartwrenching. It all began two years ago.

She was in excellent health, but had been having migraine headaches after being in a car accident. To treat

the migraines, her physician began injecting her head, neck, and face with a combination of DMPS and procaine.

Within a few weeks of treatment she was unable to defecate or urinate and became extremely bloated. She said her digestive tract just shut down. Her liver and kidney tests revealed substantial impairment. She began having heart palpitations and her headaches intensified.

Within a short time her hair and skin turned gray. The ringing in her ears is so severe that she can no longer hear the rain and she can't hear her beloved bird sing. She is so disabled and fatigued that she is essentially housebound. After reading the results of her lab tests, her new doctor doesn't know how she has survived. Indeed, she refers to herself as "the walking dead."

This committee is in a powerful position to affect patients' lives. The facility with which DMPS was placed on this list was frightening to me. I believe that this committee has been misled as to the "safety" of DMPS, and in light of this information, I ask you, no, I don't ask you, I beg you, to withdraw your recommendation of this very dangerous drug.

Thank you and I am willing to answer any questions here or later.

DR. JUHL: Thank you for coming to talk to us.

Are there questions or comments from the

committee?

MS. NESTLERODE: Thank you for hearing me.

DR. JUHL: I am sorry. Go ahead, Sarah.

DR. SELLERS: It was just a general question, not necessarily for you. But is this something that the FDA can look into?

MS. AXELRAD: Yes. We have the comment letters on the rule, and we will certainly take your remarks into account when we decide whether to put it on the list.

MS. NESTLERODE: Thank you very much.

DR. JUHL: Refresh my memory, but I think the basis for our discussion about this drug was as an antidote for real mercury poisoning, wasn't it?

MS. AXELRAD: Right.

DR. JUHL: That was our consideration. That was the only information that we had at that time?

MS. AXELRAD: Right, and I believe it is used in Europe for actual metal poisoning there.

MS. NESTLERODE: Yes. Heyl is the primary manufacturer out of Berlin, and they say that parenteral use should be used only in acute poisoning cases. It is being used widespread by psychiatrists, by doctors, by dentists now for everything because mercury poisoning causes everything.

MS. AXELRAD: One thing we can do is review the

literature to see whether the literature, in fact, limits its use to oral use or suggests safety issues associated with parenteral use, because one of the things that we did for some of the other drugs on the bulks list was limit it to a particular type of use where we felt there were safety concerns with other kinds of administration.

DR. JUHL: I do see a letter in here, although the top of it is cut off, but I think it is from the New Jersey Poison and Information system, Dr. Steven Marcus. In his letter, he suggests that the drug is available by emergency IND, and I think you had mentioned that, as well, which would be apparently an alternative route for availability for those cases that truly need it, so there may be an alternative way that we can accommodate both its legitimate need and be able to diminish its illegitimate need.

MS. NESTLERODE: I would agree with that. I agree with Dr. Marcus that in acute poisoning, the IND method is appropriate and necessary.

What has happened now with its inclusion on the bulk drug list is that its proponents are telling everyone that it is an approved drug. It has become used more widespread. I am getting more reports at my web site. I am fearful of the increase in the human carnage that is coming with this.

Thank you.

DR. JUHL: Thank you.

If we then could have an update of your findings at our next meeting or an interim if you have something sooner than that, we would appreciate that.

Other questions or comments on this topic by the members of the committee?

MR. RUSHO: The director of our Poison Control Center has forwarded the E-mails on this topic, and there is a lot of traffic on this. The Poison Control Centers, I can tell you are very upset about the approval of the drug on the list.

MS. AXELRAD: Dr. Juhl, can I ask the committee, do they have any feelings or information with regard to whether it is safe if used orally as opposed to parenterally, whether there is some legitimate use for this with an oral capsule or a tablet as opposed to parenteral?

DR. JUHL: I don't know that anyone on the committee is prepared with additional information.

MR. TRISSEL: Maybe you could refresh my memory. The committee looked at whatever was presented to it in the way of toxicity information originally, and I have absolutely no recollection of that at this time of what was presented, but it must not have been a striking number of cases, and it sounds like there are more out there than had been identified.

Will the agency be following up, can they get case reports for some of these people?

MS. AXELRAD: We can certainly look at our databases to see if we have any adverse event reports in the system concerning this product.

DR. JUHL: It sounds like the poison center database would be another place to search.

MS. AXELRAD: We can look at that.

DR. SASICH: May I make a comment to what Jane just said?

DR. JUHL: Dr. Sasich, would you identify yourself?

DR. SASICH: Oh, excuse me. Larry Sasich, pharmacist with Citizen's Health Research Group.

I checked the FDA's database for DMPS reports, and there are none in the current database.

MR. TRISSEL: Then, you will have to go outside the database to find that.

MS. AXELRAD: We will look at the Poison Control database.

DR. SASICH: Janet just raised an important point. If it is not approved drug in the United States and it gets reported to the FDA associated with an adverse drug event, where does it go?

MS. AXELRAD: I think we might have some reports

in the system of even of unapproved drugs, yes, we would get something like that possibly.

DR. JUHL: Other comments or questions?

[No response.]

DR. JUHL: Our second speaker is Larry Sasich, who was just at the podium. I would like to ask you to return. Larry Sasich has asked for eight minutes worth of time.

DR. SASICH: Good afternoon. As the FDA I am sure is aware, and perhaps the Advisory Committee members are also aware, that Public Citizen has long been opposed to the pharmacy compounding provisions of the Food and Drug Administration Modernization Act.

These anti-scientific provisions of the law permit compounding pharmacists to conduct an "end run" around the FDA's drug approval process. They have opened the door for unethical pharmacists to abuse a professional privilege granted to them by the public and to perpetrate the quackery that now goes on, for all practical purposes, unrestrained, as we have just seen.

Given the few options available to this committee and the FDA within the pharmacy compounding provisions of FDAMA, we do support the science-based approach taken by the agency in its concept paper on developing a list of drugs that cannot be compounded by pharmacists.

Clearly, Congress was concerned about the safety

and effectiveness of drug products compounded by pharmacists when it said in FDAMA that the FDA has the responsibility to identify and place on a list of drugs that cannot be compounded any product that, "presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that product."

The FDA's approach in developing the list has been to include certain categories of drugs that are sophisticated final finished dosage forms and whose production is technologically complex or requires highly specialized facilities and trained personnel. This is scientifically sound, it's intuitive, and within the common and legal definition of a drug.

Science-based regulation has evolved over the past century with the purpose of preventing avoidable harm to patients. History and science have taught us that waiting for a tragedy to materialize before taking regulatory action needlessly harms patients. Primary prevention, in the form of enforceable regulations, has always been the best approach to protecting the public from avoidable drug-induced injury and death.

Any suggestion that the safety of pharmacy-compounded products is proven because there have been few reports of serious adverse events is clearly

absurd. The FDA's postmarketing adverse event reporting system does not and cannot identify all instances of harm to patients from prescription drugs, let alone those from compounded ones, and this system does not have the sensitivity to detect a negative impact on patient survival from the drugs that patients receive.

Compounding pharmacists are well aware that they are under no regulatory requirement to report adverse events that are associated with the use of their products. Their financial self-interest makes it even more likely that they will not report these adverse events.

Public Citizen agrees that transdermal delivery systems, metered dose and dry powder inhaler products must be placed on the list of drugs that are demonstrably difficult to compound.

We also agree that it should not only be appropriate, but mandatory, to include all sterile products that are not compounded in accordance with Chapter 1206 of the United States Pharmacopeia, on the list, with one exception.

We do not agree that the procedures described in Chapter 1206 for compounding sterile products from non-sterile bulk drug substances, even if these procedures could be enforced, would ensure the safety or effectiveness of these products. We believe that it is essential that all

sterile drug products that are compounded from non-sterile bulk drug substances be on the list.

