FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Of:

PHARMACY COMPOUNDING

ADVISORY COMMITTEE

October 14, 1998

Proceedings By:

CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, Virginia 22030
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P R O C E E D I N G S (8:44 a.m.)

Agenda Item: Call to Order/General Introductory Remarks .

DR. JUHL: Well, good morning. Welcome to the inaugural meeting of the Pharmacy Compounding Advisory Committee.

We have a few preliminaries to get out of the way before we get down to business. So, let's attend to those. I would like first of all for all members of the committee to practice with your microphones. Remember, you need to get them close to your mouth when you speak, but not so close that it feeds back, being careful of the water glasses.

I will ask each member of the committee -- everybody at the table -- to identify themselves and their affiliations. We will start with Dr. Rhodes.

DR. RHODES: Christopher Rhodes, the University of Rhode Island.

DR. CATIZONE: Carmen Catizone with the National Association of Boards of Pharmacy.

DR. LA FOLLETTE: Joan LaFollette, Bristol-Myers Squibb, Princeton, New Jersey.

DR. SELLERS: Sarah Sellers, Infusion Pharmacist, Network Pharmacy, Gainesville, Florida.

DR. RUSHO: William Rusho, University of Utah.

MS. MC CLAIN: Anna McClain, retired.

DR. MC BURNEY: Elizabeth McBurney, dermatologist, Louisiana State University School of Medicine.

DR. TRISSEL: Lawrence Trissel, University of Texas, MD Anderson Cancer Center.

MS. TOPPER: Kimberly Topper. I will be the exec sec for this meeting.

DR. JUHL: My name is Randy Juhl. I am from the University of Pittsburgh School of Pharmacy.

DR. PECK: Garnet Peck from Purdue University School of Pharmacy.

DR. RIFFEE: I am Judy Riffee from the College of Nursing, University of Florida, Gainesville, Florida.

DR. ALLEN: Loyal Allen, International Journal of Pharmaceutical Compounding.

DR. RODRIGUEZ: William Rodriguez, Children's Hospital, Washington, D.C.

DR. WELDER: Tony Welder, Dakota Pharmacy in Bismarck, North Dakota.

DR. LIEBMAN: David Liebman, compounding

pharmacist, IACP.

CAPTAIN TONELLI: I am Bob Tonelli with the Office of Compliance in the Center for Drug Evaluation and Research.

MS. AXELRAD: Jane Axelrad in the Center for Drug Evaluation and Research, FDA.

MS. OGRAM: Lana Ogram, Center for Research, FDA.

DR. JUHL: Thank you. Now I would like to call on Kimberly Topper, our executive secretary, for the reading of the waivers.

MS. TOPPER: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made as part of the record to preclude even the appearance of such at this meeting.

Since the issues to be discussed by the committee will not have a unique impact on any particular firm or product but, rather, may have widespread implications with respect to entire classes of products, in accordance with 18 USC 208, waivers have been granted to each member and consultant participating in the committee meeting.

A copy of these waiver statements may be obtained from the agency's Freedom of Information Office, Room 12-A-30, in the Parklawn Building.

In the event that any discussions involving the other products or firms not already on the agenda, for which

an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interests of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

DR. JUHL: Thank you, Kimberly. I will make a few introductory remarks to get us started and review what we hope to accomplish during the next two to three days.

For the guests in the audience, there were handouts of the agenda and a number of things at the door. I hope you had the opportunity to pick those up and give you an opportunity of where we are going.

I mentioned this is a new advisory committee. It is not only new in name, but it is also different than most advisory committees that the agency has.

The more normal activity for an advisory committee is to consider a new drug application where, after several years and $100 million of work, a company brings forward a new drug that perhaps has a 90 percent rate of success compared with 30 percent in placebo, and everyone says it is a wonderful drug and it is a good deal and the advisory committee is kind of the last step in the agency's process

of double checking a new drug application.

While we are real happy about that 90 percent, there is always the 10 percent or 20 percent of people who don't respond to these new drugs.

They may respond because they had the wrong diagnosis, because they had a drug that didn't work for them. They may have been non-compliant with the protocol; they couldn't swallow the tablet; perhaps the tablet or capsule had a dye in it to which they were allergic, it had a bad taste. There may be a number of reasons why this 10 percent didn't respond.

It is that 10 percent, the outliers, the non-responders to normal therapeutic products that are on the market, that we are focusing on today.

Some small portion of that 10 percent may be helped by the extemporaneous preparation of the product by a pharmacist who is skilled in the art and science of compounding. That will be the focus of our activities here.

Pharmacy compounding is an ancient art that has been modernized by many practitioners in the field, and can prove to be a valuable tool to that small group of patients who, for some reason or another, aren't responding to commercially available, well tested, well quality controlled kinds of products.

The pharmacist who does his or her job right in

this area can be of great benefit.

However, there has also been a down side to pharmacy compounding. There are those who perhaps lack sufficient training, skills and equipment to conduct compounding.

The profession has not come forward with a set of standards that has been widely accepted as a whole. That makes it easy for the professional pharma to say, this is how we do things.

There are people who are specialists in the area, but as I said, it hasn't been applied widely.

There in the past have been drug products and drugs of questionable quality and safety that have been dispensed, and there have been some who have hidden behind the guise of pharmacy compounding to conduct what amounts to large-scale manufacturing.

So, we have, as any drug, both the good effects and the bad effects that can stem from pharmacists extemporaneously compounding medication.

It is this contrast of good and bad that have led the profession of pharmacy and the FDA to argue with each other over many years about various aspects of pharmacy compounding.

Into this fray of disagreement, in 1997, stepped the United States Congress. Both sides, along with

Congress, sat down and hammered out some things that will draw a line between pharmacy compounding and pharmacy manufacturing, set some broad general standards about pharmacy compounding and, I think in general, have made a very good starting point to help resolve these conflicts that have existed between the agency and the profession for these many years.

One of the things that was mandated in the Food and Drug Administration Modernization Act of 1997, Section 127, which is pharmacy compounding, is an advisory committee.

That is why we are here today to serve the role of both check and balance and perhaps provide a public forum for dispute resolution on some of the issues that I still know are not entirely resolved between the agency and pharmacy compounders, between the pharmaceutical industry, between certain consumer groups as well.

So, there are a number of issues that need to be resolved. Our role during this initial meeting of the pharmacy compounding advisory committee is to address two issues that were mandated in the act.

One is the bulk substance list, which you will hear much more about today, and the second is the withdrawn for safety and efficacy list which we will talk about, hopefully, tomorrow.

We thought that the way to begin this process was to have those folks who were stakeholders in the negotiations that resulted in Section 127 of the FDAMA, dealing with pharmacy compounding, to have those people come to us today to give us both their view and their history.

Our first speaker today is Kate Lambrew Hull, who is the legislative assistant to Senator Tim Hutchinson. It was through Senator Hutchinson's office that this issue was brought into FDAMA and finalized.

It was, as were all sections of this act, a long and painful process with compromises being given and taken on both sides.

I thought it would be very useful for us to hear the background of how this came about, some of the particular criteria that Congress chose to incorporate into the act.

I think for the benefit of the committee and the audience as well, this will be very helpful in terms of background.

Everyone that I have talked to has said "that Kate Lambrew Hull is the one who is the guru on pharmacy compounding on the Hill.

With that distinction, I would like to welcome you to the panel today and we look forward to hearing from you, hopefully, tomorrow.

Hull, Legislative Assistant to Senator Tim Hutchinson.

MS. HULL: Good morning. As Dr. Juhl mentioned, I am Kate Lambrew Hull and I am a legislative assistant to Senator Tim Hutchinson, who was pretty closely involved in all the discussions and negotiations that led to Section 127, otherwise known as the pharmacy compounding provision of the Food and Drug Administration Modernization Act.

I thought it might be helpful this morning just to take some time to touch upon what Congress' intent was in the crafting of Section 127, especially as this advisory committee is going to be lending its expertise to the FDA in terms of the numerous requirements for the FDA under the provision.

This initiative was born out of concern regarding FDA's treatment, in certain instances, of pharmacy compounding as drug manufacturing, and the resultant fear that all compounding, regardless of circumstances, would be treated as drug manufacturing, which is obviously subject to the new drug provisions, as well as adulteration and mis-branding provisions of the Food, Drug and Cosmetic Act.

It is Congress' view, as Dr. Juhl stated, that pharmacy compounding is a valuable tool in terms of individualized drug therapy, which should continue to be made accessible to patients.

It was Congress' intent, in drafting Section 127,

to provide a safe harbor for legitimate pharmacy compounding activities, as well as to draw a distinction between those activities and drug manufacturing under the guise of compounding, and also to maintain the purview of the state boards of pharmacy over the legitimate pharmacy compounding activities.

In establishing the criteria by which compounding activities would be eligible for this safe harbor, we created a number of requirements, those that speak to the distinction between pharmacy compounding and drug manufacturing, as well as those that speak to the quality of pharmacy compounding.

These parameters can be divided into two categories, as I just mentioned, distinguishing characteristics between pharmacy compounding and drug manufacturing, as well as those that just speak to pharmacy compounding itself.

I am going to take a little bit of time to just run through those requirements, both for the audience's sake and for your sake, although I know you are familiar with the provisions.

As far as distinguishing between pharmacy compounding and drug manufacturing, there are three specific requirements in section 127 that address this issue.

Key to this distinction is that compounding is

done on an individual patient basis. Section 127 explicitly states that legitimate compounding is performed at the unsolicited prescription order of a physician for an identified individual patient.

Conversely, just to give you the other side of our discussion, drug manufacturing, as you know, is generally mass production for unidentified patients.

Also, under section 127, a pharmacy or pharmacist is prohibited from advertising or promoting a certain type of drug, class of drug, although this doesn't prevent a pharmacist or pharmacy from promoting their general skill of compounding.

Conversely, again, drug manufacturers obviously advertise their specific drugs and actively market those to providers.

Yet another key distinction and safeguard against manufacturing under the guise of compounding will be the definition of regularly or inordinate as it applies to quantities of compounded drug products that are essentially copies of commercially available drug products.

The Secretary is charged with defining regularly or inordinate, and I am sure she will be seeking the help of this committee in that regard.

I might just note that there was significant discussion over the meaning of essentially a copy of a

commercially available drug product.

It was, I think, agreed upon, and you can see that in report language, that in a majority of cases, we would defer to a physician's judgement.

However, if there is overwhelming evidence that products are being produced that don't have a very significant difference for the patient, that obviously that will speak for itself. I am sure that will be open to further debate as you consider this.

As far as the quality of compounding, again, it is under the purview of the state. We do set a number of criteria that do need to be met in order to meet the safe harbor requirements under Section 127.

