DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING

ADVISORY COMMITTEE

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Friday, July 14, 2000

8:30 a.m.

Advisory Committee Conference Room 1066
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. JUHL: Good morning. Welcome to Day 2 of the Pharmacy Advisory Compounding Committee. Today we will be considering the portion of the agency's proposed White Paper on difficult to compound that deals with sterile products, a continuation of discussions that we began yesterday.

The first order of business this morning is to conduct an Open Public Hearing. We have a number of speakers that have requested before us. We will go through the list and, if there is still time remaining of the hour that we have allotted, we will give the opportunity to those who may not have scheduled themselves, an opportunity for brief comments, if they desire.

The first person that I have listed is Susan Guzzo. Susan, are you here? Susan is from the Office of General Counsel at Boehringer Ingleheim Pharmaceuticals. She has requested ten minutes to talk with us. Welcome.

Open Public Hearing

MS. GUZZO: I apologize for yesterday and I appreciate your accommodating me for today. I am a registered pharmacist. Also I am an attorney and I am with Boehringer Ingleheim, Pharmaceuticals.

Of course, I would like to provide you with some information about products whose integrity we believe is

drastically compromised when they are compounded and, as a result, do pose a serious threat to public safety.

The first area of concern that I would like to speak to you about is the unit dose inhalation vials. The FDA has long recognized the importance of sterility for these inhalation products. Nonsterile products that are introduced into the lungs pose a safety risk, but, often, these patients are already immunocompromised because they are either elderly or they have a disease.

Therefore, the FDA has always imposed the strictest standards of manufacturers to insure sterility. The manufacturing that we do is all done, or performed, in a high-containment filling area. This means that there are hepafilters that continually clean the air. It also means that access by personnel is extremely restricted and those that do enter must wear an air-suit gown before entering.

Also, all equipment, tanks and filling equipment are clean-steamed sterilized before each and every batch. High-purity water is used in all preparations and there is a sterile filtration of the product.

The resins that we use in the vials are high-temperature heated rendering them sterile and pyrogen free before they are filled. Procedures are in place to insure there are no traces of other drug product that could possibly contaminate the product and as well stability

testing is done on every batch that can verify that the product is sterile eighteen months after preparation.

These are the standards that we impose and we meet to insure the public safety of inhalation products that we produce are sterile. Sterility has not waned as a public safety issue in the FDA's view and it is still evident because the FDA has recently issued that sterility requirement for aqueous-based drug products that becomes effective in May of 2002.

Just to mention the same issues of sterility also apply to morphine for intrathecal use and also for cafcit oral solution which is administered to premature infants who don't even have a developed immune system.

A second reason why inhalation products should be considered seriously is because of the containers in which they are packaged. It has been demonstrated by FDA, by us and by others, that the low-density polyethylene vials allow impurities to migrate into the product. As a result, we, as manufacturers, are not even allowed to affix a label to these vials.

Rather, we have to emboss the name of the product on the vial and then we have to enclose all these low-density polyethylene vials in a foil pack to prevent exterior contaminants from migrating in. Migration of contaminants is really a safety hazard, so much so that one

manufacturer has recently recalled 60 of its own lots because there was a migration of packaging material into the product.

I have not even heard this being considered to date. Packaging and compounding would probably have to meet some kind of standards as well.

Another area of concern, however, and grave concern, quite frankly, is the use of benzalkonium chloride in many of these UDV vials. It is used as a preservative in many compounded formulations, but the difficulty is that this product has been used to show bronchoconstriction. This is exactly the thing that the medications are trying to prevent.

So we do not use this preservative in our component formulations exactly for this reason. Nonetheless, it is routinely used by compounders. Because it is an adjunct ingredient, it is not required that the compounding pharmacist reveal this or disclose this to the patient.

So, if the patient has bronchoconstriction, they don't know if it is from the benzalkonium chloride, or they say to their doctor the drug is not working. So that is another area that I hope you will consider.

Finally, at this time, anyway, there is no mechanism in place to gather adverse events on compounded

products. As manufacturers, of course, we are required to gather this information and report all these adverse events, but when you consider that approximately 50 percent of all inhalation UDVs are being compounded in the State of Florida and there is no way of gathering this information as to the ill effects that the process may have, that is also a grave area of concern.

So, for these reasons, for sterility, stability, packaging containers and nondisclosure of potential--of adjunct ingredients and, perhaps, not a safety-reporting mechanism in place, I would hope that you would consider looking at UDVs as one of those products that would be placed on a negative formulary.

Do any of you have questions for me?

DR. JUHL: Questions from the committee?

DR. SELLERS: Can you comment on the quality of bulk materials that are used in manufacturing sterile products?

MS. GUZZO: I can, to some limited degree. I can tell you that, for instance, morphine for intrathecal use; we, as manufacturers, start with a sterile, dry-powder product. Our morphine is sterile to begin with.

If, in fact, you come in with a nonsterile product, a bulk ingredient product, sterilization of that after the fact is almost impossible. So I don't know, Sara,

if that goes to your question. But, other than that, if you would need more information, I am happy to provide it for you at a later date.

DR. JUHL: I have a question. The compounded products that you are speaking against, and I guess without naming drugs or products, I am wondering are they essentially copies of commercially available products?

MS. GUZZO: Yes; exactly.

DR. JUHL: So that they are already in violation of the--

MS. GUZZO: Yes; exactly. There is information that I can provide to you. I think we are not here today to talk about the difference between manufacturing and compounding, but when you walk into a nursing home, 100 percent of those patients are receiving a compounded product when, in fact, commercial product is available, I think that that is directly the issue.

As you know, I am a pharmacist and there is a need for compounded products, but this may be that line that you are speaking of, Randy.

DR. JUHL: The venue in which these products are used are primarily nursing-home, institutional, settings, outpatient or is it a variety that--

MS. GUZZO: It is a variety. Yes.

DR. JUHL: Thank you.

Other questions or comments?

MS. GUZZO: I appreciate the time. Thank you very much.

DR. JUHL: Thank you.

Next we have comments from Shelley Capps, International Academy of Compounding Pharmacists. Shelley?

MS. CAPPS: Good morning. Thank you. Initially, the International Academy of Compounding Pharmacists was prepared to make a scientific presentation today. Upon reading the issues for this meeting, we asked our previous representative at this meeting, Gina Ford, to attend and speak.

Gina is compounding pharmacist who would have addressed the more practical concerns that were talked about yesterday. However, because this committee has already voted and made recommendations on all but one issue, we did not want to waste your time and, instead, will just submit comments to the FDA by the August 15 deadline.

Instead, what I would like to do today is to discuss our disappointment in the procedural design of this meeting. I would like to offer some suggestions about how the Academy can and would like to work with this committee in the future.

Ideally, the concept paper would have been published well in advance of this meeting. The public would

have been given at least 45 days to comment on this paper and then the committee would have been apprised of the public comments prior to the meeting.

As it now stands, the committee has made recommendations only a few days after the concept paper was published without the benefit of thoughtful comments from practitioners in the industry that will be directly affected by this concept paper. The public was given less than 15 days notice of this meeting. The public was only given two days to respond and request to present at this meeting.

The concept paper was released on June 29. This is only two business days prior to requesting participation here today. FDA's extensive bibliography has still not been put on display at FDA dockets. This makes it far more difficult to review the references cited by FDA. All of these factors have severely hampered input to this panel.

In addition, no agenda was provided. If it had been given, Gina would have requested to participate in the first day's discussions and would have been available to address practical concerns.

The issues you have addressed are critical to our membership, pharmacists who work with tens of thousands of physicians who treat millions of patients. This network of professionals and patients puts us in a unique position to provide this committee with information.

For example, yesterday, the committee had questions about 4-AP. If ICP had been notified in advance of this discussion, we would have been prepared to assist the committee. The committee suggested a stability study for this substance. With three months' notice, we could provide this information to the committee.

In closing, we believe this committee has been greatly disadvantaged because public comment here has been limited. As I stated yesterday, ICP believes strongly that this concept paper strays from Congressional intent for determining what is to be considered demonstrably difficult.

As stated twenty-five times in the legislation, including four times related to demonstrably difficult, a drug product and not a technique or class of delivery systems must be proven demonstrably difficult. For this reason, we believe that the concept paper, itself, is flawed.

Had notice been given and public comment allowed prior to this meeting, this legal argument could have been made and resolved. I only address these issues--I know you have pointed out that it is a legal issue, but I only address them because I want to convey to the committee that we very much want to work within this forum and help this to be an effective meeting.

Thank you.

DR. JUHL: Thank you very much.

Let me kind of go through by point. We will have some additional information on 4-AP at the end of the meeting I think will get us past the point we were yesterday. With regard to the design of the concept paper and its treatment by class, I would invite comments by the committee, not on the legal basis but on the common-sense versus non-common-sense approach that was taken on this.

I think that would be helpful to the agency although the legal issue that specifically is raised is a different one, my one opinion is this seems to be a common-sense way to approach the issue, again avoiding the question as to whether or not that is within the strict legal reading of the law.

Are there other comments on that that the committee would like to offer?

MR. TRISSL: I couldn't agree with you more. The issue is demonstrably difficult to make correctly without having these facilities and equipment and training and procedures all in place. It is not a molecule-specific problem. It is an issue that spans the entire spectrum of drugs and, unlike stability, which would be molecule-specific, this is something that applies to anything that is going to be made as a sterile product.

So I see no other way to approach this in any kind

of reasonable manner but as an issue that spans everything. Unlike, say, the silver nitrate that we put on a list that you can't compound, this doesn't preclude compounding anything. It just says that you must have a certain level of quality assurance to make this in a safe and sane manner.