We have particular concerns about the preparation of sterile products. Our objection is due in part to a study cited in the FDA's concept paper that evaluated the sterility and concentration of 100 samples of 1 percent pilocarpine eye drops. Of the 100 samples, 66 were prepared by local pharmacies and 34 were prepared by FDA-regulated manufacturers.

Of the 66 solutions prepared by local pharmacies, 52 or 79 percent were contaminated with bacteria or fungi or both, whereas only one of 34 or 3 percent of samples prepared by regulated manufacturers were contaminated. This result is chilling and it will be repeated more often as a result of the irresponsible action of Congress in passing the pharmacy compounding provisions of FDAMA.

Chapter 1206 of the USP provides two examples of high-risk sterile products intended for IV injection that can be produced from non-sterile bulk drug substances, morphine and total parenteral nutrition solutions. Because these products are readily available in a variety of formulations, we can conceive of no medical reason why they should be compounded from non-sterile bulk drug substances.

Morphine injection is available from numerous FDA-regulated manufacturers in a large number of varying

concentrations including preservative-free morphine injection.

TPN solutions, including dextrose solutions, vitamins, and trace elements that may be needed to meet the individual requirements of a patient are available as sterile products for injection from a number of FDA-regulated manufacturers.

Public Citizen is unable to conceive of a legitimate medical scenario in which the benefits to a patient from compounding an injectable product from a non-sterile bulk drug substance would outweigh the risks. This is particularly true if the compounded product is intended to be used in a setting other than an organized, professionally staffed health care facility.

In addition to the products just mentioned, we urge the FDA to include in the list of drug products that present demonstrable difficulties in compounding the following categories of drugs: all sustained or time-release dosage forms, re-flavored antibiotics that according to their FDA-approved labeling require reconstitution by a pharmacist at the time of dispensing, and enteric-coated products. All products intended fro sublingual use should also be considered for listing.

An article appearing in the September-October 1998 issue of the International Journal of Pharmaceutical

Compounding, a trade publication of the International Academy of Compounding Pharmacists, concerning the compounding of TPN solutions from non-sterile bulk substances plainly reveals that the motive for compounding these solutions is not the health and welfare of patients. It is instead, in substantial part, financial.

I would like to read this brief paragraph.

In an effort to eliminate the threat of product shortfalls and remain competitive with home infusion companies that were divisions of amino acid solutions manufacturers, HHCA, which is a home health care company, refined and developed this compounding method. The company determined that compounding TPN solutions using bulk drug substances would be the first step towards full vertical integration and decreased costs.

That concludes my comments, and I thank you very much for your attention.

I just have on observation about your earlier discussions today. There is an old word that when I was a real pharmacist that we used to use when we took FDA-approved sterile products and manipulated them in an aseptic manner and under environmentally "conditions," and we called this admixing, not compounding.

I think it might be easier in your discussions if you make the distinction between sterile products that are

FDA-approved and manipulated properly and bulk drug substances that are prepared from non-sterile, excuse me, sterile products that are prepared from non-sterile bulk drug substances. Only as a suggestion. It was very difficult for me to follow the conversation this morning. It seems you were jumping back and forth between two different types of products, FDA-approved products and non-approved FDA products.

I would be happy to answer any questions.

DR. JUHL: Thank you very much.

Questions or comments?

[No response.]

DR. JUHL: I think we will take up those topics tomorrow, but I would appreciate it, when we get to that tomorrow, if anyone on the committee could response to his challenge of a legitimate medical scenario where there is a need for bulk drug substances used in TPN or in preparation of a preservative-free or otherwise morphine.

We had reserved some time for Susan Guzzo, but I don't believe she is here. I think we may have miscommunicated with each other on which day she was going to appear, and we will provide time tomorrow.

Shelley Capps of the International Academy of Compounding Pharmacists has asked for a couple of minutes.

MS. CAPPS: I really just have a question and

appreciate the opportunity to pose it.

Will the committee reconsider some of the decisions that it has made once it hears all of the public comments, because we are not scheduled to speak until tomorrow, and many of the things that we are talking about have been addressed today, so it would seem essentially, our comments would not be important to the recommendations that are being made by the committee unless we are given an opportunity to speak, and then I guess recommendations could be reconsidered.

DR. JUHL: That is why I wanted to make sure that you had the opportunity to speak on the earlier discussions that we had. Is there other information on metered dose inhalers?

MS. CAPPS: Our fundamental concern is actually the law, the language in the law. It specifically says that a drug product should be considered demonstrably difficult and does not talk about complete categories of drug products.

So, looking at broad-sweeping categories, this morning I felt like it was very specific, you got down to the canisters, and that is probably okay, but as we move into these other broad categories, there is great concern and I don't -- that is not what Congress intended. It says four times in that demonstrably difficult clause that a drug

product should be considered, and FDA's own definition of a drug product is a finished dosage form, for example, tablet, capsule, solution, et cetera, that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient, but is intended to be used as a placebo.

So, that clearly defined a drug product, and that is the term that is used in legislation. So, that is our fundamental concern with the approach that this committee is taking, and if you find that valuable, then, maybe some of the recommendations that you have made would need to be reconsidered.

DR. JUHL: I appreciate that. I think that is a valid question to be asked, however, it is a question of law and interpretation, not one of scientific or professional practice, which is what I view this committee's prerogative to be.

Obviously, if the attorneys determine that your interpretation is better than their interpretation, then, that would require the committee to reconsider their decisions on these things, too, but at this point, I think my choice is not to engage the committee in a discussion of law. We are not prepared for that. Technically speaking, we are a scientific advisory committee.

MS. CAPPS: Okay.

DR. JUHL: But that is not to say you can't make your case on the topic tomorrow either.

MS. CAPPS: Oh, we certainly will, yes.

DR. JUHL: Okay.

MS. CAPPS: Also, I would love to claim for the International Academy of Compounding Pharmacists the International Journal of Pharmaceutical Compounding, but it is not our trade journal. So, I just wanted to make that clarification.

Thank you.

DR. JUHL: Thank you for the clarification.

Comments or suggestions on the Academy's comments?

[No response.]

DR. JUHL: Is there anyone else in the audience who would like to avail themselves of the opportunity to make a presentation to the committee?

[No response.]

DR. JUHL: Seeing none, we will move forward with the next topic on our agenda.

We will continue with our Demonstrably Difficult to Compound discussion. The next topic is Transdermal Delivery Systems. Dr. Vinod Shah and Dr. Amit Mitra, both of CDER.

Welcome.

Demonstrably Difficult to Compound (Continued)

Transdermal Delivery Systems

DR. SHAH: Thank you, Chairman, and I want to thank the committee for giving us this opportunity to discuss the difficulties of compounding especially the transdermal drug delivery system.

[Slide.]

What I will be talking today is primarily the system which is coming out as a patch, and I will not be discussing the areas of other types of skin delivery system, drug delivery system called the iontophoretic drug delivery. So, that is not going to be discussed today, it is only discussing the transdermal drug delivery system, so I just want to make that differentiation between the two types of products which are available for skin drug delivery.

[Slide.]

The transdermal drug delivery system is a self-contained discrete dosage form. It delivers the drug through intact skin at a controlled rate into the system circulation. Also, it delivers the drug at the controlled rate through the skin where the skin or the membrane are the controlling drug delivery factors.

[Slide.]

The transdermal system is a sophisticated complex delivery system difficult to formulate. It requires

specialized manufacturing process and the equipment.

It is formulated to meet specific biopharmaceutical and functional characteristics. The materials of construction, how to make a transdermal system, the configuration and the combination of the drug with the proper cosolvents, excipient, penetration enhancers, and membranes are carefully selected and matched to optimize adhesive properties and drug delivery requirements in the transdermal drug delivery system.