We think this is very helpful in establishing uniform standards of quality for the industry, and there are several of those requirements.

First, there are a number of requirements with regard to bulk drug substances, which obviously is going to be one of the subjects of your deliberation in the next few days.

The first is that bulk drug substances used in compounding must meet one of three requirements. They either have to be a component of an approved drug product, or the subject of a USP or national formulary monograph, or if it doesn't fall into either of those two categories,

recognizing that there are some bulk drug substances that do not, we have created a third category, and that is that they must appear on a list that is developed by the Secretary. Obviously, you guys will have input on that.

Congress was very specific about those substances in terms of what criteria they should be held to, which I will address later.

Yet another requirement for these bulk drug substances is that they must be manufactured by an establishment that is registered under Section 510 of the Food, Drug and Cosmetic Act, or Section 510(1). They also must be accompanied by certificates of analysis.

A separate requirement, as far as licensed pharmacists and physicians go, is that they may not compound a drug product that appears on a list published by the Secretary of products that have been removed from the market due to safety and effectiveness reasons, which is yet another subject that you will be addressing in the next few days.

A drug product cannot be compounded if it is identified by the Secretary in regulation to present demonstrable difficulties in compounding, that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.

I would like to state that the rules set forth in

Section 127 are intended to carve out pharmacy compounding that is distinctly under the jurisdiction of the state boards of pharmacy, while allowing the FDA to do its job, obviously, of regulating drug manufacturing.

Again, we are trying to draw some distinctions to help in this issue area, which has, as Dr. Juhl mentioned, been very ambiguous in the last. few years.

There have been some cases of drug manufacturing under the guise of pharmacy compounding, while there also is very legitimate pharmacy compounding occurring in this country that serves a great deal of patients' needs.

We want to allow that legitimate pharmacy compounding to continue, while allowing the cases of drug manufacturing under the guise of pharmacy compounding to be pursued.

These regulations, again, are not intended to supersede state boards of pharmacy regulations, but rather, to supplement them.

Such regulations, as I just mentioned, will help make clear when the FDA has jurisdiction, which of course would be in cases of drug manufacturing.

Clearly, this will require a cooperative relationship between the states and the FDA, which brings me to the next issue, which has to do with compounded drug products being entered into interstate commerce, which is

yet another issue that is addressed by Section 127, in a section that refers to a memorandum of understanding that is entered into by the states.

Once again, the Secretary will be developing a model MOU. It really is to establish a cooperative framework between both the FDA and the states in terms of responses to out-of-state complaints regarding compounded drug products that cross state lines.

It is also to help clarify to both states and the FDA when which party should pursue a particular case and really, once again, to establish a cooperative relationship between the FDA and the states, which we believe is very necessary to the success of Section 127.

I will note real briefly on the MOU provision that it is not intended to set a floor or a ceiling with regard to the quantity of product that enters into interstate commerce.

However, if a state doesn't enter into an MOU, we do have a requirement. It is that in states that do not enter into MOUS, a licensed pharmacist or physician or pharmacy may not distribute compounded drug products out of state that exceed more than five percent of the total prescriptions dispensed by that pharmacy of physician.

This is, I think, a key issue, because we really want states to enter into this MOU. Again, we want to

foster the greatest atmosphere of cooperation between the FDA and states on this matter. We really want states to enter into an MOU.

Obviously, there are pharmacies and pharmacists and licensed physicians in their state who, if they do not, will be subject to this five percent restriction.

That again brings me to the advisory committee. I thank you all for being here today and taking time out of your busy schedules to focus on this important issue.

The advisory committee, as envisioned under Section 127, is intended to provide expertise on pharmacy compounding to the FDA, and is responsible for requirements that are included in Section 127.

I think this is especially important in terms of development of lists and definitions concerning pharmacy compounding, since many of you have a great amount of expertise on compounding and pharmacy in general.

I think that the FDA has a lot of expertise, obviously, on drug manufacturing. We would like you to supplement their knowledge on this particular issue since, again, it is that 10 percent of patients who are in need of individualized drug therapy.

Hopefully you will bring a pool of knowledge that will help the FDA in terms of the requirements under Section 127,

I understand that the advisory committee will, this afternoon, turn to consideration of the list of bulk drug substances that don't meet the requirements of A, the subject of the USP or national formulary or national formulary monograph, or B, are not components of approved drug products.

I would like to speak to, really quickly, what Congress' intent was with regard to this third category, the list of substances that the Secretary will develop.

Congress has stated very clearly that the bulk drug substances in this category should not be held to the requirements of a new drug.

Congress further stated that pertinent data such as peer reviewed medical literature, documented historical use and, as mentioned in an FDA publication earlier this summer, whether the substances recognized by foreign pharmacopoeias should be a consideration in determining whether a given substance is appropriate for the list and can be used in compounding.

Of course, any safety and efficacy data should not be precluded from consideration, although the likelihood of an abundance of that data is not as high. Of course, it wouldn't be precluded from consideration.

However, we don't want to set the bar so high as to not have any substances on this list, because we intended

that substances will appear on this list, obviously subject to your review.

It is further the intent of Congress that each of the current submissions be thoroughly examined and decided upon on an individual basis.

Surely, each presentation that will be made to you will have varying data and information about the substance, and obviously will require some individual examination and weight .

Surely, we also hope that further submissions of bulk drug substances for inclusion on the list will be considered in a fair and expeditious manner.

In conclusion, I know this is a short presentation, but I am more than happy to answer further questions.

If there is anything regarding the intent of Congress that my comments haven't already addressed, I am always open to questions and your phone calls or any other consultation.

Just to wrap up real quickly, I think this is a provision, as the FDA notes, that required a lot of deliberation and some long discussions and negotiations.

We think that it really strikes a good balance in terms of drawing the line between pharmacy compounding and drug manufacturing.

It also will help both the state boards of pharmacy and the FDA in terms of where to step in, in terms of their jurisdictions.

Again, we are not trying to reduce the authority of the FDA over drug manufacturing. They wholly have that duty.

We also want the legitimate pharmacy compounding activities, which have traditionally been under the purview of the states, to remain that way, with some additional criteria that we have set forth in Section 127, to assure the quality and legitimate purpose of pharmacy compounding.

Again, we think it is a vital component of individualized drug therapy that should continue to be made available. I look forward to your work on implementing Section 127. Thank you very much.

DR. JUHL: Thank you, Kate. Questions? I don't want to hear this afternoon that you really wish you would have asked the question of Kate while she is here. This is the opportunity.

MS. HULL: You know where to find me in case any arise.

DR. JUHL: Let me ask one if I could.

MS. HULL: Sure.

DR. JUHL: Another issue we are going to take up probably tomorrow is the withdrawn for safety and efficacy

list.

On the surface, that appears to require very little judgement because we can rely on past history. Was there discussion about drugs to be included on that list?

Were they just a list of drugs, or was there judgement supposed to be made if perhaps we had a situation where a drug was withdrawn for lack of efficacy but now it is being used for something else.

MS. HULL: I know that there was some discussion of that. Maybe some of the other folks who have greater expertise on that particular area may be able to offer you some more valuable device.

I assume it would be based on the list that has been developed in the past. Surely there may be some circumstances in which there may have to be a judgement made in terms of something that has an irregular history in terms of either being withdrawn for one reason and not the other, or maybe has been put back on the market for another purpose.

Obviously, if it was put back on the market for another purpose, you would think you would consider that.

DR. JUHL: I don't mean to put you on the spot. I guess I was just interested in the intent of Congress, if that was an issue of discussion.

MS. HULL: It wasn't a lengthy issue of

discussion. Thank you.

DR. JUHL: Other questions?

Thanks for making the trip up. I appreciate it.

MS. HULL: Sure.

DR. JUHL: We next have a group of four or five speakers representing organizations that have an interest in pharmacy compounding.

I would ask that the speakers limit their remarks to no more than 10 minutes. I have a handy dandy little timer so that all will be treated fairly, providing that I can operate the timer.

First on our list is John Gans. Dr. Gans is the executive vice president of the American Pharmaceutical Association. I welcome you to the meeting and to the microphone, John.

Agenda Item: Presentations from Invited Speakers.

John Gans, American Pharmaceutical Association.

DR. GANS: Good morning. It is a pleasure to be here.

Just to start out by saying, this is a very important issue. You may not think that compounded prescriptions are significant.

When we began to be challenged by the Food and Drug Administration about whether or not a pharmacist could compound, it was very easy for us to find patients in every

community who were helped very day.

Let me give you an example. If you have ever had someone who has had intractable pain, say from oncology drug, and they have nausea and vomiting, and they have symptoms so bad that they can't even take drugs orally, there is a company now that is available that will compound a suppository and will guarantee the physicians who run the hospice program that within 72 hours the patient will be down below level IV in pain control, which means they can be functional, and all their symptoms will be controlled by the use of a compounded suppository.

There are patients in every community that are allergic to preservatives or ingredients in drug products who can't take the manufactured products, and they have to be in the manufactured products to sustain their shelf lives.

Every day pharmacists compound those products and make them for patients on an individualized basis. It is a critical service, and actually an expanding service, as more and more of us become allergic and become sensitive to ingredients that must be put into manufactured long-term products, so that they can maintain their shelf life.

Probably everybody in this room and on this committee has had a compounded prescription. If you have ever been in hospital and had an IV, usually there is more

than one product within that IV, and that is a compounded drug product.

It is not something that is sort of a side issue or a side bar that is kind of out there. It is mainstream, medical practice and pharmacy practice in this country.

That is why APhA fought for clarification. Over the years there has been basically an erosion of the pharmacist's autonomy in this area.

Historically, although we have prepared all the drug products and manufacturers have come along, the cost of bringing a drug product to the market, the cost of developing dosage forms of products for small niche groups, I practiced for 15 years with long-term care products.

We traditionally would grind up the medicines and put it in the applesauce. Well, we would always have some question whether the patient ate all the applesauce and therefore got all the drug.

so, we would make liquid products for patients, and this still goes on today.

Well, why don't manufacturers go into the process? It is very expensive to make a liquid product. The last time I checked, they had to have a return on their investment to their stockholders.

So, you are seeing less and less of the wide variety of different vehicles and forms that drug products

come in, just because of the cost.

We worked on the modernization act and APhA championed the provision of this panel, because the practice is distinct from pharmaceutical manufacturing.

We know there is a huge lobby out there of pharmaceutical manufacturers who constantly put pressure on defining basically what we do.

I remember talking to a lobbyist who said, well, you know, you pharmacists can do that, but you can't make any money at it. There can't be any economic role in all of this.

I looked at him and said, well, can we do that for you, too, so that when you manufacture products, you can't charge for them either? It just. didn't make any sense.