I think it is a perfectly reasonable approach.

DR. JUHL: Other comments?

DR. PECK: It would appear one has to start somewhere in terms of discussion of drug products that may be compounded. One approach could be to divide the products that might be considered to be compounded into certain groups. It is not necessarily to slot these particular products into this group, but it does happen, the way they are delivered. So the approach here would be to consider the drug delivery system and its complexities.

I think what we discussed yesterday, the several that we discussed, I think, thoroughly, can be well defined as products and we can approach it from that standpoint. There are a number of things that were pointed out in terms of what the committee was going to look at and then we had a series of questions that we have to respond to.

But I think the original paper did divide the considerations into seven areas of consideration. These have to be looked at in light of the products and they can be put into certain categories, and they can be treated as a

group.

So we need to, certainly, move on in terms of the deliberations. One way to move on is to group the information under consideration into categories. So I think that is the reason for treating the categories and to try and address the complexities of certain categories of drug products and their delivery.

DR. ALLEN: I have just one comment. Many of the presentations yesterday were almost classic academic presentations, you know, that many of us have made. We have made them in the past primarily from an industrial, manufacturing standpoint because those are the factors or considerations in preparing those types of products.

But we also have to keep in mind that compounding for an individual patient is different from manufacturing for tens of thousands, or hundreds of thousands, of patients. And I would hope that, of those factors that were discussed yesterday, that we always keep that in mind, that we are not after manufacturing a product for hundreds of thousands of patients but for compounding for individual patients.

That would be one of my main concerns. We looked so much yesterday at an industrial orientation as compared to a compounding orientation. Granted, you know, I don't have any problem with what was done yesterday but I would

hope in the future that we keep that in mind, that they are two separate things.

DR. JUHL: The categories that we considered yesterday were ones that, apparently, no pharmacists are doing yet and all that we had available to us was the industrial model. And all that we had available to us was the industry model, but I would certainly hope if we get to categories where pharmacists are doing them, we would be able to present from both perspectives.

DR. SELLERS: Just a follow up. Even if we are compounding for individual patients, we need to have a baseline system established so that each individual patient, their products are compounded in a safe and effective manner and it needs to be standardized.

DR. JUHL: Other comments on the approach?

MR. RUSHO: Just another comment to follow up on Larry's. If I were to teach the sterilization of each and every individual drug product, first of all, I would never get through the lectures. You have to lump these as a group in order to do it. That is the way we teach our students. It is a rational approach to the problem.

DR. JUHL: The curriculum committee thanks you.

MR. WELDER: I guess I wasn't aware of the short time span that was afforded this committee on the agenda. I got mine when I got here, I guess. But is there a way that

these reports could be issued a couple weeks or so before this meeting so other people can respond and help this committee?

DR. JUHL: I am sympathetic to that portion of the Academy's comments.

MS. AXELRAD: I would like to address that. First of all, we get it out as quickly as we can. This was actually put up on the web, I believe, at least two weeks before the meeting. It was up on the Internet and available for people to comment on. We put it up on the web at the same time we sent it out to the committee members.

Also, I would like to say, this is only the beginning of the public process. We have allowed for a comment period after the meeting where people can submit comments. We will be taking those comments into account as well as the deliberations of the advisory committee at this meeting and preparing a proposed rule on this which will then be published for public comment with an ample period for people to comment.

There will be other opportunities for us to bring this and other issues associated with this subject back to the committee. So I think we are at the very beginning of the public process.

DR. JUHL: This thing that we have been calling, or at least I have been calling, the White Paper is not even

a formal proposal as yet.

MS. AXELRAD: That's right. It is not a proposed rule yet. We wanted to bring it to the committee and hear from the committee and then we will develop the proposal which will then, again, be put out for public comment.

DR. JUHL: Although that may have been on the web two weeks in advance, the agenda, I don't believe, was.

MS. AXELRAD: The concept paper we--

DR. ANDERSON: The concept paper, I think, was up June 20-something.

MS. AXELRAD: June 20-something. It was up a couple of weeks ago.

DR. JUHL: But the agenda wasn't.

DR. ANDERSON: The notice for the advisory committee meeting?

DR. JUHL: No; the agenda.

MS. AXELRAD: The subjects that were covered were in the Federal Register notice. I am not exactly--Igor, do you know when the notice was published?

DR. CERNEY: I believe it was about three weeks before the meeting is when the Federal Register notice was published.

DR. JUHL: But the issue was that the agenda wasn't published and those that would like to comment on a particular issue that was on a particular day were not made

aware of that. The committee--I am assuming we got the agenda as soon as everybody else which was the day when we got here. I think that would be helpful to have that--that may not be regulatorily required, but as a courtesy, I think that if we can do that, it would probably be appreciated.

Other comments from the committee?

Let me move, then, to Dr. Henri Manasse, Executive Vice President of the American Society of Health-System Pharmacists. He has asked for ten minutes of our time.

Henri, welcome.

DR. MANASSE: Good morning. Thank you, Chairman Juhl and members of the advisory committee. I am pleased to be here. My name is Dr. Henri R. Manasse and I am the Executive Vice President and Chief Executive Officer of the American Society of Health-System Pharmacists, formerly known as the American Society of Hospital Pharmacists.

AHSP is the 30-thousand-member national professional and scientific organization that represents pharmacists who practice in hospitals including outpatient services as well as health maintenance organizations, long-term-care facilities, home-care agencies and other components of organized health-care systems.

I am pleased this morning to speak to FDA's Pharmacy Compounding Advisory Committee about our members' perspectives on the concept paper that the agency has

developed on drug products that present demonstrable difficulties for compounding because of reasons of safety or effectiveness.

ASHP will provide FDA with written comments on the entire concept paper by the 15th of August deadline so I will limit my comments today to the section of the concept paper dealing with sterile products.

It clearly would not be in the public interest to ban pharmacist compounding in organized health-care settings of sterile products given the decades long experience, constructive experience, of hospital pharmacists serving patients by performing this function well.

Hospital pharmacists in the United States have been providing centralized intravenous admixture compounding services since the early 1960s when the concept was pioneered at the National Institutes of Health Clinical Center and other leading hospitals throughout the United States.

In general, we think the FDA has come up with a good approach in dealing with pharmacist compounding of sterile products by recognizing that one, there are risks associated with compounding sterile products and, two, that risk can be managed successfully and effectively if pharmacists follow appropriate practice standards and procedures.

I would like to express ASHP's appreciation of the FDA's extensive use in the preparation of its concept paper of ASHP practice standards and guidelines, technical assistance bulletins and other research on this subject that has appeared over the years in the American Journal of Health System Pharmacists, previously known as the American Journal of Hospital Pharmacy.

ASHP has demonstrated its serious commitment to keeping all its practice standards and guidelines up to date and reflective of current scientific knowledge and professional practice. I pledge to you that that commitment will continue.

Now, on to some concerns. Our first concern has to do with FDA's intentions relating to Section 503A, subpart (f), of the Food, Drug and Cosmetic Act, which states that, "the term 'compounding' does not include mixing, reconstituting or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling," and I close quote from the law.

We believe that FDA's concept paper has not clearly differentiated between the actions noted in Section 503A, subpart (f), of the Act, and the commonly accepted professional understanding of compounding of sterile

preparations.

For example, in discussing the complexity of preparing sterile products, the agency says, on Page 7 of the concept paper, "Each time a pharmacist removes a sterile product from its original container or reconstitutes," and I underscore the word reconstitutes, "a sterile product, a risk of compromising the sterility of the product exists."

The use of the word reconstitutes in this context implies to us that the FDA intends to regulate reconstitution according to manufacturers' instructions as well as compounding. We believe that a determination that reconstitution consistent with product labeling as demonstrably difficult would be contrary to the intent of 503A, subsection (f) of the Act. ASHP requests that FDA correct this erroneous implication by using a different term or completely deleting any reference to reconstitution.

We are pleased that the FDA is advocating that professional practice quality-assurance standards must be applied to sterile product compounding. ASHP agrees with that philosophy as reflected in our long history of developing applicable practice standards and fostering the application of those standards in various articles published in our peer-reviewed professional practice journal and, as well, in our educational program and training conferences and various specific training seminars on this subject.

However, if the FDA is suggesting that only the standards in Chapter 1206 of the United States Pharmacopeia, when applied to the compounding of any sterile drug product, would reasonably assure the potency, purity and quality of the drug product, we must object.

As you know, just last month, ASHP issued and published its guidelines on quality assurance for pharmacy-prepared sterile products which updates a document originally created in 1993. ASHP believes that the FDA should strongly encourage state boards of pharmacy to base their oversight of sterile drug compounding on both--on both--Chapter 1206 of the United States Pharmacopeia currently in the process of revision and our newly revised guideline for the compounding of all sterile products as well as new scientific knowledge that may not have yet found its way into these documents.

ASHP believes it is appropriate for the FDA to suggest to state boards of pharmacy the standards they should apply in the oversight of sterile compounding. This will foster the establishment of a national quality-assurance standard for compounding sterile drug products in all pharmacy-practice settings.

The use of both the USP Chapter and ASHP's guidelines as well as the latest scientific knowledge in the literature would provide the assurance the FDA is seeking

for the safety and effectiveness of these products.

There is little practical difference in content between the ASHP and USP documents. We recognize this. However, in a 1996 article by Laura Thoma comparing Chapter 1206 of the USP and ASHP's document, it was noted that ASHP and the USP documents both contain much useful information and each has a unique perspective and contains some information not covered by the other.