The system is also formulated to deliver the drug at an optimized rate into the systemic circulation, so that it should adhere to the skin surface for the expected duration of time. For example, in some cases, it may be for a day or in some cases it may be a week, seven days. So, the transdermal system should stick to the skin for the expected length of time, and should not cause any skin irritation or sensitization reactions when it is being used.

[Slide.]

There are four different major types of the transdermal drug delivery systems. One is called the liquid reservoir patch where the drug is in solution or suspension, and it is kept between the backing layer and the rate controlling membrane.

The other type of the system is called the drug in adhesive patch where the drug is dispersed in adhesive, and

it is in direct contact with the skin where it delivers the drug.

The other system is called the polymer matrix patch where the drug is kept in solution or suspension, and it is dispersed within a polymer.

The last type is a polymer laminate matrix patch where the drug is dispersed in adhesive in multi-layers separated by the membranes.

The following slide just shows you an example of the different type of the membranes and the compositions as to how these patches are being prepared.

[Slide.]

It is important to keep in mind that we need these types of sophisticated membranes and the drug dispersions for the appropriate drug delivery into the skin.

[Slide.]

Now, we have considered seven different factors to see whether the drug product could be manufactured or not. So, the factors considered to show that the products are demonstrably difficult to compound are the drug delivery system itself, the drug formulation and consistency, the bioavailability of the dosage form, and also the complexity of compounding, facilities and the equipment needed to manufacture such patches, the training needed to make such patches, and the testing and the quality assurance aspects.

These are the seven factors that we have considered in evaluating the transdermal dosage form. The first three factors, the drug delivery system, formulation and consistency, and the bioavailability will be discussed by me. After that, Dr. Amit Mitra will come on the podium and will discuss the other three factors, which is the complexity of compounding, facilities and equipment, training, and then I will come back and give you my concluding slides.

[Slide.]

Now, the drug delivery system, as indicated before, each transdermal system is optimized to deliver the drug at the desired rate into the systemic circulation. The components are selected based on the physicochemical and pharmacological properties of the drug to optimize the drug penetration rate.

The variability in the component mixture or manufacturing process may not ensure adequate biopharmaceutics quality of the product.

Appropriate quality control measures and the stability of the formulations are essential to ensure dosing accuracy and reproducibility. It is important to make sure that each product, each dosage from one after the other will have the same type of properties, and it will deliver the drug at the same rate.

[Slide.]

The drug formulation and the consistency. The proper formulation is essential again to provide the consistency and the reproducible drug delivery. Components of the formulation, which includes the vehicle, the penetration enhancers or surfactant and adhesives must be adequately tested and studies for compatibility. You cannot just take a few components, try to mix it, it may be incompatible. So, those things need to be studied before it is being used.

These components affect the release rate of the drug and adherence of the device to the skin, which is the essential for efficacy of the drug product.

[Slide.]

The other factors are the vehicle selection is very important. A vehicle that optimally delivers one drug substance may not be appropriate for delivery of a different drug substance.

Vehicles can grossly affect the drug bioavailability and influence the clinical outcome of the drug.

[Slide.]

Drug formulations and consistency. The adhesive selected should provide good skin contact over the total area of application for entire duration to ensure adequate

drug delivery.

Interactions with all the components including skin irritation and sensitization need to be evaluated to ensure dosing accuracy and reproducibility.

[Slide.]

From the biopharmaceutics point of view, it is important to ensure that the product effectiveness, the rate and extent of drug delivery, the pharmacokinetic reproducibility, and the optimization of application site with the formulations are really evaluated before the transdermal drug delivery system is being introduced. These are the factors which are being studied extensively before a formulation is being approved.

[Slide.]

The bioavailability aspects. Appropriate biopharmaceutical properties of the transdermal drug delivery system is most vital to deliver the drug at optimized rate for therapeutic effectiveness of the drug product.

Lower rates of delivery may result in ineffective drug concentrations, and higher rates of drug delivery may result in toxic and adverse reactions.

The optimized formulation with adequate adhesive properties at the site of application are important to assure reproducible bioavailability and drug effectiveness.

These transdermal delivery systems are generally replacing the orderly administered drugs at different time intervals. Once a transdermal system is applied, it is being kept maybe in some cases up to five to seven days, or three days, and the drug concentrations are maintained. They are maintained at the constant level profile, and that is really essential to have the product efficacy.

If the rate infiltrate is varied or changed, those levels will be varied, and the patient may not have a constant therapeutic effect, and therefore, the proper rate input is essential for the product quality and effectiveness to assure that.

I think at this stage, Dr. Amit Mitra will be coming, and he will be talking about the three other factors before I come back to the last conclusions of the quality.

DR. MITRA: Thank you, Vinod.

[Slide.]

As Dr. Shah mentioned, there are several types of transdermal products. There are three major types that we have seen in both my industrial career, as well as in the FDA - drug in adhesive, drug in reservoir with a membrane, and drug in matrix with adhesive overlay.

The third one, it dropped off because of the size disadvantage, and now these two categories, that is what we see.

[Slide.]

Of the component and composition, of course, there is an active moiety, and the active moiety, it could be a new molecular entity or a compendial item, and since a lot of these transdermal products, they are not new molecular entities, these are relating to the different type of dosage form. Therefore, these are compendial.

These are pressure sensitive adhesive, solvent, penetration enhancer, backing, and release liner. On top of that, the drug in reservoir formulation would have a membrane, and I will go into the functionality of each one of those and why those are important.

The third show would show you the schematic of these. There are five components in the drug in reservoir. Going from the back, there is a backing here, and then there is drug in the reservoir form with penetration enhancer and solvent, and then there is a rate controlling membrane on top of that, and, of course, the adhesive has to be there, so that the product can be sticking to the skin. There is a peel-up release liner for this type of product.

For the drug in adhesive, it is simpler. There are three components. There is the backing portion, there is drug into solution, adhesive formulation, and then there is a peel-up release liner.

[Slide.]

As I mentioned earlier, the functional components are adhesive, penetration enhancer, backing, release liner, and membrane. I will go into each of them in detail, what they are composed of, and why they are difficult to control.

The adhesives are made out of either silicon or acrylate or rubber-based polymers. These adhesives would have to maintain a skin contact for long period of time, either one to seven days as Vinod mentioned.

The penetration enhancer and the backing, the penetration enhancer has to be compatible with the adhesive, as well as the active component will have to be compatible with it.

The companies employ technical staff to determine the suitability of the pressure sensitive adhesives and the penetration enhancers. It is a very costly process, and the penetration enhancer itself is responsible for the penetration enhancement.

What we have seen, there are penetration enhancers like ethanol, which is fairly pure, but there are penetration enhancers which are like surfactants, which is a combination of various different components.

For characterization of this type of ingredients, high performance liquid chromatography is necessary to maintain the consistency in the product performance.

The backing is a functional component. The

surface of the backing has to be characterized and carefully evaluated. The corona treatment is a process where an electrostatic charge is placed on the backing to make it adhere to the adhesive.

With proper characterization and quality control, the performance of the product would not be achieved. The release liner has, even though it looks simple, but it has a functional property to release easily, so that the patient can take it off and apply the patch quickly.

For the drug in reservoir type systems, the membrane permeability is very important, whereas, the porosity and the gurley properties of the membrane, in a sense determine the permeability of the membrane is important. Without that, the drug would not be delivered at the proper rate.

Ultimately, the pouch is a configuration which is used for storing these transdermal products, and especially important for the products components like ethanol. These components, as I mentioned before, like penetration enhancers, those enhancers, the penetration rate through the skin, and if it is not stored properly in a safe manner, the ethanol is going to evaporate off and we wouldn't get the efficacy we need.

[Slide.]

The facilities and the equipment. The facilities

involve the installation of the following equipments, like mixer, dryer, coater-laminator, Slitter, die cutting, and the pouching equipment.