I think that is the area where we need to maintain the clarity, and that is what is the difference between manufacturing and compounding.

There were three issues, as we saw it. First, from APhA's perspective, compounding is conducted for an individual patient, versus mass production of medications for broad populations.

In fact, that is the only reason that we do it, because we need an individualized product for that patient. Maybe it is an allergy, maybe it is a combination of ingredients.

Number two, patients' needs cannot be met by any mass produced product that is out there. Therefore, pharmacists and physicians need to have these products.

Thirdly, the compounding conducted by, or under the direct supervision, of a health care professional is not the manufacturing of large quantities.

You have to go into a pharmaceutical manufacturing plant to see how drugs are manufactured, all the quality control that they need.

No manufacturer can tell you with a certainty what is in their product, because they don't analyze for every possible contamination or chemical product that could be put in there.

We have recalls every day in this country by the top manufacturers in the world. Don't be scared off by saying, well, you have to have quality control.

When you have one pharmacist compounding a product from start to finish, that is the best possible quality control that you have, because that pharmacist is involved in every step.

In a large manufacturing product, you have people with different levels of education and understanding of the product who are involved.

Distinctions require differences in the quality assurance of products. When the FDA Act, FDAMA, was

approved, the provision on compounding really clarified a lot of areas, I think. It really balanced, I think, the FDA's role.

First, it said the state regulatory boards -- and I am glad we have NABP and Carmen Catizone on this group -- because they have the primary role in regulating compounding.

FDA needs to be concerned with quality of products used, and the distinction between compounding and manufacturing.

Lastly, this committee will be essential in that process, because this area is always growing and changing, as the needs of the American public change on almost a daily basis .

APhA is most interested in providing any information that we can, bringing people forward to help you make the most informed decisions that we can, and to keep this provision available for the American consumer.

There are three key topics as we see it for the committee's discussion. The first is a list of bulk drug products that may be used in compounding. That is essential .

APhA sees this as an ongoing process of the committee to ensure that the patients have access to vital products that are available.

Today, with the internet and availability of information, patients get information from all over the world, and bring it to their pharmacist or their physician to find out if it is available, or if the pharmacist can manufacture or compound that product for the patient.

Number two, the definition of compounded products, the whole issue of regularly and inordinate amounts, must o consider that many compounded products change based upon patient care settings.

For example, in a community pharmacy versus a large teaching hospital, where you may be compounding IVS ahead for 500 patients on a daily basis, versus a nursing home practice or a mail service company, no longer are pharmacies just categorized as little independent community pharmacies.

There are chains of pharmacies. Centralized compounding may evolve to support the pharmacist, where the expertise is available and all the equipment and the right type of room and supply of products would be available.

Lastly, is the interstate distribution of compounded products. Think if you live in the metropolitan D.C. area. The physician writes a prescription in the District of Columbia.

The patient walks over to Virginia. They may get the prescription filled in Maryland and go home to Virginia

or go back to D.C. It is a challenge that I think you are going to have to deal with.

You have the internet and you have information flow across these lines, and patients move around very significantly today.

You will always find, I think for the most part, two or three pharmacies in every major metropolitan area, who focus their practice on compounding. It is almost a specialty practice within the practice of pharmacy.

We think this committee is probably the most important step forward that we have. We urge you to maintain the distinction between compounding and manufacturing in your deliberations.

Remember that this is not a minimal practice of pharmacy. Every day there are millions and millions of doses of compounded prescriptions that are dispensed to patients in this country, everywhere from a lollipop to a compounded suppository for cancer nausea and vomiting, that are manufactured and distributed by pharmacists.

I purposely used the word manufacturing, because I am very comfortable saying that. That is what people basically, when they look and see what we are doing, they don't know what compounding is; the patient doesn't know what that is.

Basically, when you go back and look at it, it

always involves an individual patient and an individual physician and an individual order. It is an individual process for the process.

We think your focus is on assuring that the practice of compounding remains available to the public, and to encourage the profession of pharmacy to do what it needs to do to ensure the confidence of the American public that the products they are being dispensed meet the standards necessary for the quality of treatment. Mr. Chairman, any questions?

DR. JUHL: Thank you very much, John. I appreciate you comments.

Next we have Bruce Roberts. Bruce is with the International Academy of Compounding Pharmacists, and will present the view of that organization. Welcome, Bruce.

Agenda Item: Presentations from Invited Speakers. Bruce Roberts, International Academy of Compounding Pharmacists.

MR. ROBERTS: Thank you. It is nice to be here today. This is a very important. subject to me.

I am a compounding pharmacist at Leesburg Pharmacy, which is about 45 minutes from here, right across the river.

I have been in practice for 23 years. I always considered myself a pharmacist that did compounding. Some

six years ago, I became real involved in the art of compounding, and have practiced with a couple of specialties in the area of hospice care, which is probably the primary thing that brought me to recognize the tremendous need that we as pharmacists and the medical community in general, need the services of the compounding pharmacists. I also do a lot of work in the veterinary end as well.

One of the things that is real important in compounding is that we operate under the triage of the physician, the patient and the pharmacist, all in the loop, and that the services that we provide have to be kept within that triad, so that it is very clear what we are trying to accomplish.

What I would like to talk to you just a few minutes this morning about is to maybe give you an example of a particular case that occurred with me just recently, that kind of brings it down to, what really happens in the independent pharmacy or the community pharmacy, and how compounding is such an important aspect of our practice.

In dealing with hospice patients, the terminally ill -- and we have a population of 100 to 120 patients at any time, we are met with many challenges of that particular patient group.

I had a call recently for a patient, at 2:00 o'clock in the morning, from a hospice nurse that was almost

desperate.

She had a patient who was terminally ill, had bone cancer, tremendous pain, tried many narcotic analgesics. The patient was on, at this point, 200 milligrams of morphine every two hours with no relief, and tremendous nausea, and just was really at wit's end as to what to do.

Family members were just desperate for some type of relief for their mother. So, this was 2:00 o'clock in the morning, I get this call.

We get the physician on the phone, start to talk about what the options are. We know from our work in hospitals that drugs administered rectally in many instances work much better, because you deliver on the first pass.

Specifically, the drug ibuprofin is just a tremendous value if given in a rectal form and works real, real well.

What I suggested to the physician that we try this patient on was 800 milligrams of ibuprofin rectally. What we also know from our work in hospice and from much of the research that is out there, that dextromethoraphan is another drug that is very, very effective at potentiating the effect of not only the non-steroidal but also the narcotic analgesics.

so, we incorporated some dextromethoraphan into this suppository form of ibuprofin.

For the nausea, they had been through things such as promethazine and proclaperazine and they had tried zofran, with very little success.

One of the things that we have had a lot of luck with in hospice patients is a combination of atavan, metclopramide, haloperidol and lorazipam in a suppository form as well, with just tremendous benefits with nausea.

We started this, prepared these dosages for this lady. We put her on this at 4:00 o'clock in the morning. I am finished with this patient. We have got the two daughters of this mother have been with me through this ordeal . They go home to try to see if they can get their mother some relief.

What brings it all together and makes it all worthwhile for the things that we do as compounding pharmacists, the next day afternoon I have the two daughters come back into the store.

Obviously, my first question is how is she doing. They start out with -- these two daughters happen to be nurses who have dealt in the medical profession for years and years.

They tell me, first of all, that they have never ever encountered a pharmacist that did the type of things that we did. They thought pharmacists just count and pour the pills that manufacturers make, give a little bit of

advice, and that is it.

They came to me and said, their mother was out of pain; the nausea had subsided; she was comfortable. They went on to say what a difference that I had made in their mother's life and how much they appreciated it.

She went on and she died a couple of weeks later. I got a letter after that to say what a difference we had made.

That is what compounding pharmacists and compounding can do to make a difference in people's lives, and how important it is to the practice of pharmacy.

There are compounding pharmacists out there all over this country doing these types of things, operating within the triad of the physician, the patient and the pharmacist, making a difference in people's lives.

We have the International Academy of Compounding Pharmacists, of which I am a board member, and proud to be a board member, and proud to be a member of that organization, which sets very high standards.

I am a fellow of that organization. As a fellow, you are required to have a certain amount of continuing education a year in compounding, and it is just real, real important that the art of compounding, which has been around for hundreds of years, continue, and that we continue to meet the patients' needs that are out there.

That is all I have. Any questions I will be glad to answer.

DR. JUHL: Thank you for coming and talking to us today. We have a couple of minutes left over for questions.

DR. RODRIGUEZ: You described to us one aspect of compounding, essentially the use of approved medications, or approved FDA-type list, very creative, very reassuring.

How often do you get to do compounding with products that are not in the mainstream, for example?

DR. GANS: I think of some of the substances that you have before you today and tomorrow that you are going to look at.

One substance that we do a lot of work with that is not in one of the three groups that you are going to have to consider is metronidazole benzoate.

We do a lot of work, as I said, in veterinary medicine, a lot of work in pediatrics as well. If you have a need for a drug like metronidazole. The metronidazole base absolutely is not palatable.

There is absolutely no way that you can get a cat or a dog or a small child to take it. That is one thing -- the metronidazole is basically a tasteless salt of the base and is something that is used a lot.

DR. JUHL: Thank you very much.

Our next speaker is Dr. John Siegfried. John is

senior medical advisor of the Pharmaceutical Research and Manufacturers of America. Welcome to the meeting.

Agenda Item: Presentations from Invited Speakers. John D. Siegfried, MD, Pharmaceutical Research and Manufacturers of America.

DR. SIEGFRIED: Thank you very much and good morning. My name is John Siegfried. I am a physician and the senior medical advisor to the Pharmaceutical Research and Manufacturers of America.

I was also reminded by Dr. Gans' comments that in my more than 20 years of private practice of pediatrics in a suburban Philadelphia community, of the many, many times that I was involved in compounding products and working with both hospital pharmacists as well as community pharmacists, to get formulations that we could use with children, be they the cherry syrup, the chocolate syrup, the applesauce, rectal solutions.

This is a situation that I am personally familiar with for many, many years.

I do appreciate the opportunity and, Mr. Chairman, my comments take 7.3 minutes unless I sneeze or yawn, and we will be fine on time.

I do appreciate the opportunity to provide PhARMA's comments to FDA’s newly established pharmacy compounding advisory committee, on the implementation of the

pharmacy compounding provisions of Section 127.

As the advisory committee and FDA address each of the important issues, they must keep in mind the careful balance that Congress struck in enacting Section 127, namely, to preserve the appropriate practice of compounding based on individual medical needs, identified by the physician and pharmacist, while assuring that compounding is not used to evade the important federal requirements that exist to regulate drug manufacturing and protect public health.