This was due to the fact that the original USP chapter was limited to home health-care-practice settings while the ASHP document applied to pharmacy services in various and broad practice settings.

The ASHP guideline also refers to Chapter 1206 for specific methods such as environmental monitoring, sterile process validation and end-product sterility testing. The ASHP guideline provides useful shelf time and temperature criteria for risk-level determination and the use of barriers and isolators and auto-compounders.

The author of the comparison concluded, and I quote, "It is recommended that both documents be read for further information and that professional judgment be used in applying these guidelines to individual practice settings."

The role of enforcing the application of specific quality-assurance standards in pharmacy practice is one that

is well established in law and in practice for state boards of pharmacy. ASHP believes that the FDA has a role to play in insuring that state boards fulfill this responsibility by encouraging that the standards in both Chapter 1206 and ASP's guidelines are followed.

We strongly recommend that the FDA delegate to state boards of pharmacy the responsibility for overseeing pharmacists' adherence to those standards rather than assume this responsibility directly.

ASHP has solicited comments from our members throughout the country on the FDA's concept paper which will be incorporated into a written commentary that we will submit to the agency next month. Some of the comments we have already received, however, testify to the many lives that have been saved thanks to the dedication, skill and professional judgment to pharmacists who have compounded sterile products that otherwise may not have been available.

The important drug products that provide significant public-health benefits and appropriate patient care should not be considered demonstrably difficult to compound. We look forward to the continued opportunity to advise the agency on this important public-health and pharmacy-practice issue.

Thank you for the opportunity to present and I would be pleased to respond to any questions.

DR. JUHL: Thank you, Henri. If I could have you just stand by for a second, our next speaker is going to require a computer hookup. I wonder if we could endeavor to do that while we are having some discussion.

Let me take the questions that Henri raised and see if we can address them here. The reconstitution effort would appear to be a use of words that we weren't precise in; is that accurate?

DR. ANDERSON: No; that's right. We could clarify that. It doesn't apply to reconstitutions within the labeling. It is just compounds.

DR. JUHL: So anything that the pharmacist is instructed to do within the approved FDA labeling--

DR. ANDERSON: The way the law states; right.

DR. JUHL: Is not compounding, legally speaking.

DR. ANDERSON: Right.

DR. JUHL: The question of guidelines. You have obviously made good use and the ASHP guidelines are certainly respected and useful to pharmacists. Given the Congressional instruction to work with USP and the history of USP as being a legally recognized body for other things, I guess it was quite reasonable and logical that you would choose to use the USP Chapter rather than the ASHP guidelines, even though, as Henri points out, they are very similar.

Are there views on the committee about the two-guideline approach that has been suggested as opposed to the singular guideline approach? Loyd?

DR. ALLEN: If I could make a request. You know, the new Sterile Products Compounding Committee of USP has just been named. The Chapter 1206 is under constant revision, as you are aware. What I would like to request, if possible, would be any of the components with the ASHP guidelines that are not in 1206.

I am sure those are going to be looked at and quite possible or probably incorporated into 1206. I guess what I am asking is if it would be possible to get some type of summary of the information that is in your guidelines that is not in 1206 and that can be presented to the committee that will probably have its first meeting around the 1st of September or so.

Is that reasonable?

DR. MANASSE: Yes; I think that is quite reasonable. In fact, ASHP does have a standing committee that relates to USP. We can ask for that summarization from our documents and then transfer that to dialogue with the USP. Very reasonable.

DR. JUHL: Other comments or recommendations of the agency on the use of guidelines? Elizabeth?

DR. McBURNEY: In your paper that you presented,

that we got your written comments, you said there is little practical difference in the content between ASHP and the USP documents. Are you aware of any conflicting or discordant information between those two documents?

DR. MANASSE: I am not aware of that directly right now, but we will do a careful review and will include that in our written commentary.

DR. JUHL: Sara?

DR. SELLERS: Are you advocating, then, that these remain guidelines and not requirements?

DR. JUHL: The 1206 or the ASHP?

DR. SELLERS: Or the combination of both.

DR. MANASSE: My impression is that the suggestions of FDA staff is that Chapter 1206 essentially be considered as requirements. ASHP's documents are guidelines, a technical-assistance paper. We don't have the authority of law, if you will.

We obviously feel, as I said, that perhaps the translation of ASHP guidelines into state law, particularly that govern the compounding of sterile products, is a reasonable direction.

DR. JUHL: Have you reviewed your guidelines in relationship to the NABP proposed section of the Ideal Pharmacy Practice--

DR. MANASSE: In the model acts? That is

currently in process.

DR. JUHL: Other questions on the guidelines? I think the last issue that Henri had raised is the agency delegating to the state boards the authority to overview this. I think that has already happened, although it was probably delegated by the Constitution and not by the FDA, so the agency and the state boards would like to work together on this, but the practice of pharmacy is governed by the states.

MS. AXELRAD: I think that the interrelationship between the states and federal government is addressed in the compounding provisions. We will be working with the states, with the states having the principal responsibility in terms of enforcing all of the provisions. But we will be working together, basically, on that.

DR. MANASSE: Our underlying recommendation here is to reinforce the fact that all practice acts should have the model language. That is presently not the case and, perhaps, this committee, in its work and its recommendation, could move that along.

DR. JUHL: Other comments for Henri? Thank you.

DR. MANASSE: Thanks for the opportunity.

DR. JUHL: Our last scheduled speaker on the open public hearing is Gregg Jones, Inspector for the State of Florida.

MR. JONES: Good morning. I apologize if I seem a little disorganized this morning. I returned from vacation on Wednesday and learned that I was going to be here, so I have put this together pretty hastily.

[Slide.]

My name is Gregg Jones. I am a pharmaceutical program manager with the State of Florida Department of Health. I work in the regulation of drugs, devices and cosmetics. I have been an inspector for fifteen years this week. In our responsibilities, we monitor the manufacture and distribution of drugs, devices and cosmetics in Florida.

The purpose of my visit today is to share with the committee some of our findings in Florida on compounding. I am not here to discuss the safety, efficacy of products or the legal issues but just to give the committee an inspector's perspective of what we see when we go into certain compounding situations.

We have seen the compounding of respiratory-therapy medications, in particular, bronchodilator drugs, as the main thrust of all of the compounding that we have had in Florida and I am going to spend the first part of the presentation talking about the large amount of compounding that occurs in that area and some of the problems that we see.

[Slide.]

I would like to give you a little bit of historical perspective on our dealing with compounding. The best place to start is here with respiratory-therapy medications. In the mid-1980s, Medicare covered nebulizer devices for inhalation of medication. They did not cover the medication that went into the device.

A resourceful home-medical-equipment dealer in Florida convinced Medicare that, to be truly effective, they needed to cover the medication. So Medicare began covering albuterol sulfate, among many other respiratory-therapy drugs. Medicare does cover many medications used in the home under Medicare, Part B, despite the common misunderstanding today that Medicare doesn't cover any prescription drugs.

The patients, prior to using these unit-dose medications, would be dispensed a concentrated bottle of albuterol sulfate, take this medication home, drop it into the nebulizer using sterile normal saline and administer the medication. The manufacturers, Schering being one of the first, came up with the unit-dose medication that you see on the screen in a 3 cc vial with the most common dose in the 0.083 percent.

At this point, this became better patient compliance and Medicare's reimbursement rate for this product was somewhere in the range of $1 per cc--that is $3

per vial, roughly--given three times a day for roughly $300 a month.

This was a large amount to pay for these medications but this was based on the brand-name price. What we were seeing in Florida was an escalation in the use of these products because durable medical-equipment dealers were allowed to bill Medicare as opposed to a pharmacy billing Medicare, or a pharmacy billing for drugs which is the traditional way that occurs.

Occurring on a parallel track in the mid-80's was a sort of a reintroduction to compounding, in general, basically brought about by a company in Texas that was reintroducing pharmacists to techniques used in compounding and making certain chemicals available to them for that purpose.

This is not the compounding that we were seeing escalating at that point. What happened, on a parallel track to that, is that the respiratory-therapy medications, pharmacists in Miami learned that they could take the concentrated solution and place it in the 3 cc vials and continue to bill Medicare, but they started using the concentrated solution.

Soon after this, about 1989, they had access to albuterol powders. They started acquiring these from various sources and started to compound what you see on the

screen, which is a product made from a powder that has been imported.

[Slide.]

These are just a few of the many different products that we have seen. There is no consistency in the production of some of these products. They have no lot numbers. Many of them have no expiration dates. They have no indication of the strength and no indication of the quantity.

[Slide.]

This picture was taken about ten years ago in Orlando in the back of a regular community pharmacy. It is rather difficult to see, but this is behind the traditional pharmacy. This is the storage area for storage of supplies. These are the 3 cc vials. This is the area where the mixing of the albuterol solution is occurring and the filling of the vials and the capping, and this is where the solution is stored after it is mixed.

[Slide.]

This picture was taken very recently at a pharmacy where they continue to fill the 3 cc vials out in the open. This is in the shipping area of the pharmacy. This particular pharmacy is making a large volume of respiratory medications for pediatric patients using combinations, half strengths of albuterol and other medications as well as

antibiotics.

[Slide.]

This particular pharmacy, about a year and a half ago, was making 30,000 to 40,000 of these unit-dose vials per day, all under compounding regulations. These people sitting at the desk are placing a 30-day supply of these vials into boxes and are labeling.

[Slide.]