For mixer, usually, the high shear mixer is used for proper uniformity of the active and the penetration enhancer in the system. The coater and laminator can be purchased from outside vendor, however, there is a drying step involved, which needs installation of an explosion-proof oven, because of the fact that there are volatile components involved, and which could be explosive in nature.

Because of the problem associated with installation of both vacuum processor as well as the dryers, it is difficult to install in a non-industrial setting.

For proper ventilation of the solvent, we need the ventilation of solvents like hexane, toluene, heptane, ethyl acetate, which are fairly toxic, and also the pressure sensitive areas has a small concentration of monomers and which are fairly toxic, and those have to be ventilated.

It is essential that the facilities used have adequate space to install the equipment and that individuals with sufficient engineering knowledge and the training be utilized.

[Slide.]

The hazard involved, for storage of adhesives and

solvents, special solvent cabinets for explosion-proof solvents are necessary, and as I said earlier, these are part of the formulation which are operated up. Since flammable solvents are driven off during the preparation of the laminate, installation of the explosion-proof oven is necessary. Moreover, ventilation of the solvents and monomers are of utmost importance for safety reasons. In certain areas, the workers need to be put on respirators to avoid exposure to solvents.

[Slide.]

As far as the quality control of the finished product, these are the attributes that are tested - content of the drug, active drug, which is 90 to 110 percent as a limit, and assay of the penetration enhancer, and high performance liquid chromatography is used for determining the content of the drug of penetration enhancer.

The content uniformity, the criteria should meet USP 905. For release rate, several USP apparatus, recommended apparatus, App 5, 6, and 7, so installation of this equipment and proper training of the staff to run this equipment is necessary, along with an HPLC apparatus, and the staff to run this equipment is necessary.

For residual solvents and residual monomers, since they are toxic, irritating, or sensitizing, GC is recommended for monitoring those.

The microbiology, it's a non-sterile product. We ask for total aerobic and mold count, and also absence from objectionable microorganisms.

Finally, there is a pouch integrity test, as I mentioned earlier. The pouch is where the transdermal drug is stored, and if a volatile component is there, you have got to make sure that the pouch is sealed in a way that the solvent doesn't evaporate off.

With that, I will have Dr. Shah make the preliminary conclusion for FDA.

DR. SHAH: Well, we just heard the importance of testing and the quality assurance from product to product, from one patch to the next patch, and that is very essential to assure that the product effectiveness would be maintained when it is being applied.

[Slide.]

With these seven factors now then already considered, our preliminary findings suggest the following: difficulties in compounding results from the following characteristics and requirements.

The transdermal drug delivery systems are sophisticated and complex. It requires extensive experience to develop a product that can ensure dosing accuracy and reproducibility.

Sophisticated equipment and facilities are needed

to ensure proper compounding of the transdermal drug delivery systems.

Sophisticated technical training is essential to ensure the proper compounding of the TDS products, and also again sophisticated, difficult to perform testing of the compounded product is required to ensure product-to-product uniformity from one batch to the other batch, potency, purity, and quality of the drug product prior to the dispensing of the product.

[Slide.]

The preliminary conclusions are we have tentatively determined that the transdermal drug delivery system drug products present demonstrable difficulties in compounding, and these difficulties would likely have an adverse effect on the safety and effectiveness of such drug products.

Those are our preliminary conclusions, and we will be happy to answer any questions that the committee may have.

DR. JUHL: Thank you, Dr. Shah and Dr. Mitra.

We will open it up to discussion amongst committee members.

Committee Discussion

DR. ALLEN: Very nice presentations. I don't have any problems with that. I don't think anybody is actually

compounding transdermal patches anyway, but I would have one request, and that is, in the definition, at some point, where we read that it is self-contained discrete dosage forms, et cetera, could we also include the terminology commonly called patches, so that we would differentiate patches from other transdermal types of dosage forms.

DR. JUHL: Such as a transdermal cream?

DR. ALLEN: Ointments, creams. At least this way we know exactly what we are referring to.

DR. JUHL: It is my understanding that was the area that you carved out to include.

DR. ANDERSON: Yes. I think we worded it, saying we are only talking about these four types, that is listed in the paper.

DR. JUHL: And it doesn't include creams, it doesn't include topicals that are on an adhesive, used for direct application or direct action.

DR. ANDERSON: Right, it is the only the four types that we had put in the paper. Dr. Shah had mentioned it in the beginning.

DR. JUHL: If you would add that clarification, then, we would be clear.

DR. ANDERSON: Sure.

DR. SHAH: May I make a comment on that? Generally, the transdermal drug delivery system is defined

as one in which it is applied to the skin, the drug is delivered through the skin, and it goes into the systemic circulation for any activity.

Now, only the nitroglycerine cream and ointment are the only ones where it does not fall into that category that it is a patch, because in that case also, it goes to the skin, and it is being used for the systemic activity, so that is an exclusion, and that is why we had the cream on that solvent, I showed you the different types of the systems.

DR. JUHL: So that I am real clear in what is included in the area of the types of the products that you are recommending not be available for compounding, they are patches only?

DR. SHAH: Yes.

DR. JUHL: And they don't include creams and ointments.

MR. TRISSEL: With that in mind, the second category there includes cotton pads, and I am not sure that is what you are talking about. That would be band-aids and cotton plagets, and whatever.

DR. SHAH: Band-aids are different. I am not talking about the band-aids. I am talking about the therapeutic drugs where it is prepared, manufactured in the form of a patch, transdermal delivery, and then it is being

administered.

MR. TRISSEL: Then, perhaps the terminology cotton pad needs to be deleted from that.

MS. AXELRAD: Could you say for the record where that is in the concept paper?

MR. TRISSEL: It is on page 20, about the second paragraph, second item.

DR. ALLEN: It is actually in the third paragraph under B, Transdermal Systems. The paragraph starts, "The four major types," and then you have got number 1, number 2, and it's the matrix type.

DR. ANDERSON: The four major types?

DR. ALLEN: Yes. It says, "matrix, which consists of a solution or suspension."

DR. ANDERSON: Why don't we just take the word "cotton pad" out of the definition.

MS. RIFFEE: I think there is further clarification at the last paragraph on that page, where it specifically says this does not include things like --

DR. ANDERSON: Right.

DR. JUHL: Other comments? Does anyone on the committee have knowledge of pharmacists that are making patches? Does the Academy have knowledge of pharmacists that are extemporaneously preparing patches?

Let the record show that heads were shaking in the

no direction.

Are you ready for the question or is there other discussion?

Question No. 4. Do you agree that the class of transdermal drug systems, as defined in the concept paper, should be included on the list of drug products that may not be compounded because they are difficult to compound properly?

MR. TRISSEL: Can we amend that to say "commonly called patches" or something, so that we are clear on what we are enacting here?

DR. JUHL: We can do that.

Do you agree that the class of transdermal drug systems, as defined in the concept paper, and commonly called patches, should be included on the list?

Are you ready for the question?

All those who agree with that recommendation, please signify by raising your hands.

[Show of hands.]

DR. JUHL: It is unanimous. Thank you very much.

We are now an hour ahead of time. Is the individual who is scheduled to present the overview for the committee for tomorrow here, and could we get that out of the way now?

MS. AXELRAD: He isn't here, but we could probably

see if we could get him here, if you could give mr perhaps five minutes, and let me see if I can contact him.

DR. JUHL: We can take a 15-minute break and decide our strategy at that point.

[Recess.]

DR. JUHL: We will begin. We appreciate the flexibility of both the FDA staff and the committee members for allowing us to alter our agenda slightly.

We were scheduled tomorrow to have a presentation to the committee on sterile drug products by Dr. Peter Cooney, and we have located him, and he has graciously agreed to give the presentation now, so that will help us get a headstart tomorrow morning.

Please rest assured that the open public session for 8:30 tomorrow will go off as scheduled. We will not change that part of our agenda, so that does mean we will be here overnight for committee members.