To preserve this balance, FDA should restrict the compounding of a commercially available product to an emergency situation, for example, when a patient needs a prescription filled immediately and the pharmacist has no way to obtain the product from another pharmacy to fill the prescription in a timely manner, without compounding the commercially available product.

In the absence of an identified medical need to compound a product that is not commercially available, or an emergency which justifies compounding a limited quantity of commercial product, there is no longer a public health justification for a pharmacy to manufacture a product.

In addition to limiting the circumstances under which compounding commercially available products is permissible, FDA must rigorously examine claimed differences

between a compounded drug and the comparable commercially available drug product, to determine whether they are essentially copies.

Compounding should not. be allowed based on minor differences between products that do not have clinical significance or medical justification.

Medical justification supporting the need to compound a modified product could include a patient's allergy to some component of the commercial product, such as a color additive, or an inability to use the commercially available provided dosage form -- capsules versus liquids.

FDA should require that the clinical justification for compounding be identified by the prescriber, so that FDA or a state inspector will be able to determine whether the compounded product is different from the commercial product in a medically significant way or just a copy.

For compounded products which are not copies of commercial products, significant concern arises when pharmacists or physicians compounds more than a limited quantity of a product before receiving a valid prescription calling for a compounded drug.

First, when compounding is not based on individual prescription order or an anticipated individual prescription order, the compounding becomes simply manufacturing a product for sale, rather than compounding a product based on

an individual therapeutic need.

Second, the greater the amount of compounded product a pharmacy stores, the greater the concern about product stability.

The stability concern involves both the stability of the compounded substance and the selection of a storage container to avoid storage problems, such as may occur if the product is exposed to sunlight.

In view of these concerns, FDA should set limits of the quantity of drug product that a pharmacy or physician may compound, and require that no product be held beyond the period established by stability data, such as the beyond use dates in the USP's good pharmacy compounding practices.

In addition, no pharmacy or physician should be able to compound in bulk for distribution to other pharmacies or physicians.

The Food, Drug and Cosmetic Act is grounded in the principle that there should not be a clinical use of a substance unless the substance has been reviewed and approved by the FDA, or the substance is generally recognized as safe and effective.

Accordingly, no bulk drug substance that is neither the subject of a USP or national formulary monograph nor an FDA approved drug should be used in compounding.

Allowance for the use of an approved drug

substance in compounding could effectively create an unregulated mechanism for developing and distributing new drugs that would not be subject to the rigorous review that FDA conducts, to ensure that only drugs proven to be safe and effective are given to the public.

To avoid this potentially dangerous scenario, FDA should carefully consider whether it should accept any nominations it receives for unapproved bulk drug substances to be used in compounding, pursuant to the recent notice that FDA published in the Federal Register April 7.

Section 127 also directs FDA to promulgate a list of products that may not be compounded. The following types of products present technical challenges for proper compounding, and should be included on that list: one, modified release products; two, sterile dosage forms; three, narrow therapeutic index drugs for which precision and dosage strength is vital; and four, dosage forms which contain small amounts of potent drugs for which content uniformity or lack of content uniformity could yield either supra or sub-potency.

For other products that may be compounded, good compounding products such as those issued by USP should be followed for all compounding.

The memoranda of understanding that Section 127 directs FDA to enter into with the states should reference

the importance of good compounding practices, and should ensure that the state will have appropriate inspection processes to help enforce the provisions of Section 127.

The memoranda of understanding should also encourage states to consider requiring that accredited pharmacy schools include good compounding practices as part of their required curricula, either in the initial degree training or as a post-graduate course, and that demonstration of competency in the principles and the application of good compounding practices be a necessary prerequisite for engaging in compound, or a component of pharmacy board licensing exams.

As a general principle, there should not be clinical use of a substance unless the substance has been reviewed and approved by the FDA, or the substance is generally recognized as safe and effective.

Accordingly, no bulk drug substance that is neither the subject of a USP or national formulary monograph, nor a component of an FDA approved drug should be used in compounding.

Finally, the FDA should enforce the restrictions in 127 on advertising and promotion of compounding services.

Again, I appreciate the opportunity to be with the advisory committee. PhARMA has previously submitted fuller comments to the docket. Thank you.

DR. JUHL: Thank you for coming today. I appreciate it.

Our next speaker is Deborah Brownstein, director of marketing for Dey Laboratories. You are here representing the generic pharmaceutical industries.

Agenda Item: Presentations from Invited Speakers.

Debra Brownstein, Generic Pharmaceutical Industry.

MS. BROWNSTEIN: Good morning. I would like to mention that my comments are on behalf of the National Association of Pharmaceutical Manufacturers.

We would like to thank the FDA for inviting the generic drug industry to participate in this process, which is so important to many members of our association.

We would like to acknowledge the ongoing work on this issue by our fellow industry associates in the pharmacy profession and in academia.

The issues you are about to address are not as simple as they would assert, and not as complex as others would have you believe.

It is not just about the rights of any one profession over another. This is about the protection of the public safety and nothing else.

Although most university schools of pharmacy have historically and currently continue to teach compounding skills, as well as the premises of good manufacturing

processes, it is our contention that this education is not at a sufficient level to warrant any type of large-scale or broad-based compounding practices that would be designated to meet the exacting requirements of the intention of any university, the GMPs or FDA with regard to the expectations of consistency and quality of prescription and non-prescription drugs.

Traditional pharmacy compounding is something different, and we believe does have its place in pharmacy practice.

The generic drug industry would draw the line clearly at commercially available products which have been approved by the FDA through the NDA or the ANDA process for prescription drugs.

We have experienced first hand the difficulties associated with simply formulating a chemical copy of a product, and expecting it to behave identically to the marketed product.

It does not work that way, and we have proven it time and time again. Therapeutic equivalency, bioequivalency and equivalency in delivery systems are crucial determinations in the development of any prescription drug, and should not be presumed to exist just because of chemical sameness.

Moreover, the issue of chemical sameness cannot be

inferred, but must be proven beyond simple monograph recommendations, including impurity profiles and degradation product characterization.

The generic drug industry has invested billions of dollars in development of scientific methods explicitly for the determinations that two products are, in fact, within a suitable clinical range of sameness.

This is not the same as following a recipe for compounding, and expecting the resultant product to be, in fact, equivalent to anything.

We would call your attention that there is no apparent reason for any pharmacy to compound any commercially available product, prescription or non-prescription drug.

There may be two exceptions to this. One would be a national shortage of a life saving product, a situation which is quite rare, and two would be the motive of profit.

It is this latter reason that you must be very careful of. The real motive for any of us to be in this business in the first place is the protection of patients and cure of disease.

Here is an example of what I hope you will find fault with and devise a system that will ensure that it will not continue to happen as it is continuing today.

A patient contacts a pharmaceutical company to

complain that her medicine made her sick. She has taken a prescription drug manufactured by the company in the past and presumes that she still has that product.

She states she developed a lung infection after taking an inhalation solution and was hospitalized for four days before she recovered.

She returned some of the product that she was taking to the company for investigation. The product was received and evaluated by the company in an independent testing laboratory.

The inhalation solution was packaged in plastic test tubes with friction fit caps, entirely unsuitable for any pharmaceutical liquid.

It was improperly labeled, indicating only the active ingredient, albutyrol sulfate, with no concentration, expiration date or identity of manufacturer.

The physician's name was not on the label. In fact, not all the containers were labeled.

Upon chemical examination, the concentration of the active ingredient among samples tested varied by as much as 120 percent.

Its excipients were detected, but some were unidentifiable . Benzoclonium chloride was detected in some samples at extremely low levels, and not at all in other samples.

Most surprisingly, all samples were infected with pseudomonas species.

Although FDA was informed through the Medwatch program, no action was taken. It was suggested to the company that they contact the Florida state board of pharmacy where the product was made, which they did.

Month later, a letter was received stating the board of pharmacy evaluated the information and decided to take no action.

This is a serious issue. It will either be decided by this advisory group with recommendations by the public or through policy making by FDA, or it will be decided in the courts.

Rest assured, it will end up in the courts anyway, because the issues at hand are, indeed, life threatening.

Although this example is only one of the everyday situations that exist, it is by far not the worst.

We recommend that you consider the following restraints on traditional pharmacy compounding as official policy:

First, pharmacy compounding should not be encouraged or permitted for commercially available product of any dosage form, unless specifically required by the directions for use of the marketed product, and as approved by the FDA.

Specific dosage forms, because of their highly complex nature, and dependency on exacting manufacturing processes and extensive laboratory testing that are necessary to ensure consistency and reliability should be excluded from pharmacy compounding.

These include sterile products, including injections, inhalation solutions, ophthalmic products and irrigation solutions, controlled or sustained release products of any type, antibiotic or anti-infective products of any type, any product requiring the use of an antimicrobial preservative for safety or efficacy purposes, any product prescribed for life threatening illnesses.

Third, no pharmacy compounded product should be permitted in interstate commerce.

Fourth, all pharmacy compounded products should incorporate a label on each individual point of use container, clearly identifying the product to have been produced by the pharmacy and to have been permitted by the attending physician, along with other information consistent with pharmacy practice, according to federal and state regulations.

Fifth, all pharmacy compounded products should be tested for conformance to some agreed-upon specifications, and to meet those specifications through a labeled expiration date.

Sixth, patients must have the right to be informed that a pharmacy is proposing to fill their prescription with a pharmacy-compounded product, and must have the right to refuse such product at their own discretion before it is dispensed.

Finally, the FDA and state boards of pharmacy should adopt consistent definitions of what constitutes manufacturing as opposed to pharmacy compounding, and should prepare to enforce those definitions consistently.

The practice of pharmacy compounding must be differentiated from manufacturing by simple and clearly-defined means.

Large-scale manufacturing is not within the scope of pharmacy practice and should not be treated as the right of the licensed pharmacist. There are more important duties for this profession. Thank you..

DR. JUHL: Thank you very much.

Our last guest this morning before we take a break is Larry Sasich. Dr. Sasich is here representing Public Citizen Health Research Group.

Agenda Item: Presentations from Invited Speakers.

Larry Sasich, Public Citizen Health Research Group.

DR. SASICH: Good morning, and thank you. I am Larry Sasich from Public Citizens Health Research Group.

Health Research Group was formed in 1972 by Ralph

Nader and Dr. Sid Wolf, and we are a research based consumer interest organization.

I am a real pharmacist. I have compounded drugs in community pharmacies. I have prepared sterile products in hospital pharmacies. I have taught sterile technique at the university level and at colleges of pharmacy, and I have an accredited pharmacy in radiopharmacy, where I have prepared sterile radiopharmacy dosage forms.