This is the stock shelf where the products are maintained after they have been produced by the pharmacy and then pulled from here for shipping to the patient.

[Slide.]

Typically, we were seeing, a couple of years ago, that the preservative used for these is benzalkonium chloride.

[Slide.]

These are just a few of the containers that we have encountered that are used to store the product once it is produced. This is a commercial container, but we often see various types of plastic jugs used to hold the products.

[Slide.]

Sterile water for irrigation or injection is often what is used to dilute the powder. The powders can come from wide, wide varieties of sources. Some pharmacies import directly through chemical importers. Some buy from

some of the major chemical distributors.

[Slide.]

This picture was taken at a pharmacy in Miami. These are bulk solutions of albuterol sulfate that have been prepared, ready for bottling. As you can see, it is just kept in the refrigerator with the other items such as their lunch.

[Slide.]

This picture was taken in the bathroom of a pharmacy where stacks of the container-closure systems were kept.

[Slide.]

This particular photo was taken in Miami where the finished product has been stored in the bathroom. These are the finished vials of albuterol sulfate.

[Slide.]

Because of the tremendous amount of profit in compounding these products, various home medical-equipment companies developed brochures, they developed sales forces and sales promotional material which would be detailed to doctors. Here you can see an example of what would be given to the representative.

A good prescription is written for compounded inhalation solution. A bad prescription would indicate the name of the product. Here, the products, as you can see, it

is stated they could be shipped directly. Here, they are not saying they are going to dispense the name-brand product but that they would have to go through the extra step of contacting the physician to change the order.

[Slide.]

What you are looking at here is the back of a pharmacy. All of these containers have n-acetyl-cysteine in them, one product. I would like to share with you some of the information that has been obtained in the past couple of years on this particular product.

Within the past couple of years, the number-one billed product by pharmacies for home respiratory care has become ipratroprium bromide. But the acetyl-cysteine, up until about a year ago, was the number-one billed product. In Dade County, the county where Miami is located, there were ten pharmacies that were billing in excess of $5 million a year for the one product.

100 percent of that was compounded. The tenth pharmacy on that list was billing Medicare for more compounded n-acetyl-cysteine than all of the rest of the pharmacies in the country combined. So this gives you some idea of the amount of volume of these products that are being produced.

[Slide.]

We did some analysis with other agencies on some

of the products, and I believe that, out of ten samples that were tested, only one met the potency standards. This particular one, and it is very difficult to read but it failed the assay test with 0.092 percent acetyl-cysteine found which is less than 1 percent of the declared amount of acetyl-cysteine.

[Slide.]

This, again, is a document to show you how commercialized this has become. This particular company was promoting to pharmacies and to home-medical equipment companies that if you use manufactured respiratory medications, "We can assist you to establish your own compounding pharmacy. We give you the necessary marketing information and you will be able to compound the 3 cc vial," that I showed you a picture of, "of albuterol 0.083 percent for 12 cents a unit dose."

Remember, at that time, the time this was taken, the reimbursement rate was something around $3 per vial, so you see the huge incentive for making this yourself.

[Slide.]

I would like to move on to just some of the general findings involving sterile products that we have seen in Florida, quite a few products for use in impotency and injection of prostaglandin products and combination products. I would like to pass around--I have some examples

of this and some of these others. I would like to pass them around and let the committee take a look at these, and then I will collect them over here at the end.

We have also seen, in some pharmacies, the preparation of preservative-free morphine sulfate. This was for intrathecal administration. Pretty commonly, we see the production of morphine sulfate for use in pumps. It is still occurring, primarily used in hospice situations.

We very seldom see any type of testing, potency testing, sterility, pyrogenicity testing, and very rarely any stability testing.

[Slide.]

This is an example of a pharmacy that is making products for the treatment of impotency. These are the vials where the solutions have been prepared using powders that you see some of them down here. These are the finished syringes that are going to be shipped out to patients.

[Slide.]

I have some examples of those in here.

[Slide.]

Pharmacies don't enjoy the privilege of knowing when inspectors are coming and, unfortunately, we walked in right after the Christmas party. But this focus on this area here is where a community pharmacy was preparing some impotency injection using papaverine and prostaglandin in

this particular environment.

[Slide.]

This is where they were storing their empty vials, in the food section.

[Slide.]

This picture didn't copy very well, but I wanted to demonstrate for you a real typical procedure that we have observed for the production of prostaglandin. This is a vial of spectrum prostaglandin E1 for research purposes. This is a bottle of grain alcohol from the ABC store. Typically, what will be done is some alcohol will be drawn, injected into the vial here to dilute the prostaglandin.

Am amount of sterile water will be added to the graduate cylinder here, mixed with the powder solution, drawn into a syringe and then transferred through a 0.2 micron filter to another syringe and then injected back into an evacuated vial.

[Slide.]

This is another pharmacy where we encountered the same alcohol, type alcohol, being used.

[Slide.]

The first picture I showed you, this is a hood, here. Next to it in this compounding room is a bulk container. It think this is a 50 kilogram barrel of sulfadiazine used to compound some veterinary products.

[Slide.]

This is the area of that room on that very opposite end where a number of various products are being compounded. You can see the condition of that compounding area.

[Slide.]

This procedure indicates the production of preservative-free morphine sulfate, which Medicare, by the way, does cover and pays a lot more for this particular product than they do the non-preservative-free. This is a small boat that is used to weigh out the morphine sulfate. It is diluted with preservative-free water and then mixed and transferred through 2.2 micron filters to the syringe which is used in the intrathecal pump.

[Slide.]

Not all of the places that we visit are quite as unclean as the other picture that I have showed you, and we don't often take pictures of the good things we see in compounding. But I don't want to imply from these pictures that everywhere we go, we see nothing but problems in compounding because we do see some very advanced systems.

This particular room you are looking at is a clean room in a regular community pharmacy that is doing some IV compounding. They are JCAHO inspected using JCAHO standards for this clean room. They have hepafilter-positive airflow

coming into this room. They have another laminar-flow hood where the work is done.

They do take some swabs and do some culturing of this area on a periodic basis, so I don't mean to imply that everywhere we go, we encounter a problem because there are some pharmacists that are going to extremes to insure a quality product.

[Slide.]

This is the pump that I was mentioning to you before which is used in the morphine injection.

[Slide.]

In this particular pharmacy, they were making pellets for implantation under the skin. These are the machines that are used to press the pellet.

[Slide.]

This is an autoclave which is used to sterilize the product.

[Slide.]

This is the finished product here, a pellet which is inserted under the skin for hormone-replacement therapy. That is my thumbnail, so you get an idea of the size of these. This tape is a temperature-sensitive tape which changes colors when the autoclave reaches a certain temperature, which is when the product is removed.

[Slide.]

This is the dispensing of that product, Estradiol, 25--I can't tell if that is milligram or microgram--pellet which is sent to the doctor and then inserted by the physician.

[Slide.]

As far as the active pharmaceutical ingredients, we have seen all types of products being used, some imported, this one imported from the Czech Republic, this one from an unlicensed distributor in I believe it is Minnesota, and this one, another unlicensed company. This is actually for a research chemical, prostaglandin, from Spectrum Chemical.

[Slide.]

This product, phentolamine, which is one of the ingredients used in impotency treatments. The common product, prostaglandin used, but it is also being used in combination with papaverine and phentolamine for bimixes and trimixes. The phentolamine, which is the brand name, Regitine, as used primarily in emergency-room situations, is not readily available and it is inaccessible to pharmacists. They have had to obtain this product from various sources and compound it. They virtually cannot get their hands on the Regitine.

We went into a pharmacy in a Central Florida town and told them that they are using this phentolamine which is

labeled for research purposes only, they had no certificates of analysis on it.

The next week, we went to another pharmacy in that general vicinity, and you see what was on the bottom of that same type of label. They have removed this information.

[Slide.]

I want to briefly touch--I know my time is up--but on a couple of issues that you will be addressing in the future which is sustained-release products. These are bags full of methylphenidate and a diluent. They are filling these bags with hydroxymethylcellulose, I believe. These are methylphenidate tablets. These will be ground up and put into capsules as sustained-release capsules in various strengths, depending on what the doctor needs.

Some of these vary from 1.5 milligrams to 35 milligrams per cap. This particular unique dose was 13.75 milligrams.

[Slide.]

This is the common sustained-release chemical that is used.

[Slide.]

These are morphine sulfate which is used in this extensively in hospice situations which are commercially available strengths that are being made.

[Slide.]

This particular group of controlled substances was taken--this picture was taken in a pharmacy where over 80 percent of all their medications they were dispensing to hospices were compounded.

I think that concludes it. I am sorry, Mr. Chairman, for running over my time.

DR. JUHL: Thank you for the information. Let me ask the obvious question. Do you have the regulatory and legislative power that you need to shut places like this down?

MR. JONES: The office that I work in regulates manufacture and distribution of these products. Our board of pharmacy regulates the practice of the profession of pharmacy which includes compounding. Every state differs in how they regulate it but, traditionally, all of the compounding activities have fallen under the purview of the boards of pharmacy.

When we find products that I showed you that were grossly under their potency, we have taken action on those. When we see chemicals that may indicate that they are not for human use, we take action on some of those. But, in general, there have been very few actions taken on the actual controls used in compounding products.

DR. JUHL: But many of the products that you showed us were essentially copies of commercially available

products, the products for inhalation and so on.

MR. JONES: I would say the majority of those products have been just copies of the commercially available product. Under Florida law, and I don't know how the other states handle this, but if a doctor orders a product that is essentially similar to a commercially available product and the patient is aware of it, then the pharmacy may compound it.