So, let us proceed. Dr. Cooney.

Sterile Drug Products

DR. COONEY: Thank you. Apparently, my voice mail didn't work, and I did get contacted, and I am here.

[Slide.]

The topic, of course, for discussion in this time slot, as just stated, is the inclusion of sterile drug products as a class on the list of products that are

demonstrably difficult to compound if they are prepared on procedures other than those described in Chapter 1206 of the United States Pharmacopeia.

Now, the comments that I want to make are from the perspective of the preparation of drugs as that process applies to sterilization, sterility assurance, and microbiological safety of drug products.

The FDA and sterile drug product manufacturers are well aware of the difficulty in production of these drugs, the pitfalls that can be encountered, and the consequences to the public health if the processes used to make such drugs are not well controlled.

Sterility of parenteral, ophthalmic, and aqueous inhalation solution drug products is a fundamental and essential quality attribute of these products, and as such, is a critical aspect of the safety assessment of these products.

Sterility assurance cannot be tested into a product, nor any tests sensitive enough to detect unacceptable sterility assurance levels in these products. The preparation of sterile products is an exacting, difficult, and highly controlled series or processes especially in the case of aseptically filled products.

Critical scientific assessment of the experimental methods in process controls, tests, and other aspects of

this processing is essential to ensure adequate safety of these products and to protect the public health.

Determination of the efficacy of a given sterilization process for a specific drug product entails a series of protocols and scientific experiments designed to demonstrate that the sterilization process and associated control procedures can reproducibly deliver a sterile product.

The data derived from the experiments and control procedures allow certain conclusions to be drawn about the probability of non-sterile product units, sterility assurance level.

The scientific validity of the protocols and methods, the scientific validity of the results, and the conclusions drawn from those results constitutes a validation of the efficacy of the sterilization process.

Product testing in concert with total control of the manipulations, processes, equipment, environment, and highly trained personnel are required to ensure that the produced product is sterile.

When preparing sterile products, there is essentially only two ways to do it. Products can be terminally sterilized, that is, sterilized in their final containers with no further manipulations which could result in contamination.

Examples of terminal sterilization processes are autoclaving, radiation, or ethylene oxide. For drug products, use of autoclaves is by far the most common method.

The other method of preparation, that is, the other method than terminal sterilization, is by aseptic processing. Aseptic processing involves the use of components which are independently sterilized and then assembled together aseptically.

The difference is significant in that there is no manipulation of product components after sterilization for terminally sterilized products, whereas, there is such manipulation for aseptically produced products.

[Slide.]

Now, so far, all I have talked about concerns sterility aspects of sterile products. This is, from our point of view, particularly important because of the potential for even a single microorganism in a product to proliferate.

Hence, the risk associated with these types of operations is linked to the potential for introduction of microorganisms into the product through manipulation during compounding, and whether the organisms introduced can proliferate in the product, and under what conditions of storage, that is, time and temperature, that the product is

stored after compounding.

[Slide.]

Now, USP Chapter 1206 utilizes the concept of relatively low risk and relatively high risk compounding operations for production of sterile finished drug products. Essentially, relatively low or high risk is defined by the potential for introduction of microbial contamination.

Relatively low risk operations are those in which commercially available, presterilized drug products and components are used. In addition, the production or compounding process involves only a few simple and basic aseptic manipulations in which "closed system" transfers are used.

What is meant here I think is a transfer where there is a minimum exposure of the contents of a container to the outside environment. As an example, the penetration of elastomeric closures with a needle or cannula.

Note that the whole idea here with relatively low risk products is that the chances of inadvertent contamination are relatively low.

[Slide.]

Relatively high risk operations are simply those that offer higher risk of contamination. A relatively higher risk of contamination could occur because intermediate closed systems or open systems are used in the

compounding operation.

Why is that? Because the system containing sterile product had a greater exposure to the environment.

A high risk operation could be one where complex or numerous aseptic operations are carried out over longer periods of time. Here again, because the greater the number of the more complex or the longer the operation is, the greater the chances for inadvertent contamination.

Finally, a relatively high risk operation could be one where non-sterile drugs substances or components are used to compound sterile products. Here, additional risk is added because the non-sterile components have to be sterilized in-house using a validated sterilization process, a step not involved in the compounding when presterilized commercially available materials are used.

Now, further concern, of course, is the presence of contaminants other than viable microorganisms. Such contaminants, which may be introduced to or contained in or on the materials used to make the product, may include products of microbial origin, such as exotoxins or endotoxins, or non-viable particulates, or chemical contaminants.

It is important to realize here that filtration of the liquid portion of such products through bacterial retentive filters will not remove molecular contaminants.

So, for example, use of filtration to prepare a sterile parenteral solution from a non-sterile endotoxin contaminated powder will not remove the endotoxin component.

It is also important to be aware that bacterial retentive filters, also referred to as sterilizing grade filters, are not as they are purported to be, absolute. That is, they do not always render a liquid product sterile since they will not retain viruses, and they may not retain all bacteria, especially those of diminutive size.

[Slide.]

I mention all of this just to emphasize three points. First, sterility must be built into a product through the preparation process and its associated controls.

Secondly, the preparation processes and associated controls are unavoidably complex even for the most sophisticated commercial manufacturers of sterile products.

Lastly, any lapse in controls and processes used to manufacture or compound sterile products can result in significant public health hazards.

[Slide.]

Now, I would like to turn for a minute and discuss the evaluation factors that were discussed earlier this morning in determining the potential effect of compounding on the quality, purity, potency of a product as those factors may relate to the safety and effectiveness of the

product.

Four of the factors we have determined in a preliminary sense show a potential to demonstrate adverse effects of the safety and effectiveness. Those factors are complexity of compounding, facilities and equipment, training, and testing and quality assurance programs.

[Slide.]

Complexity of compounding. The manipulations, processes, and controls necessary to successfully compound a sterile product make the procedure unavoidably complex. As previously stated, the relative risk of a compounding or manufacturing operation for a sterile product is linked to the risk for inadvertent contamination.

Each step of the process provides an opportunity for inadvertent contamination. Since contamination by even a single microorganism may lead to proliferation with time, significant public health consequences may be the result. Importantly, the contamination event would be totally undetected at the time it occurs, and hence, extreme care must be taken during processing of sterile products.

In addition to the possibilities of a single microorganism contaminating the product, other contaminants, such as endotoxins, particulates, and foreign chemical components must be excluded from certain types of sterile products.

Contaminants, whether viable microorganisms or others, can originate from any or all of the sources during the preparation of a sterile product. They may come from the drug substance itself, the water, the containers, the closures, the equipment, the environment, or maybe, most importantly of all, the personnel.

Exclusion of contaminants then is a complex and difficult process, so that the manipulations and processes must be tightly controlled. This factor, namely, complexity of compounding, would support we think the inclusion of these products as a demonstrably difficult to compound.

[Slide.]

Facilities and equipment. The highly controlled environment and procedures used require exacting standards and often require sophisticated facilities and equipment. Since contamination may come from any and all sources during preparation of sterile products, the facilities and equipment used in such preparation must also be tightly controlled.

Even if all the components used in the preparation are of the highest quality possible, contamination can result from the environment, facilities and equipment, in which the sterile drug is prepared.

Environmentally controlled work spaces suitable for aseptic processing are necessary, such as laminar air

flow work benches or rooms with concomitant design considerations for surrounding areas.

The facilities and equipment are specialized in design for the purpose of preparation of sterile products. In other words, they are designed to protect the product from contamination.

A tentative conclusion regarding this factor would be that it also supports a difficult to compound classification for sterile products.

[Slide.]

Training. Pharmacy compounding of sterile products is likely highly personnel intense, and therefore, pharmacy personnel involving compounding sterile products must, of course, have sufficient knowledge, training, and experience to perform the tasks correctly and safely.