The deceptively named Food and Drug Administration Modernization Act of 1997, or FDAMA, adds to the continued perversion of what was once arguably the world's gold standard for consumer protection to a level reminiscent of the snake oil era of the late 19th Century.

The pharmacy compounding provision, along with numerous other aspects of FDAMA has, for the first time since the passage of the pure food and drug act of 1906, weakened rather than strengthened the laws intended to protect consumers.

FDAMA, by codifying the FDA's once informal exemption of pharmacist's compounded drugs from the requirements for safety and efficacies that manufacturers must provide, has created a dangerous double drug standard in the United States, FDA approved drugs, and drugs compounded by pharmacists.

Drug-induced tragedies compelled Congress, in

1962, to amend the Food, Drug and Cosmetic Act, to set strict requirements for prescription drug safety and efficacy, based on rigorous science and final FDA review of the evidence.

This was done for one reason, consumer protection. Contributing to the adoption of these amendments was the recognition of two facts: first, the inability of ordinary physicians using uncontrolled observation and anecdote to differentiate safe and effective drugs to drugs that were ineffective or even dangerous; and second, that widespread use of acceptance and use of a drug was proof neither of safety nor efficacy.

The pharmacy compounding industry continues to use the same low standard of analysis used by physicians, that led to the passage of the 1962 amendments, uncontrolled observation and anecdote as evidence.

FDAMA does exempt compounding pharmacists from safety and efficacy standards. Congress and compounding pharmacists cannot alter the fact that rigorous science is the only known method for providing valid evidence that drug products are safe and effective, and that these products will perform consistently.

The assertion that compounded drugs fulfill compelling medical needs is an affront to the public’s intelligence.

There are no compelling medical needs for those compounded drugs that have not been shown to be safe and effective.

The FDA's role in the pharmacy compounding affair has been dismal. The agency shrank from its legislatively mandated responsibility, consumer safety, in the early 1990s, under pressure from the burgeoning pharmacy compounding industry, and pharmacy trade groups best known for their political dogma and self-interest before the public health, and failed to regulate the proliferation of compounded drugs as unapproved new drugs.

Now, FDAMA immunizes pharmacy compounding from FDA regulation and places the public's health in the hands of state boards of pharmacy.

Public Citizen has no confidence that state boards of pharmacy have either the resources or the expertise to adequately protect the public's health from compounding pharmacists.

It is appalling that we were able to fax prescriptions to a pharmacy in Virginia for cyclandelate, a drug whose marketing approval was revoked in the United States in 1997 for lack of efficacy, and for the popular third world brain tonic, piracetam, or otropil.

This is a drug that I have had personal experience with in the third world, having lived in the third world for

five years. This drug is not approved in the United States.

We were informed that. our prescriptions will be sent to us by Federal Express later this week. Unfortunately, because of the Columbus Day holiday, the pharmacist couldn't get the drugs flown in in time.

Equally appalling was the telephone call we made to a compounding pharmacy in Illinois, inquiring about obtaining estradiol pellets for surgical implantation.

To the best of our knowledge, numerous new drug applications have been submitted and resubmitted for estradiol pellets, none of which have been approved by the FDA, presumably for lack of proof of safety and efficacy.

The friendly compounding pharmacist told us that he makes estradiol pellets every day and can ship them anywhere.

It is clear from the above examples that if the profession of pharmacy and state boards of pharmacy took their societal covenants seriously, to protect their consumers from derelict practitioners, it would not have been possible for Public Citizen to obtain drugs that are unapproved or have been disapproved in the United States.

Both cyclandelate and piracetam are nominees from the International Academy of Compounding Pharmacists for inclusion on the list of unapproved bulk drug substances that can be used in compounding.

Reviewing this list has been chilling. Public Citizen looks forward with curiosity to what possible kind of evidence that compounding pharmacists will be present to support legitimate medical needs for these chemicals.

Judging from a number of these nominated chemicals that stimulate or are precursors to acetylcholine, a compelling medical need has been created for brain tonics.

There is no justification for placing the public needlessly at risk by allowing the use of any unapproved drug substances in pharmacy compounding.

The FDA must consider, in developing the list of drugs that present demonstrable difficulties in compounding, that a drug is not a bulk chemical, but a final finished dosage form.

A number of dosage forms are too technologically complicated to be made safely in unregulated facilities not adhering to good manufacturing practice guidelines.

These dosage forms include, but should not be limited to the vast majority of sterile products other than those that are manipulated according to their labeling, inhalation solutions, prolonged, sustained or delayed release dosage forms of any kind, the reflavoring of antibiotics .

Concerning commercially available products, these should not be allowed to be copied by compounding

pharmacists . This places the public needlessly at risk and is nothing more than stealing.

Compounding pharmacists, seeing their survival threatened, alleged because of managed care and low reimbursements, are misusing their professional status to sell unapproved or disapproved products to an unwitting public.

Few options are available to protect the public in the current pro-business anti-consumer environment other than providing the public with sufficient objective information to protect themselves from health care providers seeking their own economic survival.

The National Round Table on Health Care Quality convened by the National Academy of Sciences Institute of Medicine offers the only solution to providing the public with this type of information, its regulation.

They said, and I quote: "regulation is the only mechanism we have to protect the public from egregiously poor providers. "

Public Citizen urges that the FDA require in the pharmacy compounding regulations that an auxiliary label be attached to all compounded drugs saying, this drug has not been tested or reviewed by the Food and Drug Administration for safety and effectiveness, and has not been produced in a facility meeting good manufacturing practice guidelines.

This simple, factual statement will provide consumers with at least some objective information to make an informed decision about accepting or rejecting the risks from pharmacy compounded drugs.

Surely, compounding pharmacists must agree with the public's right to objective information about their drugs, in order to make informed. decisions about their health.

In closing, Public Citizen has communicated to FDA our concerns regarding consumer representation on the pharmacy compounding advisory committee.

FDAMA requires that one member of this committee be a representative from a consumer organization, and this is not the case.

We are concerned that the consumer perspective be adequately represented on this committee for two reasons.

First, there is little public awareness that pharmacists can produce in unregulated facilities products that have not been shown to be safe and effective.

Second, consumers are the only groups whose safety is at risk from drugs that are produced and sold by pharmacists, that have not been shown to be safe and effective, and are produced in unregulated facilities.

For this reason, the FDA's compliance with the statutory requirements regarding the committee's membership

is crucial, and we hope that the situation can be resolved amicably before future meetings of the pharmacy compounding advisory committee. Thank you. Questions?

DR. JUHL: Thank you, Dr. Sasich.

That concludes the list of speakers that we have for the preliminary portion of this morning. To the committee, I think that gives you a snapshot of the disparity of opinion that were in play, that went into the production of Section 127.

Some of the things that were expressed this morning are messages for the agency, perhaps some for Congress and, thankfully, fewer of them to us, as we look forward to our opportunities this afternoon to review the bulk drug list.

We are on schedule and we will, I think, take a break and reconvene at 10 minutes after 10:00.

[Brief recess.]

DR. JUHL: We will reconvene. I apologize for the delay. Dr. Woodcock got caught in traffic somewhere between here and there and we are waiting for her to magically appear. She may yet, but at this point I think we need to go on.

As you may have noticed, I like to keep things on time. So, we will, for the time being, skip over Dr. Woodcock's remark and go to the FDA's overview of the

pharmacy compounding legislation.

Jane Axelrad, associate director for policy in CDER and also the co-chair of the pharmacy compounding steering committee for the FDA will make that presentation. Jane ?

Agenda Item: FDA Overview of Pharmacy Compounding Legislation.

MS. AXELRAD: I am really sorry that Dr. Woodcock isn't here yet. She will be joining us. I know that she wanted to welcome you to the first meeting of the pharmacy compounding advisory committee.

As you know, I am Jane Axelrad, the associate director for policy in the Center for Drug Evaluation and Research.

With me at the table is Lana Ogram and a member of her staff, Bob Tonelli. Lana is the director of the division of prescription drug compliance and surveillance in the Office of Compliance in CDER.

Lana has been working on the issue of pharmacy compounding for many years, and the primary responsibility for this program lies with her division.

At this time, you may have noticed that there are quite a few FDA staff sitting behind us over there. These are the members of the steering committee that the FDA has created to deal with the issue of pharmacy compounding.

I would like to ask the members of the steering committee to introduce themselves and to mention their affiliation within the agency.

DR. JUHL: You will need to move to the microphone, so that you can be heard and the transcriptionist can hear you as well. Any microphone will do.

MR. ROMANI(?): Hello, I am Porico Romani from the office of compliance, division of drug compliance and surveillance. I am a pharmacist. Thank you.

MR. MITCHELL: Wayne Mitchell, regulatory policy staff. I am a regulatory counsel there.

MR. SCOTT: I am George Scott, regulatory operations officer, office of compliance.

MS. ANDERSON: Kathy Anderson, consumer safety in office of compliance, division of prescription drug compliance.

MR. RICHMOND: I am Fred Richmond, a team leader in the office of compliance.

MS. PALACE: I am Luanne Palace. I am a consumer safety officer in the division of manufacturing and product quality in the office of compliance.

DR. JONES: My name is Mike Jones. I am in the office of the center director and I am a pharmacist.

MS. MELAY(?): My name is Yana Melay. I am with

the compendia operation staff, which is the group that liaisons between CDER and the USP.

MR. SCHWARTZBARD: My name is Rick Schwartzbard. I am a regulatory counsel in the Center for Drug Evaluation and Research.

MS. HEINER: I am Betty Heiner. I am with the office of regulatory affairs, Division of Federal/State Relations.

MR. LENISH(?) : I am John Lenish. I am with the office of planning and evaluation, economic staff.

MR. KORB: I am Lee Korb. I am with the regulatory and policy staff.

MR. OSTERBERG: I am Bob Osterberg, toxicologist with the Office of New Drug Evaluation.

MR. HOROWITZ: David Horowitz, associate chief counsel for drugs.

MS. HOFFMAN: Anita Hoffman, office of compliance, consumer safety officer.

MS. AXELRAD: I would also like to mention, Stephanie Gray is also here in the audience. She is the director of the office of compliance. Many of the people who just introduced themselves are part of her staff.

Well, you have heard from the previous speakers that there is certainly a wide diversity of views on the issue of pharmacy compounding.

1 think you got a fairly good feel for the kinds of challenges that are facing the FDA, as we go to implement the Food and Drug Administration Modernization Act, which I will be referring to as FDAMA, since that is the acronym that we in Washington use to refer to that statute.

My task today is going to be to talk to you about where we have been on the issue of pharmacy compounding, where we are today, and where we hope to go in the future on this issue.

Pharmacy compounding has been acknowledged within the agency as a very complex and challenging issue for more than 20 years.