What we have seen, in the Miami situation, is that they will order, in the case of the acetyl-cysteine--it is available, I believe, in 4 ml and 10 ml quantities, commercially, in unit dose, they will order 5 cc's. By ordering the 5 cc volume, the pharmacy then will compound and dispense that amount as opposed to combining commercially available quantities.

That is very, very typical. Efforts have been under way by various offices in Miami to educate the physicians because the physician typically will write whatever the patient tells them that they have been taking before and not know what volumes are available commercially.

They will write 5 cc's not knowing it is not available. Many of the actions taken on the acetyl-cysteine in interviews with the doctors indicated they were not aware that the product was actually compounded from a powder.

DR. JUHL: Federal law now prohibits producing,

essentially, copies of commercially available products and they speak to the issue of changing just a little tinch to make it different. Has that been, at the practical level, a useful piece of legislation for enforcement or is it people don't know about it, or--what I am asking is is there anything we can do to be helpful here?

MR. JONES: I don't think it has slowed down any of the practices that we have seen involving the respiratory drugs; no.

DR. JUHL: Other questions? Rose-Ellen?

MS. HOPE: Could you give me some indication as to how frequently a pharmacy in the State of Florida would expect to be inspected?

MR. JONES: I believe pharmacies are required to be inspected annually in Florida.

MS. HOPE: Okay, because some states, now, it is only about every three years. I am thinking in terms of how long it would take to uncover something like this that was a developing problem in some states.

MR. JONES: In Florida, they are inspected annually.

DR. JUHL: There appear to be enough inhalation products billed to serve the entire country. Can I assume that many of the products that are being produced and billed are not actually going to patients but just being billed on

a fraudulent basis?

MR. JONES: I think there is a tremendous amount of fraud involved there. I am not sure they are not going to the patients. They may be going to the patients and not being used, I think is what some of the findings are.

DR. McBURNEY: Mr. Jones, thank you very much for coming from Florida on such short notice. We appreciate your presentation. One of my concerns with the data that you presented--could you give us a little perspective as to what numbers we are talking about here in regard to compounding pharmacies. We have seen some overwhelming examples of abuse and inappropriateness.

Is this the norm, or is this a small percentage of the compounding pharmacies, to kind of put it in perspective for us?

MR. JONES: Most of the photos that I have showed you were taken in an effort to go out and look at some of the areas such as injectables and some of the respiratory situations that we knew posed some public health hazards. But what I can address, as far as volume, is the respiratory element. I talked with a person yesterday who works in this routinely and I think we can safely say that there are hundreds of pharmacies in Miami, alone, Dade County, that are compounding respiratory meds daily.

DR. McBURNEY: Of those hundreds that are

compounding, could you make a reasonable or an educated guess as to the number that are doing it properly versus improperly?

MR. JONES: Most of the smaller pharmacies that are doing that are not following any type of controls in producing them.

DR. McBURNEY: The other question; I was not clear from the presentation--you stated that Medicare paid the durable-goods companies for these medications.

MR. JONES: Yes.

DR. McBURNEY: Are these pharmacies subsidiaries of the durable-goods companies or are they free-standing pharmacies?

MR. JONES: Medicare changed their policy in, I believe, it was 1996. Now they will only allow a pharmacy to bill for those medications, so they no longer will allow the home-health company to bill for them. That policy has increased the number of small pharmacies that are now billing and producing those products.

DR. McBURNEY: If I understood you correctly, the issue of sterility, that would fall under the board of pharmacy to enforce, not under your agency.

MR. JONES: Right; compounding is included in the definition of the practice of the profession of pharmacy.

DR. McBURNEY: I see. Thank you.

DR. JUHL: Realizing that you are only one state, but could you give us an idea of the interest of the state board of pharmacy to deal with this kind of issue or are they understaffed, underresourced and it is not high on the priority list?

MR. JONES: I don't feel really qualified to speak for the board since we work in an entirely separate section.

DR. JUHL: How responsive is the board when you provide them with reports of these kinds of activities?

MR. JONES: The actions that we have taken, we have taken independently under the Drug, Device and Cosmetic Act under misbranding provisions. I am not sure what the board's actions have been on other violations.

DR. JUHL: When you find things that are, in your mind, things that pharmacists shouldn't be doing that the board should have called to their attention, is the board responsive to these kinds of things?

MR. JONES: I believe so; yes.

DR. JUHL: Thank you.

DR. SELLERS: I can state, just from reading the disciplinary actions from the state boards that you rarely ever--I have never seen a disciplinary action taken.

DR. JUHL: Bill?

MR. RUSHO: Just a couple of questions. On your slide where you showed the prostaglandin being prepared, you

said that they injected alcohol into the vial. Are you saying that these pharmacies do not have analytical balances necessary to weigh out that material?

MR. JONES: That is a good question. Some do weigh it out with some sophisticated balances. This particular example that I showed you, the company has the stated amount of micrograms on the vial that comes from Spectrum. What they will do is produce the concentrated solution in the--the impotency drugs have disappeared. This would have a concentrated amount of the solution, and then this would be drawn off.

I have seen a sample of this sent to an analytical laboratory to actually determine the exact concentration because when you are talking about 10 micrograms as a dose, and you may have 100,000 micrograms in this concentrated solution, they need to make sure that, as they dilute it, they get--you can't just assume that when you start to dilute this 100,000 micrograms, you are going to end up with anything close to your target, 10 micrograms or 15.

So they will do--in one case only, I have seen this concentrated solution analyzed as a starting point on how to determine the exact concentration.

MR. RUSHO: What I was trying to get at was we talked about some of the difficulties in compounding here at this meeting. One of the things that we were interested in

was the proper equipment in order to do to compounding. That is why I was asking you about the analytical balance.

MR. JONES: Many of the ones that were making this would start with a given amount of prostaglandin and dilute that and base their further dilutions on the assumption that that was the exact amount that was weighed in the vial and not do any weighing of the product.

MR. RUSHO: Have you seen these products being dispensed as generic equivalents?

MR. JONES: In Florida, the product is written for albuterol, for instance. That is the common way it is written. The pharmacist can substitute a generic. We don't regulate and we don't see these prescriptions so I can't really accurately say we have seen it. But, the majority of the cases we have worked, when something is written albuterol sulfate, 0.083 percent, dispense a month's supply, they will dispense the compounded whether the doctor has indicated to dispense compounded product or not.

MR. RUSHO: So they are using it as a generic equivalent, then, without bioequivalency and bioavailability testing and everything the generic houses have to go through.

MR. JONES: Yes.

MR. RUSHO: What about the calculations of the drug dosage. I noticed one of the cartons said

0.083 albuterol sulfate expressed as albuterol. Have you noticed any problems with the pharmacist calculating that, in accounting for the salt form of the drug and waters of hydration of such?

MR. JONES: No; we didn't look at anything as detailed as that.

MR. RUSHO: Okay. Thank you.

DR. JUHL: Joan?

MR. LaFOLLETTE: Could you comment on the scope of the manufacturing? Are you actually seeing manufacturing going on whereas as an industry we are approved for certain batch sizes, or are you seeing things being compounded per patient and per prescription?

MR. JONES: Well, in some of the surveys that we did, we did see a lot of compounding done, one prescription, one product would be made. But most of the pharmacies will compound a certain supply based on what they think they are going to dispense. When you look at a bottle of 100 sustained-release capsules, they may go through those in a week. So they will make 100.

But, to extrapolate that, if you are dispensing 50,000 units a week, they make 50,000. So I am not sure what your question is, whether we have seen manufacturing. It depends on the size of the pharmacy. Some of them are rather large and do compound large amounts of those

medications.

MR. LaFOLLETTE: I am getting at that the industry has to abide by GMP regulations, and a lot of regulations. If you start to see the scope of what I would call manufacturing, from my view, especially of the inhalations on a large scale, it doesn't appear that all of these pharmacies--some may, but it doesn't appear that they would abiding by all the regulations that we have to to insure that the public is receiving a safe and efficacious product.

Along with the testing and the data that we have to do, I don't see it demonstrated that they--compounding pharmacy on the scale that some of the abuse that you are showing where it is not demonstrated to me. It makes me very nervous.

DR. JUHL: Other comments? Larry?

MR. TRISSL: Perhaps you would have no knowledge of this, but I will ask anyway. The examples you have all shown are presumably retain pharmacies. Does this practice of compounding basically copies of the commercial drugs extend to hospitals in Florida as well? Have you seen examples of that on any kind of scale that is approaching this?

MR. JONES: No; we haven't.

MR. TRISSL: Have you looked?

MR. JONES: We haven't looked.

MR. TRISSL: I am just checking. Thank you.

DR. JUHL: Jane?

MS. AXELRAD: I would just like to ask one question. All of the pharmacies that you have shown, are they still operating or have they been shut down?

MR. JONES: Many of those pictures you saw, the pharmacies are no longer operating.

MS. AXELRAD: That would have been the action that you would have taken or--

MR. JONES: Among actions by other agencies including Medicare.

DR. ALLEN: With the recent, I guess, enforceable regulations of the USP and the activities of the committee here, is there anything that you are aware of that we are not addressing that would help take care of this problem that you have seen?

MR. JONES: I think you are headed in the right direction in addressing these various areas. Without going into pharmacies more often and actually seeing what the current practices are, I couldn't really say that there is anything additional that you need to be doing because I understand, just from listening this morning, that there are various legal arguments that are going to persist in the direction that you are heading now.

I think the primary problems that we have had have

been in respiratory therapy and then the sterility of the products that are injections. Those are some of the areas that we have seen some of the major concerns.