Personnel must adhere to uniform and strict performance standards and have a fairly sophisticated level of knowledge and training in aseptic technique. Training in aseptic technique alone, however, would likely be insufficient. Cleaning, sanitizing, and organization of the laminar air flow workstation and rooms requires properly trained operators who should follow written procedures.

Special training may also be necessary for gowning and operation of critical equipment or specialized aseptic procedures, and any other operation necessary for the

preparation of the sterile product.

[Slide.]

Testing and quality assurance factor. There is a significant potential for harm to patients if sterile products are compounded without proper quality assurance programs in place. Quality assurance can be accomplished when training, testing, facilities, and equipment are properly used and monitored.

Quality assurance programs help to assure that the program for preparation of sterile products, as a whole, is under a state of control. Testing, for example, a testing program to monitor the microbiological and particulate quality of the environment is part of the quality assurance program.

For purposes of monitoring microbiological quality of the environment, non-volumetric methods, such as settling plates are used, and volumetric methods, such as rooter centrifugal air samplers can be used.

Monitoring and control of personnel, procedures, facilities, bioburden, equipment, and training programs all serve to help maintain a state of control in the preparation of sterile products.

Therefore, this aspect would also support a demonstrably difficult to compound decision.

[Slide.]

Preliminary conclusions indicate that these factors, drug delivery system, drug formulation and consistency, and bioavailability, probably are not as important as the four factors that I just discussed.

Sterile products do not usually require sophisticated drug delivery systems. They are also not particularly difficult to formulate in a consistent manner since many of them are aqueous solutions, and bioavailability of these drugs is not a major factor in most cases since most are either injected or delivered directly to the site of action.

[Slide.]

So, a tentative conclusion is that these drug products should be classified as difficult to compound. We recognize that compounding sterile products is unavoidably complex and that if such products are compounded incorrectly there could be significant hazard to patients receiving such medications.

We also recognize that there is a substantial need for compounded sterile drug products especially in the area of extemporaneous compounding.

If compounding of such products occurs without adherence to certain standards, the potential for adverse effects on the safety and effectiveness of these drugs is increased. FDA has tentatively now concluded that USP

Chapter 1206 describes such standards and that products compounded using these standards would not pose demonstrable difficulties regarding safety of the drugs compound.

[Slide.]

We are therefore today asking for advice on at least three specific questions related to this area.

The first is: Should sterile products not compounded in accordance with USP 1206 be on the list of drugs that are difficult to compound?

Secondly, is USP Chapter 1206 an appropriate standard?

Thirdly, should compliance with USP Chapter 1206 be required for compounding the relatively low-risk sterile products from sterile components?

Thank you.

DR. JUHL: Thank you, Dr. Cooney.

Do we have questions for Dr. Cooney about his presentation?

Committee Discussion

DR. JUHL: If I might, let me start out. This has to do with the suitability of the USP Chapter as opposed to, say, something else, and in general, I would like to compliment the agency for the good sense approach that you have taken in referring to an already acknowledged standard to refer to. I like doing that rather than having to hammer

that out here, and you probably like it even better than I do. I appreciate that.

There are two categories in the USP Chapter and three in ASHP. Is there a utility in the three versus the two disregarding where they came from in your review of the various standards?

DR. COONEY: My personal view?

DR. JUHL: Yes.

DR. COONEY: I believe the individuals who are involved in the compounding operation itself really are the best people suited to determine what kind of a low risk or high risk type category the operation is in.

So, the bottom line is you need more care with high risk operations than with low risk operations just because there is a higher chance of contamination. So, that is kind of a subjective judgment that occurs at the time the operation is going on.

I really don't have an opinion on whether the three categories are better than two or vice versa.

DR. JUHL: The purpose, at least as I see it, in promulgating these guidelines to have the effect of regulation is to prevent what happened in Pittsburgh with the pharmacist, who with all good intents, formulated an ophthalmic preparation that resulted in the loss of sight of some individuals, but at the same time, not to close down

every hospital pharmacy in the country.

Do you have an idea where Chapter 1206 fits on that spectrum, how many hospital pharmacy operations are able to comply with it in its entirety, and I guess a more general question, is that chapter written as a minimal standard guideline or is it written as an ultimate gold standard, things we should all reach for kind of guideline?

DR. COONEY: The chapter itself, of course, claims not to be prescriptive. The reason the FDA tentatively concluded that Chapter 1206 is a reasonable standard is that we believe that if you followed the standard, the products you would make would not be demonstrably difficult to compound, and the risk of their being contaminated would be minimized.

We would really like input here today, and one of the points of this, is to determine the practicality of complying with that standard, and that is why we asked is it an appropriate standard.

There may be parts of that, that are difficult to comply with, there may be parts that are not. It is certain, though, to respond to part of your question, it is certainly a goal to which to aspire. Whether one could actually meet every single statement in it, I don't know. Perhaps the USP could comment better on that.

DR. JUHL: I will ask them that question tomorrow.

Joe Valentino was here, and he is not here now. Oh, Frank is here.

Could I ask you to come to the microphone, please, and identify yourself for the record.

MR. BARLETTA: My name is Frank Barletta. I am on the scientific staff of the USP. I am the liaison to the Water and Parenteral Subcommittee. I have worked for the last 10 years on this chapter.

I can give you the whole history, the whole shooting match, but I think basically we will wait until tomorrow and see what develops. But I can give you USP's official statement, which I will read.

"In the May-June 2000 issue of the Pharmacopeial Forum, USP published a proposal to revise General Chapter 1206 regarding sterile preparations to expand its scope, to include products for institutional as well as home use.

"The revised chapter has not yet been made final. This USP chapter was developed as an informational chapter designed to provide guidelines as to what the USP believes pharmacists should be doing to ensure the proper preparation, dispensing, and control of sterile preparations.

"It was not developed with the intent that it constituted minimal standards that must be complied with at this time. If this is to be the case, USP would have to

review the chapter with this in mind prior to its becoming official to ensure that it was suitable for this purpose.

"In this regard, we would welcome the comments of FDA, pharmacists, their associations, and others to ensure that it was appropriate for this purpose."

The chapter has been published in the PF as a proposal. It was published in May and June. Pre-publication copies were sent to several pharmacy organizations. We are sitting waiting for comments at this point. So, that is basically where we stand right now.

DR. JUHL: Good. I appreciate that. Let me see if I understand the implications then. As I understand law, you have complied with the law 100 percent of the time. With guidelines, it is kind of like my test, if you get an 85 percent, you are doing okay, and we would like you to get 90. So, what I am hearing is that your chapter is not written for minimal standards, and it would need to be reexamined were it to be adopted as such.

So, my question to the agency, are you willing to go through this iterative process, reviewing the chapter for that purpose, or are you saying that the standards that are proposed in the chapter are what they ought to be, period?

MS. AXELRAD: I think we are certainly prepared to go through the iterative process if it were agreed that that would be a good starting point, and if the committee were to

say that as opposed to some of the other standards that are out there, that we considered, such as the NABP and the ASHP standards, you know, once we decided which of these was the best starting point for this, we would certainly be prepared to go over it and comment on it, and work with the USP process to make sure that it was appropriate for what we were trying to do with it, that may not have been intended originally when it was written.

DR. JUHL: I think given that Congress directed the agency to work with USP on other things, and the USP has a long-established open public process, that makes good sense to begin on that route.

MS. AXELRAD: I am sure we would be working on it anyway. I am sure that we will be commenting on it even were it just to be an informational chapter that had nothing to do with compounding. The people in the agency who deal with these things would be commenting on it in any event. But if we were trying to use it for this particular purpose, then, we would certainly be involved.

MR. BARLETTA: That is what the briefing said in the PF, and I will read it.