The agency has been seeking to find the right balance between too much and too little federal regulation in this area.

FDA has long recognized the importance of traditional pharmacy compounding, for patients for whom commercially available products are unsuitable or unacceptable.

The agency also recognizes the important role that pharmacy compounding has played in pediatric medicine, where pediatric dosage forms are frequently unavailable.

In some cases, the only way medications approved for adults can be provided to the pediatric population is through pharmacy compounding.

Similarly, in the dermatological area, pharmacy compounding has made available to certain patients customized medicines that otherwise would be unavailable. I think you heard this morning from a couple of the speakers about the importance of pharmacy compounding in pain management for terminally ill patients.

There is cause for concern, however. Some compounding pharmacies have engaged in practices that look more like manufacturing than like traditional pharmacy compounding, and that raise serious public health issues.

For example, one establishment manufactured over 300,000 dosage units of albutyrol sulfate and other inhalation therapies drugs per month for 6,000 patients, many of whom" lived out of state.

These patients were exposed to the risks of an unapproved new drug manufactured without ordinary pharmaceutical quality controls when an approved product was available.

Another company, operating with a pharmacy license, had hundreds of bulk drug ingredients on hand to manufacture 165 different products.

Some of the products had been sitting over a year before they were inspected and 11 products had no recorded manufacturing date at all.

When drugs are compounded in such quantities

without prior FDA approval, without adequate record keeping to retrace and recall harmful products, without appropriate labeling and without adequate manufacturing controls to ensure the safety, purity, potency, quality and identity of the drug product, there is a very real risk to public health.

Traditional pharmacy compounding is regulated by the state boards of pharmacy. To the extent that pharmacy compounding takes place in limited amounts and the compounded products are given to patients generally within the state's borders, the FDA has generally deferred to the state to regulate the practice of pharmacy compounding, and has worked closely with the states when they have requested FDA assistance.

When pharmacy compounding raises significant health risks, however, or is done in large volumes in what are essentially manufacturing facilities, and shipped nationwide, the FDA federal regulatory scheme must take precedence.

For FDA, the challenge has been to draw a line between legitimate pharmacy compounding and inappropriate manufacturing of unapproved new drugs.

Unfortunately, until FDAMA, the Federal Food, Drug and Cosmetic Act did not provide a clear basis for distinguishing between these two situations.

As a result, FDA had to work with the statute and something that the agency calls is enforcement discretion to construct a path for the regulation of pharmacy compounding.

FDA had to decide on a case by case basis whether a particular pharmacy was engaging in compounding, or whether it was engaging in practices that raised the kinds of concerns associated with manufacturing and, therefore, was subject to the new drug adulteration, misbranding, and registration requirements of the act.

In 1992, the FDA issued a compliance policy guide, describing certain factors that the agency intended to use to assist in distinguishing between appropriate pharmacy compounding and inappropriate manufacturing; for example, compounding regularly, or in inordinate amounts, drug products that are essentially generic copies of commercially available products, or using commercial scale manufacturing or testing equipment for compounding drug products.

You might notice some of these words are familiar. I was interested, when I was going back over the compliance policy guide, how many of the concepts that are incorporated in the legislation actually were being discussed and considered as part of FDA policy even before the statute was passed.

The compliance policy guide indicated that regulatory action would be taken when pharmacy practice

extends beyond the reasonable and traditional practice of a retail pharmacy, by extending into practices that are normally associated with manufacturing, and that result in significant violations of the new drug, adulteration or misbranding provisions of the act.

Even as it issued the compliance policy guide in 1992, FDA recognized that regulating in this area through case by case enforcement actions, might not be the best way to go.

FDA recognized that legitimate compounders were concerned that FDA might choose to take enforcement action against them because they were unclear how FDA would draw the line when it applied the factors in the compliance policy guide.

FDA decided that it would be appropriate to promulgate a regulation to describe when legitimate pharmacy compounding crossed the line into inappropriate manufacturing of unapproved new drugs.

FDA was in the process of preparing an advance notice of proposed rule making to define more clearly a safe harbor for certain pharmacy compounding, when the issue of compounding was introduced into the legislative discussions that produced FDAMA.

I know Kate went over some of the sections of the statute this morning. I am going to go through them again,

perhaps in a little bit more detail. I think we need to go through them because they lay the foundation for the discussions that are going to follow, particularly on the list that we are going to be discussing later today and tomorrow.

FDAMA Section 127 added a new section 503(a) to the Food, Drug and Cosmetic Act, which provides the framework under which the FDA can distinguish between legitimate pharmacy compounding and inappropriate manufacturing.

Section 503(a) exempts pharmacy compounding that meets certain requirements from the new drug provisions concerning approval of drugs under new drug applications, from an adulteration provision concerning the manufacture of drugs consistent with good manufacturing practices, and from a misbranding provision concerning the labeling of drugs with adequate directions for use under certain circumstances .

To qualify for the exemption, drug product must meet certain requirements. First, the drug product must be compounded for an identified individual. patient.

Second, the product must have been compounded based upon the unsolicited receipt of an unsolicited prescription order.

The word unsolicited is added here to prevent

manufacturing pharmacies from calling physicians and suggesting that they prescribe or substitute compounded products for economic rather than medical reasons.

It was believed that this type of practice would circumvent the important relationship between the patient, the physician and the pharmacist, and increase the volume of compounded products to unacceptable levels.

The statute does provide that a notation on a prescription order, that a compounded product is necessary for an identified patient is acceptable, if the notation is approved by the prescribing prescription.

This was included to address the situation when a patient goes to fill a prescription and the patient and the pharmacist determine that the prescription as written is unsuitable for the patient because, for example, a patient is unable to take the prescribed dosage form.

Third, the provision requires that compounding be performed by a licensed pharmacist in a state licensed pharmacy or by a licensed physician.

This provision brings the third important part of the equation, the particular expertise of a licensed practitioner to compound drug products into the statute.

The next part of Section 503(a) was written in recognition that some pharmacies compound quantities of a drug product in advance of receiving a prescription order

for the product, because experience has shown that the pharmacy received a certain number of prescription orders for the drug on a weekly or monthly basis and, in some cases, compounding a batch of the drug is more practical and convenience.

FDA recognizes this practice and has observed, in some cases, it may be better from a quality control standpoint to make limited quantities in larger batches less frequently, as long as the patient/physician/pharmacist relationship exists and the compounded products are likely to be dispensed within a reasonable time after manufacture.

Therefore, section 503 (a) allows compounding in limited quantities before the receipt of a prescription, based on a history of receiving such orders, and generated solely within an established relationship between the pharmacist, the physician and the individual patient, or between the pharmacist and the physician who will write the order.

In our general regulations, implementing section 503 (a), FDA will have to define the term limited quantities.

To qualify for the statutory exemption from the new drug adulteration and misbranding provisions, compounding under section 503 (a) must also meet certain other requirements.

Some of the most important requirements specified

in 503 (a) are those that are designed to ensure the quality of the bulk drug substances used in compounding.

Bulk drug substances are the substances that are generally considered to be the active ingredients in the finished drug product.

These are the substances that are the most important in making the product effective.

Under section 503(a), bulk drug substances used in compounding must be incompliance with an applicable USP or national formulary monograph, if one exists, and the USP chapter on pharmacy and compounding.

If no monograph exists, it must be a component of a drug approved by the Secretary.

If none of these requirements is met, it must appear on a list of bulk drug substances that may be used in pharmacy compounding, the list that is to be developed by the Secretary and regulations.

This list of bulk drug substances is one of two lists that we intend to discuss with you during today's meeting.

The statute directs FDA to develop the list in consultation with the United States Pharmacopoeia Convention.

The statute also states that the criteria for identifying such substances shall include historical use, reports in peer reviewed literature, or other criteria that

the FDA may identify.

I would like to briefly discuss the category of bulk drug substances that are components of FDA approved drug products.

Since the passage of the 1962 amendments to the Food , Drug and Cosmetic Act, the standard for approval of new drugs requires a demonstration of both safety and effectiveness .

Drug products that meet the standard have an FDA approval, in effect, and are generally listed in the publication entitled, Approved Drug Products for Therapeutic Equivalence Evaluations, commonly referred to as the orange book .

FDA intends the orange book to serve as a reference source for compounders, to identify FDA approved drugs for the purposes of determining whether a bulk drug substance is a component of an FDA approved drug.

Drug products that were discontinued from marketing before the 1984 amendments to the Food, Drug and Cosmetic Act, are not listed in the orange book however, even though they may still have approvals in effect; that is, approvals not formally withdrawn by FDA.

When necessary, compounders will be able to ask the agency whether a particular drug product that does not have a current USP or national formulary monograph, and does

not appear in the orange book, is nevertheless an approved drug for compounding purposes.

Returning now to the new statutory scheme, section 503(a) contains other provisions that are designed to ensure the quality of bulk drugs used in pharmacy compounding.

Bulk drugs used in pharmacy compounding must be manufactured in an establishment that is registered by FDA, and they must be accompanied by a valid certificate of analysis.

This provision is designed to ensure that FDA will know about, and periodically inspect facilities that manufacture bulk drug substances used in pharmacy compounding, to safeguard the quality of those substances.

The requirement that the bulk drug substance must be accompanied by a valid certificate of analysis is designed to ensure that the pharmacist who purchases a bulk drug substance for use in compounding has assurance that the substance meets the specification it purports to have, that will help ensure the quality of the final dosage form.

A certificate of analysis is a document that shows that the substance has been tested in accordance with certain specific tests often described in USP monographs, if one exists for a particular substance, and that the substance meets certain specifications which also may be described in a USP monograph.

For example, a product might need to be of a certain potency and purity. The certificate of analysis will show that it has been tested and shown to meet the specified standards.

These are the main requirements in section 503(a) applicable to bulk drug substances. I am going to turn now to the requirements for other ingredients in pharmacy compounding.

The statute specifies that these other ingredients, sometimes known as inactive ingredients or excipients, must comply with an applicable USP or a national formulary monograph if one exists, and the USP chapter on pharmacy compounding.

These inactive ingredients include substances such as starches, preservatives and binders. These, too, must be of sufficient quality to produce a finished dosage form that is of high quality.

section 503(a) includes four additional restrictions on pharmacy compounding to qualify it for the exemptions under the statute.

Drug products that appear on a list of drug products published by the FDA in the Federal Register that have been withdrawn or removed from the market, because such drug products or components of such drug products have been found to be unsafe or non-effective, may not be compounded

under the exceptions provided in Section 503(a) .

A proposed rule containing this list was published for comment last week. This is the second list that we will be discussing with you in some detail later in this meeting.