Anything would be better, I think, than what we have now.

DR. JUHL: Elizabeth?

DR. McBURNEY: Mr. Jones, could I not infer from your comments that the reason that you are seeing it mostly in respiratory is because Medicare is covering the cost of those medications?

MR. JONES: I think so; yes.

DR. JUHL: Other comments from the committee? If not, I appreciate your coming here. It is not information that I, as a pharmacist, like to see but it does, I think, speak to the issues that we here as a committee have to deal with. One of the definitions of a profession is that it is self-policing. Pharmacy has not done a good job of establishing standards for compounding, translating those standards into regulations and enforcing them.

That does a disservice to the many pharmacists who do compounding on a patient-specific basis and do good deeds. This, certainly, is a black eye for us and we appreciate finding out how the real world works.

Thank you.

MS. GUZZO: I'm Susan Guzzo. If I may, I would

like to offer this up to the committee. You raised the point--this is a television commercial that aired where pharmacy compounders are soliciting patients who are on inhalers to convert to unit-dose vials because they can have their medication reimbursed through Part B. It is a public commercial that aired on television, and I will leave it with whomever you think should have it for viewing.

DR. JUHL: Thank you.

I am going to continue the open public hearing and my next step, now, is to ask if there others who would with to address the committee.

MS. CAPPS: I find this very disturbing and I would like to request a copy of the powerpoint presentation so that we could show it to our pharmacists because I think many of our members would be very disturbed by it as well. That is the best way to make it known out there and, like you say, to begin the self-policing aspect of this and even invite Mr. Jones to come to one of our meetings and make this presentation would be very valuable.

So I would like to offer that.

DR. JUHL: Thank you. Are there others who would like to briefly address the committee? Larry?

DR. SASICH: Larry Sasich, pharmacist, Public Citizens Health Research Group. I do really appreciate Mr. Jones coming. I have seen this presentation before and each

time that I see it, I become more outraged than the time before and absolutely at the loss for words.

I think one of the issues that this committee has to think about, and it shouldn't have to think about, is there is no longer any affective regulatory route for preventing or protecting the public from these kinds of activities. That was eliminated with FDAMA.

If you stop and think, as I have done for the last thirty years, as to one situation, one public-health problem, or one egregious act or series of acts that has been controlled by the self-regulation either of an industry or a profession doesn't work, it simply doesn't work.

As I said yesterday, this committee has very few tools and the agency has very few tools to operate within to be able to protect the public health, until, I hope, that FDAMA goes back to Capitol Hill and that it is either totally repealed or there is a serious rewrite of what is in this piece of really, really, bad legislation.

One of the things that I think you can do in terms of sterile products that would make it very easy and plain for state board of pharmacy inspectors some of whom are probably not even pharmacists to be able to police this particular situation is to place sterile products or products that should be sterile that are prepared from nonsterile bulk drug substances absolutely on the list of

drugs that are demonstrably difficult to compound.

What we saw today from Mr. Jones' presentation and the egregious quackery that Jana Nestlerode was subjected to yesterday from injectable DMPS would be prevented. I think what I would like to see you discuss is that possibility of placing those types of compounds on the demonstrably difficult to prepare list unless they are done in an organized health-care facility; i.e., a pharmacy that meets some type of professional standards.

I know you are going to have to work out whether these should be requirements or guidelines and, perhaps, differences or similarities between the USP and the ASHP approaches.

But that is the only thing that I can see in the short term to protect a large number of citizens from what you surely have to admit is a very clear public-health problem. 50 percent of the oral-inhalation solutions in the State of Florida? That is stealing. The representative from Boehringer Ingleheim was very diplomatic but it is nothing more than stealing.

Thank you very much for your time.

DR. JUHL: Thank you. Are there other comments? If you are brief, please.

MS. GUZZO: Susan Guzzo from Boehringer Ingleheim. Before joining Boehringer Ingleheim, I was a Florida

attorney as well and I was called in on several occasions to serve as defense counsel for many of these pharmacists. I can tell you that, in fact, it is manufacturing. I declined the opportunity, after reviewing the cases, at least four of those cases that the HHS was bringing that I was not going to defend the pharmacist there because they were simply manufacturing.

Thank you very much.

DR. JUHL: We have the videotape cued up. It is only 30 seconds long so we will go ahead and run that for the committee's information.

[Video played for the benefit of the committee.]

DR. JUHL: Is that a legal direct-to-consumer ad for--

MS. AXELRAD: I don't know if it is a legal direct-to-consumer ad, but I believe it is a generic approved product. Day Laboratories has a generic product I think that has been approved.

DR. JUHL: But it is not the manufacturer who is--

MS. AXELRAD: I don't think it is a compounder.

DR. JUHL: Other comments? Larry?

MR. TRISSL: I know it is a difficulty sometimes to differentiate between larger-scale compounding and manufacturing, but at the extremes, we can identify easily what is compounding and what is large-scale manufacturing.

This would seem to fall into one extreme of those. Does the agency have no regulatory authority over an unapproved manufacturer in this regard?

MS. AXELRAD: I think that the whole purpose of the FDAMA provision was to put some structure around our attempts, over the last many, many years to try and distinguish between compounding and manufacturing. The specifics that were put forth in the exemption that it has to be by a licensed pharmacist or physician upon a prescription for an individual patient and then to define the limited circumstances in which you could compound in anticipation of receiving that and the fact that there has to be this close relationship, and then the other provisions that deal with copying regularly or inordinate amounts what are essentially copies of commercially available products, all of those parameters in the law were trying to help us, I think, try and distinguish between compounding and manufacturing.

We are going to be addressing a lot of that in our general regulations, but I think it is always going to be very difficult to try and draw the line. Some of these pharmacies that we just saw were making things in large amounts. There will be issues. Are they essentially copies of commercially available products if it is 1 or 2 cc difference in terms of amount.

Are they doing it regularly and in inordinate amounts? Do they have prescriptions for individual patients? Is there a real need for a compounded product? Is there a medically significant difference?

So all of those things are things that we would have to look at. Also, as we have been talking about, the state boards of pharmacy will have principle responsibility to do something here. I think that it is fair to say that not all states are as aggressive. Some states are less. Maybe they have too few resources or are not able to inspect as often. Maybe they don't have the expertise.

But they may not be as aggressive in terms of enforcing this as other states. In those cases, we will have to see where we would be stepping in to do something.

MR. TRISSL: I think it is unfortunate that Carmen was not able to make this meeting because the input of the Boards of Pharmacy would be very welcomed in this. Maybe we should solicit that apart from this meeting.

DR. JUHL: Loyd?

DR. ALLEN: In fact, if I could recommend that, possibly at the next meeting, maybe Carmen could even provide a report on what activities, educational, et cetera, that they are doing for the individual state boards for the enforcement of all of the new things that are going on.

MS. AXELRAD: We can certainly try and arrange

that. We would love to hear from other states, too, about what they are seeing and what they are doing. We have tried to conduct a survey of a few states to try and find out what they are seeing with regard to compounding.

We didn't get a very significant response. We didn't hear from very many states and we also didn't get a lot of information about their practices. I think Florida, we have had more about what is being observed in Florida with regard to compounding pharmacies than any other state.

DR. JUHL: Seeing no further comments, we will close the open public hearing portion of our meeting and return to the business at hand.

Committee Discussion

DR. JUHL: We have before us our last question to consider on sterile products. Let me ask, is there further discussion before we call the question?

MR. RUSHO: I think, from my perspective, that the document is not something that I could adhere to at this particular point in time. I think I run a good shop but I think there are provisions in there, as I expressed yesterday, that need to be modified.

To use the colloquialism, I think they need to start thinking outside the box. They have taken manufacturing documents and tried to apply those to a compounding pharmacy. That doesn't work. As we heard

yesterday, when they do media fills, they are working with one medication at a time.

When I am dispensing and working in our IV center, I probably have got twelve antibiotics, pressor drugs, ionotropes, TPN, chemotherapy, epidural drugs and sometimes some sterile compounding in there. It is not feasible to put industry standards onto the compounding pharmacist. I think that document needs to be modified before we can accept it.

If we are voting on the concept of some regulatory matters, I think that is a different matter. But if we are voting on adapting that as it is written today, I can't do that.

DR. JUHL: I think yesterday we heard that both the USP and the FDA were willing to go back to 1206 were it to be required and revise it in a way that would accommodate the suggestions that were made yesterday to the extent that they can, plus others that I am sure will come forward.

So I think the question before us, and we will modify that when we call it, is to use Chapter 1206 as a starting point and not as a final document. Larry?

MR. TRISSL: I wouldn't interpret either Chapter 1206 or the ASHP guidelines as requiring manufacturing level requirements by any stretch of the imagination. They may have extracted valuable portions of the GMP style of

assuring quality but they are clearly aimed at compounding a sterile product in a pharmacy, not a manufacturing setting.

Both of those documents being so similar obviously have been developed with a rational, reasonable approach to sterile product compounding in a pharmacy. That is not to say there isn't room, because we have discussed some areas where there is room for improvement, but the general concepts that are embodied there are very applicable to a sterile-product compounding pharmacy.

While we should always work toward improving those, I think it is a good starting point.

MR. RUSHO: That brings up another point, too. I think these should be standards. I don't think they should be goals because I think people could sit there and say, "Well, I will meet those in 2050." I think these should be the standards. If people are going to compound these different levels of products, they need to meet those standards.