"The chapter will remain an information chapter since it contains no standards, tests, or assays, nor other mandatory specifications with respect to any pharmaceutical article as stated" -- and we give the chapter and verse.

It does, however, represent guidelines developed through a public process by a legally-recognized standard body, which gives it special national standing.

It is numbered 1206 because that is a general information chapter. Any below 1000 is a mandatory chapter. That was the intent of the chapter.

MR. TRISSEL: The compounding chapter is below 1000, right?

MR. BARLETTA: The compounding chapter is a mandatory chapter. It's 790-something.

DR. ALLEN: The compounding chapter originally was 11-something. It was a guideline. But now FDAMA 97 specifically referred to the compounding chapter. It has not been renumbered to 795.

MR. BARLETTA: This could become part of 795, right? We could have Part A and Part B. It could be very easily made mandatory, and we have plenty of examples where general information chapters became mandatory, like the PET chapter.

DR. JUHL: Other questions from the committee?

MR. TRISSEL: I would like to comment on your three versus two categories. Correct me if I am wrong, Frank, but really the high risk category has two subcategories within it, so it winds up being three.

MR. BARLETTA: Whether you have one and two and

subcategories, it is basically the same. I don't know how much you want to hear about this, but in the very beginning we did invite ASHP to participate in this whole process, and they chose to go off on their own and establish their own guidelines, and they changed it, so that we now have two guidelines.

The USP, however, is the national compendium, which is recognized in law since 1906. It is not an organization, professional organization that publishes guidelines for its members, so there is a big difference between their guidelines and our guidelines.

Ours is a national -- international because there are about 20 countries that recognize the USP -- I like to call it the gold standard.

MR. TRISSEL: Randy, I haven't finished yet. Not that the pitch is over --

MR. BARLETTA: I am sorry.

MR. TRISSEL: What I was getting to with that was that both standards recognize that there are some sterile product preparations that are not unavoidably complex, but nevertheless, have a higher risk to the patient, and that would be something like prefilling unit dose syringes, a very simple operation, but if they are stored for long periods of time, they wind up being a higher risk than a syringe that is drawn up and used within a short period of

time.

So, there was this intermediate category, a very simple operation, but nevertheless, stored for longer periods, and both of them have that feature in there, something intermediate.

Not all things are truly unavoidably complex, but I will say that that is true for any compounding from a raw material that is not sterile.

DR. JUHL: Sarah, go ahead.

DR. SELLERS: I have a question for Peter.

When drug delivery system was decided that it did not demonstrate any adverse effects, did you look at how some of these sterile products that are made from non-sterile materials are being used, because some of them are being used in complex delivery systems like implanted intrathecal pumps, where if you do have a variation in the concentration of that drug from lot to lot, you can adversely affect your patient. Even a small change in drug concentration can manifest in either adverse reactions or withdrawal, for instance, with morphine sulfate, additionally with nebulized medications that are used in nebulizers.

DR. COONEY: There is no question that there is risk associated with all of those things. What this was, was a preliminary conclusion on whether sterile products as

a class should be included on the difficult to compound list, if not, compounded under some certain set of standards, and there is a lot more examples of problems with sterile products like you just mentioned.

I mean, for example, bioavailability can be a problem. I mean if you put the wrong preservative in an ophthalmic preparation, you alter its absorbability into the site of action in the eye.

But in total, we thought that the four items that I talked about were most important, but the other items are certainly not without risk.

DR. ALLEN: I might mention also with the USP, the USP is never a finished document. One advantage to the USP is the entire USP is constantly under revision based upon input from all different segments of society. That is why we have basically supplements that come out every six months.

But I would anticipate that the committee, when any difficulties start coming up, that they would immediately address those difficulties, and at least the mechanism is there for constant upgrading and revision through the USP.

MR. TRISSEL: Previously, we were asked about whether there was any need whatsoever for a high risk category of compounding from non-sterile raw materials, and

I would contend that there is. It is a relatively small part of the overall sterile product preparation that goes on in this country, probably less than 1 or 2 percent, but there are a number of things, some of which this committee has already dealt with.

As I recall, there are two amino acids for supplements to TPNs, that are only available as raw powders, and they are used in supplementing TPN, so there would be an example. We have a problem with implantable pumps that you had mentioned, only these are for regional therapy for cancer treatment.

The pump manufacturers recommend between doses that a 50 percent sterile glycerine solution be put in there as having the right viscosity to keep that patent while waiting for the next dose of drug.

There is no commercial product of 50 percent sterile glycerine, so we must compound this, and yet it is in the manufacturer of the pump's labeling to use this. So, there is an example.

We just had a recent one with a leukemia drug that is experimental, it is under an IND, but the IND specified that we would acquire this from a contract manufacturer making it under GMPs, and due to an unfortunate set of circumstances, we ran out -- not my fault -- but we solicited input from the agency.

We submitted basically an amendment to the IND allowing us to compound that to keep the patients going. Unfortunately, we did not get a response for six months, and during that time we did not use the compounded product, and we wound up having the GMP product arrive before we ever needed to use it, but nonetheless, it was an attempt to use compounding in that way, to keep the patients going.

DR. JUHL: How about morphine solutions?

MR. TRISSEL: We don't personally use any compounding of morphine solutions. I was telling Rose-Ellen earlier we use morphine topically. We compound morphine topically for local application and wound pain control, but we don't do any I.V. or intrathecal preparation from raw powder, but I know it is done elsewhere in society.

DR. JUHL: Is that a common practice I guess within hospitals that hospital pharmacies are compounding what are essentially copies of commercially available products, either TPN or morphine or other things?

MR. TRISSEL: My opinion?

DR. JUHL: Yes.

MR. TRISSEL: I think morphine is the principal example, and I don't know how far it extends beyond that, but will bet you the vast bulk of those that are copies are really morphine solutions of one kind or another.

DR. JUHL: And those are almost exclusively for

financial purposes or are there medical purposes that I am not aware of?

MR. TRISSEL: For a long time it was because we couldn't get a high concentration morphine, but I think that is available now. So, it may be for financial reasons where a patient can't afford it, so it is either, you know, do this and they control their pain or they don't get it.

MR. RUSHO: Just continuing on Larry's comments, I think there needs to be a high risk category, but I would make two categories there, one, that is the individualized patient, so that I am making my morphine bupivacaine epidural for that patient, and the other one is a batch preparation, such as progesterone and oil, where I am making larger quantities.

I think there needs to be a differentiation there when you are dealing with one patient or if you are dealing with a lot of patients.

Now, as far as your comment as far as is morphine compounded, morphine is compounded at least in our institution, but it is generally with another drug. It is like morphine or bupivacaine. I can think of one patient that's a gunshot wound victim, takes hydromorphone 30 milligrams per mL, and bupivacaine 30 milligrams per mL. That is done extemporaneously, and I guess tomorrow we will be talking about quality assurance measures that we use.

But, yes, we do a lot of it because we are a referral hospital, and we do have a pain service.

DR. SELLERS: Commercial products are also copied.

DR. JUHL: Other comments or questions?

MS. HOPE: I have a couple of comments. I wanted to thank Dr. Cooney for emphasizing the thing about filtration, because I think it is not as much the type, but just, you know, I think there is a big over-reliance on filters to assure sterility, and there is a big over-reliance when we have a hood. I mean that is a pretty simple concept that we still haven't got totally across.

I think there is a big problem on quality assurance testing because, like Loyd was talking this morning, where you have sterility testing that is not back for a week, but the patient needs it within 24 hours for stability, but yet if you are going to do that procedure on a regular basis, I think there should be some testing of it on some periodic basis to know that your technique is good, and I think in most of the guidelines we have already addressed this. I think it is a matter more of enforcement.

MR. WELDER: I would just like to comment that I have a little bit of difficulty with the description that all sterile products are difficult to compound, and it is just the wording thing, but I just want to make that comment, because not all sterile products are difficult.