FDAMA also specifies that drug products that are essentially copies of commercially available drug products may not be compounded regularly or in inordinate amounts.

The terms regularly and inordinate are not defined in the statute, and they will be a challenge for us to define in our general regulations on pharmacy compounding, especially since I am sure that there will be a diversity of views on this issue, as well as on the other issues that we will be discussing.

The statute does provide that essentially a copy of a commercially available drug product does not include a drug product in which there is a change made for an identified individual patient that produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.

The legislative history on this section makes it clear that the compounded product must be significantly different from the commercially available product.

This does not include, for example, minor differences in strength that are not known to be

significant, or instances in which the prescribing physician is receiving financial remuneration or other financial incentives to write prescriptions for compounded products.

The third restriction on compounding provided in the statute is that a drug product may not be compounded if it is a drug product that presents demonstrable difficulties for compounding that reasonable demonstrate an adverse effect on safety or effectiveness.

Some drug products may require special consideration during production to ensure a safe and effective product.

FDA is working to identify those difficult to compound drug products, and will. consult with this committee about this issue at a future meeting.

The fourth restriction in section 503(a) , which several of the speakers mentioned this morning, is that a drug may be compounded under the exemption only if the compounding pharmacy, pharmacist or physician does not advertise or promote the compounding of any particular drug, class or drug or type of drug, although they may advertise the compounding service provided by the pharmacist or physician.

This provision is designed to preserve the three-part relationship between the individual patient, the physician and the pharmacist, and allow physicians to make a

judgement about whether a particular compounded product is necessary for a particular patient, without outside influence.

These are the major provisions in the statute that affect issues that we intend to bring to this committee.

In addition to these provisions, the statute also has a provision that addresses the compounding of products that are to be shipped across state lines.

The statute provides that to qualify for the exemptions in section 503(a) , a pharmacy's compounded drug products, shipped interstate, may not exceed five percent of total prescription orders dispensed, unless the state in which the compounding occurs has entered into a memorandum of understanding with FDA that adequately addresses the distribution of inordinate amount of compounded drugs interstate, and provides for an appropriate evaluation of complaints concerning such compounding.

FDA has been directed to develop a standard memorandum of understanding, in consultation with the National Association of Boards of Pharmacy that may be used to define the safe harbor.

This document is under development and a draft will be published for public comment. However, because this issue involves regulatory rather than science and technical issues, at this time the FDA does not intend to bring this

document before this committee.

That concludes my summary of the statutory scheme established under FDAMA for pharmacy compounding. As you have heard, FDA has five major tasks to complete: develop a list of bulk drugs acceptable for compounding; develop a list of drugs that may not be used in compounding because they have been withdrawn or removed from the market, because they have been found to be unsafe or ineffective; identify drug products that present demonstrable difficulties for compounding; develop a standard memorandum of understanding that can be entered into with the states regarding the interstate shipment of compounded products; develop general regulations to assist in the implementation of this section.

We will be consulting with the advisory committee before issuing regulations on the first three items, and we may bring to the committee's attention certain other technical issues that arise during the process of writing the regulations.

Before I conclude, I would just briefly like to explain to you a little bit about the regulatory processes that we will be using to issue the documents that we are going to be discussing at this meeting.

This should help the uninitiated among you to better understand some of the terminology that may be used during the upcoming discussions.

As you know, the statute directs us to issue several of the lists that I have mentioned as regulations.

The agency has decided to do this as it normally does, by notice and comment rule making.

Under this process, the agency must first write a proposed rule and then publish it for comment in the Federal Register, where all agencies are required to publish certain official documents, such as rules and notices. Then the final rule is published.

A proposed rule contains two parts, the codified language that is the actual rule that will be published in the code of federal regulations, and the preamble, which is the explanatory material that accompanies and explains the proposal.

If you look at the Federal Register notice containing the list of products withdrawn or removed from the market because they have been found to be unsafe or ineffective, you will see that the agency is proposing a new part 2-16, containing the pharmacy compounding regulations.

The list of drugs withdrawn or removed from the market will appear at section 2-16.24.

This document has a 45-day comment period. At the end of the comment period, the agency will finalize the rule.

It will evaluate the received comments in the

preamble to the final rule, explaining in the preamble why it agrees or disagrees with them. It will then publish the final rule in the Federal Register.

The agency may decide to finalize only part of the proposal, in this case, only some of the products on the list .

It could decide to reserve action on some of the products or seek additional public comment on them.

The same procedure will be followed for the bulks list. In that case, however, in order to make the draft available for discussion at this meeting, we have taken a rather unusual step of publishing a notice of availability of a preliminary unpublished draft, consistent with our regulations .

This document went on display yesterday at the Office of the Federal Register and should be posted on our web site today.

Once the official draft of the proposed rule is published, we will have a public comment period, and then publish the final rule in the Federal Register.

If we don’t have enough information to list a particular substance in the final rule, nominators will be permitted to submit additional information and we can consider it in the next cycle in the rule.

We expect both lists to evolve more frequently

than most rules because a drug product may be withdrawn from the market at any time and added to the list, and because we expect to receive additional bulk drug nominations once people become familiar with the process.

Finally, in addition to regulations, in some of the discussions at this meeting, we will be referring to certain other types of Federal Register notices.

The first is a notice of opportunity for hearing, or NOOH, which is the notice published in the Federal Register that provides the holder of an approved new drug application notice that the agency intends to initiate administrative proceedings to withdraw the approval of the application, and informs the applicant of his or her right to a hearing.

The second type of notice is the notice of withdrawal of approval of an application, which gives notice to the applicant and other interested parties, that the approval of a new drug application or abbreviated new drug application has been withdrawn.

This notice may be published after an applicant has requested that the agency withdraw approval of its application, after an applicant has refused to respond to an NOOH, or after an administrative hearing.

Once such a notice has been issued, the drug is no longer considered to be approved.

These terms will be used when discussing the documentation supporting the list of withdrawn products. They are also relevant to discussions of the bulk list, to determine whether the bulk drug substance is a component of an FDA approved drug product.

I am looking forward to our discussions over the next few days and to hearing from you and getting your advice on some of the very difficult issues that we have before us. Thank you.

DR. JUHL: Thank you, Jane. Are there points of clarification or questions that the committee has at this point?

If not, we will move forward. I would like to welcome Dr. Woodcock. We are glad you made it here. You will no longer be giving introductory remarks, but we look forward to your remarks anyway. You may use that microphone or the podium, as you wish.

Agenda Item: Introductory Remarks.

DR. WOODCOCK: Thank you. I am going to be very brief. First, let me apologize for being late. I was at another meeting that ran over.

I primarily want to thank the members of the committee for helping us embark on what is really a historic effort.

As you know, the agency has been wrestling with

the issue of pharmacy compounding for a very long time, and we have been unable in the past to work out a solution that met the needs of the various constituents, and really was a satisfactory solution to this issue.

We had legislation last year, as you have heard, that lays out a framework and requires us to implement it. This really is an historic effort, I think.

It won't be easy, though. We, within FDA, solve many regulatory problems on our own, but this one really proved intractable.

Although we do have a legislative framework, the details of how this is going to be implemented, I think, still remain controversial.

I really appreciate all of you volunteering and being willing to serve on this committee. I think we will be using your assistance heavily in thrashing out the details of how we are going to implement the different parts of the statute.

So, I look forward to the proceedings. I am going to try to be here as much as I can during the next two days, to make sure I hear all the input.

We already heard from many different stake holders. There are many different points of view about how this should all be implemented. So, your collective wisdom is going to be extremely valuable to us in coming up with a

solution that meets the needs of public health, as well as the other needs that are on the table. So, thank you very much.

DR. JUHL: Thank you, Dr. Woodcock.

We will begin now to move to the bulks list. We will do this, I guess, in a couple of parts. First of all, there are criteria by which the bulks list was developed, the proposed bulk list.

First, Bob Tonelli will provide us with an overview of the criteria. We will then allow for discussion amongst the committee members on that topic.

I should add, for the purpose of the public, yesterday at our orientation meeting, we did have an introduction to the law itself, but we scrupulously avoided discussion of the topics we need to discuss here in public today, having our hands slapped several times by the executive secretary.

The committee was ready to discuss then, but we did not because we need to do that here.

After Bob gives us an overview of the criteria by which the drugs were developed, we will allow for discussion amongst the committee.

After lunch, we will go to the list itself. There are four classifications of these drugs. Bob will present these from the agency's perspective. Gina Ford, from the

Academy, will make a presentation as the nominator of the drug, and then we will discuss each either category or individual drug as the committee wishes.

That kind of outlines the rest of today and perhaps on into tomorrow. It will take us a few seconds to get the presentation up and ready, but Captain Tonelli, whenever you are ready.

Agenda Item: Criteria for Selection of Bulk Drug Substances for List.

CAPTAIN TONELLI: Good morning. My name is Bob Tonelli. I am a regulatory operations officer in the office of compliance in the Center for Drug Evaluation and Research.

This morning's talk is to present the criteria used to evaluate the bulk drug substances. Forgive me for any parts of this that are repetitious, but part of this has to come in from what you already heard from a few speakers this morning. I will try not to be too repetitious.

The Food, Drug and Cosmetic Act, as amended by the Food and Drug Administration Modernization Act of 1997, FDAMA, becomes effective November 21, 1998.

This act provides for certain exemptions from adulteration, misbranding and new drug requirements. To qualify for the exemptions, compounded products must satisfy several important conditions.

One of these conditions restricts the universe of bulk drug substances that a compounder may use.

Under FDAMA, a bulk drug substance used in compounding must fall under one of three categories, if the compounded product is to qualify for the exemptions.

First, it must comply with an applicable United States pharmacopoeia, USP, or national formulary, NF, monograph if one exists, as well as the USP chapter on pharmacy compounding.

Second, if such a monograph does not exist, it must be a component of an FDA approved drug. Third, if a monograph does not exist, and the bulk drug substance is not a component of an FDA approved drugs, it must appear on a list of bulk drug substances that may be used in compounding which FDA develops and issues through regulations.

The statute states that the Secretary shall include in the regulations the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify. It is this list and the requirements that we are discussing in this meeting.

For purposes of construing the statutory provision, the term bulk drug substance is defined in FDA regulations to mean any substance that is represented for use in a drug and that, when used in the manufacturing,

processing or packaging of a drug, becomes an active ingredient or finished dosing form of a drug, but the term does not include intermediates used in the synthesis of such substances.

FDA solicited the participation of all interested groups and individuals by publishing a Federal Register announcement on April 7, 1998, inviting nominations of bulk drug substances for inclusion on the list.

In response to this request, FDA received nominations from pharmaceutical manufacturers, pharmacy associations and individuals. Nominations were received for 38 different substances.