DR. JUHL: I think our goal is to translate these into regulations, have them translated into regulations, at the state level that a state board-of-pharmacy inspector can utilize to say this is lawful and this isn't, we need to insure that we start at the top with the Chapter 1206, if we choose that, written in such a way that that can happen.

As we talked yesterday, there are guidelines that

are written that are stretched standards and there are guidelines that are standards of practice and there are minimal requirements. So there are a number of ways that guidelines can be written and the revisions that would need to occur with Chapter 1206 would have to be done with the state board of pharmacy in mind so that they could be utilized in that way.

I think we have made that clear and the agency understands that recommendation from us.

Joan?

MR. LaFOLLETTE: I would like make the point that, yesterday, when the USP presented, Chapter 1206 could be moved to become a requirement. I actually would be for that and see harmonization between the USP and ASHP's guidance. Right now, even if we revise it with the comments that we made yesterday, it is still a guidance and there are things in there that are lacking.

I think it needs to be thoroughly reviewed and made a requirement. Otherwise, we will never move off this mark. We will always be shooting for a future target and we will still probably hear and see problems like we saw today that are occurring in Florida.

I think we have to move and be aggressive about this.

DR. JUHL: Loyd?

DR. ALLEN: With the new Parenteral Compounding Committee with the USP--they will meeting, quite possible, the 1st of September for the first time to establish the goals for this next five-year cycle, one of the things I will carry on to the chair of that committee--I have been making notes on the discussions--would be to look very carefully at harmonization of the current 1206 with the ASHP guidelines, with the NABP model guidelines with JCAHO accreditation guidelines and see what type of document, since this is constantly under revision, to try to get one harmonized chapter which--it has been kind of my goal for the last couple of years to try to get 1206 renumbered down to less than 1000 so that it is required because I think it is very feasible.

DR. JUHL: Sara?

DR. SELLERS: One specific comment. Reading over the USP guidelines and the ASHP, I didn't see enough attention paid to the quality of bulk actives that are used in sterile compounding. I think that we run a tremendous risk now that these bulk substances are handled through brokers, are available over the Internet. I have seen many ads targeting "compounding pharmacists" over the Internet; "We like to sell to compounding pharmacists."

I did not read enough specific regulation with respect to how these bulk substances are being acquired and

how we, as pharmacists, can verify that they do meet very specific standards before they are placed into a sterile product.

DR. JUHL: Other comments from the committee? Garnet?

DR. PECK: Along with the bulk active, and I don't want to interject something that may not be that important to some, but I think the excipients, in general, should be included also along with the bulk active. I don't think we should neglect those. We don't know how much and where they are coming from they are sourcing.

The other thing I respect the document by ASHP because it represents something 30,000 members. My only concern is that there be some regularity in terms of revision. The USP works on a five-year cycle and, at least during the five years, something is going on. I would recommend that if these are looked at in conjunction with the USP chapter that ASHP recognize that we need cyclic revision of their document, whether it becomes a guideline or really part of a joint regulation.

It has to be revised on a regular basis.

DR. JUHL: What would be nice is if we had the same exact document and anybody who wanted to title it and sign on to it and publish it in their journal could well do that. But I think that is one of the advantages of using

the USP, that it has a regular, everybody knows about it, cycle for revision and it does have legal standing.

Joan?

MR. LaFOLLETTE: I just would like to say I agree with the comments that Garnet is making about excipients. There are a lot of areas that we didn't touch upon and, in industry, we have to abide by. I am hoping if we revise some of these things to make them regulations; ICH guidelines for residual solvents? We have certain maximum daily dosing, units and classification of solvents. This is such a broad topic, but there are so many other things that we should be looking at the safety and quality.

That goes to Sara's comments about the source of bulk drug substances and the excipients. So, hopefully, if we revise these chapters and harmonize them, and come up with a standard that is regulated, that we take into account some of these other points.

DR. JUHL: I think that, in some regard, has already been covered in that excipients, by the law, as I recall, need to be USP, I think, ultimately. Is that wrong?

DR. SELLERS: No.

DR. ALLEN: The terminology of the ingredients used for compounding that a USPNF chemical is the required component to use if available. If it is not available, then you use the next highest chemical grade that is available to

you as a pharmacist.

DR. JUHL: Okay.

DR. SELLERS: Any bulk chemical that is labeled USP I believe may give a false sense of security.

DR. JUHL: Well, if they don't earn the USP label, then that is another issue that needs to be addressed.

MR. LaFOLLETTE: And that is true. There is a lot of bulk chemical sourcing and vendors change their process and new solvents are introduced and you can still pass the USP test or other compendias. So it is something that needs to be considered and there are guidelines, as I said, by ICH which encompasses FDA's input in Japan and Europe for residual solvents.

DR. JUHL: Additional comments by the committee on the sterile products question in front of us? If I could ask the International Academy of Compounding Pharmacists, as I have on the other topics, are there issues of science that you would like to address to the committee for their consideration of this category of drugs?

MS. CAPPS: Shelley Capps, International Academy of Compounding Pharmacists. We will address our science concerns in the submission that we provide to the FDA by August 15. Most of our concerns here are legal concerns. Thank you.

DR. JUHL: Okay. Thank you.

Any last words from the committee? Let me try and formulate a question that we can respond to. I am reading from our prepared questions. "Do you agree that the class of sterile drug products that are not compounded in accordance with USP Chapter 1206 should be included on the list of products that may not be compounded because they are difficult to compound properly?"

Let me add the proviso that we would incorporate all of our comments for revisions and modifications of 1206 to meet the standards as we have described them when we are talking about Chapter 1206. So let's put a quote around "USP Chapter 1206" in our discussions. Is that suitable for the committee?

Ready for the question? "Do you agree that sterile products that are not compounded in accordance with 'Chapter 1206' should be placed on the difficult to compound list?" All those that agree, would you please signify by raising your hand.

[Show of hands.]

DR. JUHL: Any opposed?

[No response.]

DR. JUHL: I don't see that. That is unanimous on the part of the committee.

Continuing along. "Is 'Chapter 1206' an appropriate standard? If not, what other standard would you

suggest we use?" The issue of using dual standards has been suggested. Let's make it clear how the committee feels to the agency for their consideration.

Let me phrase it in the singular, as it is, that we would recommend that "Chapter 1206" be utilized as the sole standard but with the hope that we would engage all other standard writers and proposers to participate in the revisions of 1206 so that it could serve as a singular unambiguous standard for the profession.

Is that a suitable question and understandable to the committee? All those that agree with using 1206 as the singular standard, please signify by raising your hand.

[Show of hands.]

DR. JUHL: I see that an unanimous as well.

Are there other comments on standards that need to be included for the record?

Last question, then. "Should compliance with 'USP Chapter 1206' be required for the compounding of relatively low-risk sterile products from sterile components?" I think we need to go back and review the relatively low-risk products that we are talking about and frame the question so that we have a good understanding.

And I don't think I do at this point, so would somebody like to take a crack at that? Larry?

MR. TRISSL: Correct me if I am wrong, but I think

the agency is asking about products that are simple aseptic transfers from one sterile commercial product into another sterile commercial product where the risk of contamination, although present, is very low.

You are asking whether 1206's low-risk category is an adequate standard for those low-risk products; am I correct?

DR. ANDERSON: Correct.

MR. TRISSL: Certainly, I think that 1206's low-risk category and ASHP's, which is very similar, adequately address that issue. They define a level of facility, equipment and training that is common, or should be common, for all sterile product admixtures, low-risk, certainly, and form a basis to build on for higher-risk products.

DR. JUHL: Other comments on this question? Loyd?

DR. ALLEN: It does not address pharmacists' preparation but non-pharmacists' preparation of sterile products, physicians, nurses, whether they are in a health-care facility or whatever, if they do admixtures that the patients--or in a facility nearby, in a physician's office, how would this impact them?

MS. AXELRAD: The only thing that this will cover is compounding as defined in the statute which includes compounding by licensed pharmacists and physicians, as we indicated yesterday, we will address, in our regulations,

and people who compound under the direct supervision of those people, be they nurses or technicians or whatever.

So anybody who is engaged in legitimate pharmacy compounding as defined in the statute in our regulations would be subject to this.

DR. ALLEN: So, basically, then, they would be required to meet 1206. Okay.

DR. JUHL: Would these low-risk kinds of procedures include drying up of a mixture in insulin into a syringe from two vials, for example?

MR. TRISSL: It would seem to me that if it is within the parameters of the official labeling of those products, it does not get included.

DR. JUHL: Right.

MR. TRISSL: That is a nurse drawing it up in the doctor's office for administration or on a nursing unit for immediate administration. But prefilling a hundred syringes and storing them in a clinic for use over the period of the next week or two, that would fall under the parameters of this and that would not be considered non-compounding. It would become a compounding act.

DR. JUHL: I guess the specific question I have occasionally a physician preparing an injectable will add xylocaine or lidocaine along with whatever the product is that they are injecting and do that at the time of

preparation.

Does that fall under this low-risk category?

DR. McBURNEY: I can think of two examples. For instance, when we inject cheloids, which are excess growths of scar tissue, it is not unusual to dilute, sometimes, take kenalog 40, dilute that down to 20. Then some people may add xylocaine to that preparation for the injection to decrease the pain.

Another example would be in treating acne cysts to take kenalog 10 and dilute it down to 3.3 milligrams per cc with sterile water or saline to inject into the cyst.

DR. JUHL: Those are probably outside the official labeling.

DR. McBURNEY: I don't think either of those would be within official labeling.