You have to use the correct technique, as you do in any compounding, but they are not all necessarily difficult to compound.

DR. JUHL: As difficult for whom?

MR. WELDER: If you don't know how to do something, anything is difficult, but we do have people that know what they are doing, and it is not difficult to compound.

DR. COONEY: Perhaps a better term would be easy to contaminate.

DR. ALLEN: Following up on Bill's comment concerning the high risk, you know, he made a good observation, and that is something I think that I will mention to the committee in charge of 1206, and that is the two different levels of high risk or compounding from bulk drug substances, those for individual patients versus those that are batch compounded quite possibly, a little more detail on batch compounding with some additional testing might be a good idea.

It is hard to test individual items obviously, but you can test certain batch-prepared products.

MR. RUSHO: First of all, I disagree with testing individual items because pharmacists do have LAL pyrogen tests available to them. This is what we use on our individual products. Products do not go out of our I.V.

center that are compounded from non-sterile ingredients without an LOL test run on them.

If it is a batch-prepared, then it goes through potency testing and sterility testing also, and if we can do pyrogen testing on it, we will do pyrogen testing on it.

DR. ALLEN: Pyrogen testing is no problem. You can do that in a matter of a few hours, but what I am after is sterility testing which does take a longer time to get the results back.

MR. RUSHO: Well, I will go back to some of the comments that were made to me when I took my sterile products training down at the University of Tennessee. Dr. Avis told us at that time that a pyrogen test was a better indicator of quality control than a sterility test.

In my own products that I have made, I can make a product that is sterile, but it is loaded with pyrogens. I cannot make, I have never been able to make a pyrogen-free product that is non-sterile. I think the USP chapter needs to put more emphasis on LAL testing than on that, because it's geared towards extemporaneous type compounding. That is where it was developed was in nuclear pharmacy.

DR. JUHL: We have wandered into an area that we know something about. I love that.

MS. LaFOLLETTE: I wanted to make a comment about the bioburden loading to Dr. Cooney, especially on the high

risk compounds where we are dealing with non-sterile, and the bioburden loading could be very high and unknown with all the different components and packaging that is being used.

It is welcoming to hear that LAL is being used, I wasn't aware of that, so I would like to hear Dr. Cooney's comments because sterile filtration won't address all that, and what type, you know, is autoclaving being used in hospital settings, is LAL being done, which would be a preferred over a pyrogen test with the rabbit, comments, just open comments here I am looking for.

DR. COONEY: First, let me comment on the end product sterility test. It doesn't really tell you a lot even if you perform it before you release the product, and there is a lot of different reasons for that.

One is that it only tells you if there is viable microorganisms at the time you did the test. You could have had 10^6 per mL, and they all died off.

Also, it only detects organisms that grow in either of the two test media under either of the two incubation conditions.

Thirdly, most microbiologists recognize that only about 10 percent of the microorganisms that are around in the world have been identified so far, so there could be a plethora of other things.

You could have 100 millions AIDS virus particles in the product, and it would pass perfectly well. But what it is, as I like to comment on, it is kind of a quality control thing. It is a system check. If you are badly out of control, it will tell you that.

The LAL testing is a good idea, as well. The unfortunate part about that is for semi-gram-negative microorganisms, the LAL detection level of about 0.1 endotoxin unit per mL, you won't get that until after you have 10^5 organisms per mL, and if you have that, and you inject it into a patient, that's not good either.

But that is what I was trying to say in what I spoke about, that is why for this type of operation, system control is the only way that you can do it, and you do need some in-process quality control, monitoring and assessments of your environment, of the pieces that you are using if it's non-sterile products, and if you have a non-sterile drug substance or component that you are going to compound into a sterile product, and you do do testing, and you do find that it's very high, you have got to start questioning where you got that stuff from, and its background.

So, all of that together is useful and it is why it makes -- I appreciate the fact that difficult is probably a relative term, and not the best way to do it, but it's easy for these things to become potentially significantly

hazardous.

MR. TRISSEL: Another problem with LAL is some drugs interfere with that test, and you can't run them with LAL, and we have had to use rabbits, go back to rabbits for some things.

It is my perception that most hospital and home care pharmacies, and probably most other compounding pharmacies that make sterile products have the facilities, have the fundamentals of the facilities and procedures for making those in compliance with this chapter.

I think the problem comes when you have the products made that are truly high risk, made from non-sterile products, but treated as if they were low risk because of the lack of knowledge on the part of the pharmacist and lack of facilities and training in all the procedures necessary.

So, that is what we really should be trying to get at, is recognizing that difference.

MR. RUSHO: I realize that the LAL test does have some problems as far as some of the drugs. The drugs that we use, for example, it works fine on, and we have learned that over the years which drugs we can use it on and which ones we can't use it on.

The progesterone and oil, for example, the oil sequesters any endotoxins, and so you can't use a pyrogen

test on that. You have to depend on a sterility test.

I think, going back to your comments, there needs to be in-process controls. If pharmacists are making these on a routine basis, they need to have a dry heat oven, they need to have their beakers dry-heat sterilized, they need to have this material ready, so they reduce the bioburden when it comes to the filter.

If they don't do that, there is a build-up that you can see, and if you do the LAL test where you actually have sequential dilutions, you can see a build-up on your equipment, and that is why they need to be dry-heat sterilized, so you depyrogenate the glassware before you use it.

DR. JUHL: Other comments?

MR. TRISSEL: One more, I am sorry. The only reservation I have about Chapter 1206 in the USP is that it does not anticipate the development of improving technology. It is descriptive of a fixed technology without any potential for changing that, improving it in any way, and we are seeing the proliferation of the use of isolators in this country, in hospitals, for the first time. They have been used in Europe in 15 years, but here it is relatively new technology. It is new to the U.S., but it is probably an improvement over poorly-maintained clean rooms.

So, the only reservation I would have is whether

there should be some provision for improvements in technology that is not now in the USP chapter. That is probably best addressed with the USP.

DR. JUHL: Are you suggesting that -- I mean they do a revision, so that that could address things, but they are kind of behind -- you would like to see a paragraph or two that talks about new technology and the steps to take --

MR. TRISSEL: Right, a new technology that achieves the same end or in a better way or a better end is not allowed with that chapter, and I would like to see the chapter contain that, but as I say, it is probably a comment best directed to the USP.

DR. JUHL: Frank, if you would come forward and address that.

MR. BARLETTA: The USP has a chapter on isolators. That is why we didn't incorporate it in this particular chapter.

MR. TRISSEL: Really. Which one?

MR. BARLETTA: I am not sure if it has been approved or proposed, but that happens to be a Microbiology Subcommittee responsibility, so there is something going on there. We looked at that years ago, and we were told to bug off, that Microbiology has it under control.

MR. TRISSEL: Frank, you also ought to take a look at the PhaSeal system coming from Sweden, which is a

microisolator for single-unit vials.

MR. BARLETTA: Dr. Allen brought up the subject. He said that the USP is under continuous revision. That is what is good about the USP is that -- and it is true with every monograph and every general chapter -- as things change, and you people notify us, we revise the monograph and revise the chapter, so it is under continuous revision.

You can't hit everything, and from my experience with technology moving so fast, you would have to change a chapter every six months.

MR. RUSHO: Are we getting into specifics on 1206 or are we waiting until tomorrow on that?

DR. JUHL: I am happy to let us go anywhere we want to be taken with the exception of making our final determinations, which I think we need to do tomorrow.

MR. RUSHO: I have a couple of comments then. The section in there on using media fills, I have a real problem with that. One of the reasons I have the problem is for three years at the College of Pharmacy, I made my own soy broth medium, and you have to remember approximately 50 percent of our students have never touched a syringe in their life before they come to this class, and for three years I did not have any growth at all, and I had them making a simulated piggy-back admixture.

So, I thought maybe I had a problem with the way I