MR. RUSHO: I think you are also leaving out the emergency department and some of the other areas of the hospital. JCAHO actually has a regulation governing that on products prepared outside the pharmacy. I would rather defer to that when we get into that area because what you are describing here is more what ASHP describes as a level 2. Isn't that right, Larry?

MR. TRISSL: I'm sorry; do you mean like physician offices or something?

MR. RUSHO: Well, no. What he was saying, as far

as making a hundred syringes, or something like that.

MR. TRISSL: Yeah; that would be considered--

MR. RUSHO: Or something in storage, like that. But when you are making it and using it immediately, there are a lot of instances I can think of, ICUs, emergency department, all of those, you make those up. They can be reconstituted antibiotics.

MR. TRISSL: It is the storage issue that gives time for organisms to grow that becomes a problem. Immediate use is not perceived as a problem.

MR. RUSHO: But, if you do that, aren't you getting away from what the USP calls low risk?

MR. TRISSL: I do not recall whether that chapter--Loyd, do you know--addresses length of time. See, the ASP document addresses length of storage because that is a risk factor as well as temperature and all the storage conditions.

I think the USP Chapter needs to address that, if it does not.

DR. JUHL: I guess my concern is the thing that Elizabeth has described; is that compounding, does it fall in the below-risk, and are we making law breakers out of people who do that is the question that I am asking. At least that is my interpretation of the question we are being asked.

DR. ALLEN: Randy, one thing we might look at--incidently, the USP does address multi-day infusions, but we have got to look at the multi-day storage a little bit more. One of the things we might look at in considering, with 1206, would be that there would be a dispensing function as a part of it rather than immediate bedside use or patient-side use.

DR. JUHL: Jane?

MS. AXELRAD: If it is permissible, I think I would like to take the question off the table. I think that we are getting into details here of, you know, what parts of the chapter and how it is going to apply in specific situations that I think can be worked out when we are working with the USP to develop the chapter.

You are getting into things that are very much sort of on the fringes. I think that the advice that you have given us with regard to using the chapter as a baseline to start from is good enough.

I was going to ask if you wanted to take up the question that Dr. Sasich raised instead of this, which is whether compounding of sterile products from non-sterile products should be placed on the difficult to compound list absolutely without regard to Chapter 1206, sort of the opposite.

I thought that it was suggested that the

compounding of sterile products from nonsterile components be placed on the list absolutely without any specific standards.

DR. JUHL: if we put it on the list without specific standards, then we are saying that it is prohibited.

MS. AXELRAD: Right.

DR. JUHL: I think Larry addressed that yesterday that, although it is very unusual, there are situations where pharmacists are faced with the situation of needing to use nonsterile products to prepare a sterile product. Do I recall correctly?

MS. AXELRAD: I was just suggesting it might be useful to have an official word from the committee on that.

DR. JUHL: Are there other thoughts on that question?

DR. ALLEN: I think, in 1206, with the high-risk category, there can be additional emphasis put on some kind of end-product testing or procedures that need to be inherent prior to compounding the products from nonsterile ingredients.

MS. RIFFEE: Randy, if we are not going to consider, then, how the low risk is handled, should that, in fact, appear in the concept paper because there is a full paragraph on Page 7 that talks about low risk in kind of

loose definition.

MS. AXELRAD: I think what I would like to do is leave open the question of how the low-risk products will be handled and discuss it in the context of looking at the chapter and the section on low-risk products and how it would apply. Somehow, everyone will be involved in that. We will be working with the USP on that. If there are issues that need to come back to the committee, we can do that.

DR. JUHL: I think, at least my concern is, we make sure that practices that don't need to be done in a hood--we are not sending every physician down to the hood to make up an injection if the group that, indeed, is a reasonable practice that can be done safely with proper technique outside the hood.

We want to make sure the line is drawn right. I think, as you say, that is something that the details can be worked out. So we don't have to answer that question.

I would like to do two more things before we adjourn. One, your suggestions of potential other topics that should be considered for the difficult to compound list. We have had a couple of suggestions throughout the two days that we could make and you could add to. Sustained-released oral products has come up on a couple of occasions as to whether or not it is possible for a

compounding pharmacist to prepare a sustained-release product that actually is sustained-release and is safe in that regard.

The implantable pellets was raised but I think that is a sterile product and that would fall under that.

CAPT SCOTT: I believe they are sterile.

DR. JUHL: Well, they are supposed to be; yes. Are there other categories or specific drug entities, compounds, that we should consider? Joan?

MR. LaFOLLETTE: I would like to add biotech products to that. We may not be seeing compounding now but it may be something in the future that would come up.

DR. JUHL: Could you give me an example?

MR. LaFOLLETTE: I am just thinking of the type of products, which I am not going to talk about specifics, that we work with that are very sophisticated. The testing is totally different than the kind of testing that we are talking here. It is not even handled by CDER. It is handled by CBER. Usually, that is the way it goes.

DR. JUHL: You are talking about drugs that are composed of proteins?

MR. LaFOLLETTE: Yes; and the storage conditions are probably beyond the scope of most pharmacies, maybe not some hospital settings or universities, but unusual conditions and very sophisticated formulations.

MR. TRISSL: This products are here now. We are compounding them now in our institution for viral vectors, gene therapy. And we have done them in hospital pharmacy settings because that is the only place to do it.

MR. LaFOLLETTE: That is my comment. I didn't know if they were, but it is something that I would like to discuss at a future meeting, possibly.

MR. TRISSL: If it is still in business after all the problems they had.

MS. AXELRAD: We would only be addressing here products that would be regulated under Section 505. To the extent that a biotech product is regulated under I think it is Section 351 of the Public Health Service Act, it is not addressed by the compounding exemption and we wouldn't be addressing those here. But there may be some biotech products that are regulated as drugs under Section 505 that we could consider.

DR. JUHL: Do these include who is in charge of the--you take cells out of a person, treat them and then reinfuse those back into a person. Is that a biologic or is it a drug?

MS. AXELRAD: I don't know the parameters of exactly where that line is drawn.

DR. JUHL: That is one type of biotech where the viral vectors that are being used are all experimental now.

But, at some point, hopefully, something like that will be--

MR. LaFOLLETTE: I think what Jane is getting at is we have had certain products developed and they have to be approved, and sometimes they go through CDER and sometimes they go through CBER. So there could be a differentiation, and that is why it could fall into this area of this committee's responsibility.

DR. JUHL: Dr. Sasich?

DR. SASICH: Larry Sasich, Public Citizen. I would urge the committee to consider looking at antibiotics for children that, in their labeling, are required to be reconstituted by a pharmacist at the time of dispensing, and the reflavoring of those products. This practice is widespread. I have seen nothing to make me feel comfortable that these particular products are stable for their intended use time.

Thank you very much.

DR. JUHL: There is another suggestion. Garnet?

DR. PECK: Although some people may consider it under controlled release, I think enteric coated products should be a separate category.

DR. JUHL: Bill?

MR. RUSHO: There is also some sustained-release suspensions that are being prepared.

DR. JUHL: Any specific drugs as drug compounds,

chemicals? Okay. That is a list that the agency can consider reviewing and taking a look at.

The last thing I would like to do is clean up on our 4-aminopyridine discussion from yesterday. Jane has had some discussions within the agency and has, I think, something to propose that we do to move us on.

MS. AXELRAD: Yes. We have decided that we are going to explore additional ways of making 4-AP available under compassionate use INDs. The paperwork is not very complicated. The chemistry and making sure that the formulation that is being provided to the patient is safe would be the principle issue.

What we would like to do is invite ISTP to work with us on this. We need information about the bulk suppliers. We need information about the formulations that are being compounded. We want to know how many pharmacists are going to be compounding this, how many physicians would be enrolled sort of as investigators--that is sort of the word for it--if there were an IND held, perhaps, by a pharmacist.

And we would like to, perhaps, develop some kind of a model submission that could be used by pharmacists who want to compound this and make it available, that we could make sure that the formulation is safe for the patients who are getting it.

So what we would like to propose is that we would work with ISTP, if they are willing to do it, and develop something like this. We will not take action, a final action, with regard to 4-aminopyridine until we have had a chance to explore this further and will update the committee on progress as we do that.

DR. JUHL: Good. I appreciate your flexibility. Is the Academy willing to enter into at least an exploratory--

MS. CAPPS: Absolutely. We would be definitely willing to work with you on that.

DR. JUHL: Great. Thank you. Comments by the committee? Does that seem like a reasonable way to proceed on that? Are there other issues that need to be brought before the committee before we bid adieu? Tony?

MR. WELDER: Just a comment, since this may be my last meeting with you all. I have enjoyed the meetings. It takes me away from work, and I go to a lot meetings. One of the benefits that I have always said that occurs, for me, is to meet a bunch of great quality people, and this meeting is no exception.

I realize the charge of this committee is making recommendations to the FDA and, of course, safety for the patients is number one. I hope that, in future meetings, that you all are aware that another charge that we have is

making available those special products that a good compounding pharmacy provides.

So I say this is probably my last meeting, and I think an appropriate comment now would be that we all wish our chairman a happy birthday today.

DR. JUHL: I would just as soon avoid it if I could, but thank you very much. I will also suspend my usual modus operandi and not offer time for opposing comments.

Other comments? I would like to thank the FDA staff for their diligence in preparing this meeting for us. I know it is a great deal of work and, after we leave you, you end up with more work. But we do appreciate the efforts. I would also like to thank the members of committee for their thoughtfulness and participation in our meetings. And we are adjourned.

[Whereupon, at 10:30 a.m., the meeting was adjourned.]

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CERTIFICATE

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Lawyer's Notes

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