Of the 38 nominated substances, nine are the subject of a USP or NF monograph, or are components of FDA approved drugs.

Therefore, these nine substances already qualify for use in pharmacy compounding under the act, and the FDA did not evaluate these nominated substances any further.

The nine substances are clotrimazole, fluocinonide, hydrocortisone, hydroquinone, pramoxine, quinacrine hydrochloride, salicylic acid, tretinoin, and triamcinolone.

The remaining 29 nominated substances have been evaluated by FDA to determine whether they are appropriate for inclusion on the bulk drugs list and, therefore,

appropriate for use in general pharmacy compounding.

FDA assessed the nominations it received against three evaluation criteria. The first was the chemical characterization of the substance, second, the safety of the substance and third, the historical use of the substance in pharmacy compounding.

These criteria, as well as the bulk drugs list which you will hear later itself, were developed by FDA in consultation with the United States Pharmacopoeia Convention.

In evaluating the nominated substances under these criteria, the agency engaged in a balancing test. No single criterion was dispositive, nor was each of these criterion given equal weight.

Rather, the agency considered the totality of the circumstances and tried to balance all the information at its disposal.

The first criterion, the chemical characterization of the substance, addresses the purity, identity and quality of each substance.

FDA used this information to gauge whether the substance could be identified consistently based on its chemical characteristics.

The characteristics included such identification factors as the assay of the substance, its chemical formula,

its melting point, its appearance -- that is, its color, form such as a powder or a crystal, and its volubility.

If a substance could not be well characterized chemically, this factor weighed against its inclusion on the bulk drugs list because there could be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the agency.

Under the second criterion, FDA addressed the safety issues raised by the use of each substance in general pharmacy compounding.

This evaluation proved both difficult and unique because none of the nominated substances has been thoroughly investigated in well-controlled animal toxicology studies, nor are there any well-controlled clinical studies in humans to substantiate their safe use.

The agency, therefore, had at its disposal either none or very little of the type or quality of information about the nominated substances that is ordinarily required and evaluated as part of the drug approval process.

Under the third criterion, the historical use of the substance in pharmacy compounding, FDA considered the length of time the substance has been in use in pharmacy compounding, the medical conditions it has been used to treat, and how widespread its use has been.

This factor weighed in favor of list inclusion for nominated substances that have enjoyed long-standing and widespread use in pharmacy compounding for a particular indication.

Evidence of both widespread and long-standing use for a particular indication was viewed by the agency as indicative of the substance's perceived usefulness and acceptance in the medical community.

Fraudulent or quack remedies would likely be excluded by this historical use factor from inclusion on the bulk drugs list, because the practice of compounding such drugs is not expected to have been sufficiently prevalent and long standing.

This concludes my discussion on the criteria used to evaluate the nominated substances. This afternoon I will discuss the information and the sources of information used for our assessment under these criteria as well as discuss the assessments themselves.

We would like to ask the committee to comment on the criteria that we are proposing to use. Thank you.

DR. JUHL: Open up to the committee for discussions or questions of Captain Tonelli about the criteria.

DR. RODRIGUEZ: Length of use, how was that determined? In other words, how did you arrive at that?

CAPTAIN TONELLI: We used literature sources and we looked back at the peer reviewed literature sources as far back as we could go.

We considered them past 1980 and so forth. If we could find a history of use beyond there, we considered that a good history of use.

DR. JUHL: To follow up on that criteria, using historical use would seem to freeze in time those drugs that would be available for pharmacy compounding.

How would the criteria apply where something that, say, was well characterized but it came along yesterday?

CAPTAIN TONELLI: Under these criteria, that probably would not have been applicable. We would think that such compounds, if they were to be used in compounding, could still be under clinical research, and we did not want to actually include things that were being researched today, as clinical research, to preclude an NDA provision.

DR. LIEBMAN: Did you take into account the thought that, with more compounding pharmacists, physicians might be more predisposed to start compounding, now that they have the availability of having that occasion for their patients?

You won't have a long history of literature, but you may have a fair amount of anecdotal information or just experiential data.

CAPTAIN TONELLI: We did not take that into account. What we tried to do was use peer reviewed literature. That is the only source we really had for actually looking at these articles.

The anecdotal evidence that you are talking about we wouldn't have any evidence of. There was no way for us to see it. The submitter did not give us that evidence, if they did.

DR. JUHL: You also used other pharmacopoeias as one source of information?

CAPTAIN TONELLI: Martindale's was looked at, the British Pharmacopoeias was looked at. Some of the submissions actually had data, the pharmacopoeias, and yes, it was looked at.

DR. TRISSEL: How would the literature in foreign journals, that may establish some extemporaneous use for a product, be viewed in supporting, for example, a new drug that would be coming before the committee? Would this be a way that the practice could be established?

CAPTAIN TONELLI: It could be. If we could get translated articles from those journals -- we did have some articles that were from foreign journals, obviously. They had to be obviously English translations into one of the Medexes that we looked at. They were considered.

DR. JUHL: Other questions or comments?

DR. MC BURNEY: I am aware, Captain, that there is a reporting system for adverse drug reactions to the FDA by individual physicians or patients.

Was that data looked at when looking at safety of these drugs on the bulk drug, or are those drugs part of that adverse reaction reporting system?

CAPTAIN TONELLI: In actuality, we did look at that data base. We actually found that none of these were hit on that particular data base.

The problem there is that compounded drug does not require reporting. If the adverse reaction happened to have happened to a patient or a pharmacist, there is no requirement to report that to the FDA.

We don't know if that actually was because we just don't have reports, but none were found.

DR. WOODCOCK: Maybe I can add to that. Much of the reporting, although we have the Medwatch system that allows for direct reporting by health professionals, much of the reporting right now is done by manufacturers who market pharmaceuticals.

There are several reasons, partly the lack of a regulatory scheme in the past where people would feel comfortable reporting adverse reactions to compounded products to the FDA, as well as there is no manufacturer in these cases who is under an obligation to report to the FDA.

I think those things combined obviously made it very unlikely that we received those reports on compounded drugs.

DR. JUHL: In the Medwatch program or I guess in the USP program, is there an explicit inclusion of compounded medications and could we do that?

Is that subject to regulation or is that something that could be encouraged as part of an educational process?

CAPTAIN TONELLI: I am sure we could do that as an educational process. I don't know if we could do it regulatorily.

DR. ALLEN: USP has developed a form for an item that is compounded that may have a physical difficulty with, that the pharmacist can then report that to the USP for investigation; not necessarily an adverse drug reaction, but rather, primarily a physical problem that might be associated with a product that was prepared according to the USP guidelines.

DR. JUHL: I think there are a number of educational issues that we have seen that need to be done within the profession. I want to add that to a list of things that need to be publicized better.

DR. RODRIGUEZ: I am also wondering about chemical characterization, since there may be various manufacturers of a bulk substance.

Essentially, you may have adverse or no activity from some and you may have good activity from others. How do we, or how are we planning to ensure that there be some sort of consistency from one to the other?

CAPTAIN TONELLI: The rest of the regulation concerning bulk drug substances states that it has to come from a registered establishment. So, the establishment has to be registered by FDA. The assumption there is that it would be inspected by FDA.

It also has to be accompanied by a certificate of analysis. That should actually assure that what they are getting is what is on that certificate.

DR. TRISSEL: Can this committee encourage USP to review these for possible inclusion at some time as a USP product?

DR. ALLEN: That is one of the options that the USP has, and we probably will be looking at some of the items for developing monographs for them, as they are accepted onto the bulk drug substance list.

DR. LA FOLLETTE: Are any of the compounds that we are to look at today, are they in the process of going through the USP monograph or not?

CAPTAIN TONELLI: I am not prepared to answer that . Joe Valentino is in the audience. He may be able to answer that.

DR. JUHL: You will have to come to the microphone. If I could ask you to identify yourself for the record?

MR. GRADY: Tim Grady, U.S. Pharmacopoeia. U.S. Pharmacopoeia, with extensive discussions with the Food and Drug Administration and, of course, our advisory panels, will be developing monographs right now.

We are currently working on metronidazole benzoate which is already in the British pharmacopoeia. We have been in contact with them. They also have been asked to develop a monograph for the suspension, at least in the last couple of weeks. We will be doing that.

We are also looking right now, we just finished collecting the data on myrrh, the very confusing data on the nine or ten species, and sources of commerce and the old Arabian distribution system and all of that. That will be a very interesting challenge.

In answer to your question, Dr. Trissel, the USP are the public standards and you, indeed, are the public. If you say there is something that needs to be done that is consistent with what the FDA is allowing to appear in the marketplace, then USP ought to do it.

DR. JUHL: I wonder if you could, for the uninitiated, give a brief description of the USP monograph process.

MR. GRADY : The USP monograph process allows recommendations to come from anywhere, consistent with being a public standard -- from industry, university, compounding pharmacists, other pharmacopoeias. We have an arrangement with a couple of pharmacopoeias in Latin America.

so, we would develop a monograph. We publish in our periodical, Pharmacopoeia Forum, for public comment, so that everybody has a chance to say something. We don't play surprise, gotcha.

After a public comment period and the comments are resolved, then things go on to an official publication, which is a supplement, and that is available both print and electronic.

In the case of compounding pharmacy monographs, all compounding pharmacy monographs being published in Pharmacopoeia Forum are being done in our home laboratory with a stability study in our own laboratory, to support the work of the compounding pharmacy panel.

There are a number -- eight or nine of them already -- out there, that people can take a look at the data that is going to support the adoption of these monographs .

Right now it is open ended. As long as the pharmacy compounding panels recommend individual monographs to USP, they will be processed.

I should say that, in looking at what originally looks interesting, sometimes a laboratory stops because it was not really going to end up in a reliable preparation or reliable sourcing or whatever, so that not everything that might get referred to the USP laboratory will, indeed, emerge as a successful monograph.

DR. JUHL: You are testing it primarily in vitro. Does the USP conduct an in vivo bioavailability of a --

MR. GRADY: USP has itself no facilities for biological testing. What we have done in the case of sodium hyperchloride -- there were a lot of these AIDS patients being treated with fairly irritating preparations before, so a buffered pH controlled preparation was made.

Then we sent that out to contract laboratories to assure that that concentration was still bactericidal and viricidal .

Other than that, we are not presently contemplating anything like placing any contracts for bioavailability studies.

That would come up possibly in the subject of metronidazole benzoate. We have not done that.

The question there is that you would have to then come to -- just as people come to think about appropriate technology, what is an appropriate bioavailability study, when you are talking about like brand versus generic and all

that thing.

To confirm, at this stage, after 30, 40, 50 years thinking about bioavailability, some of these tests really ought to be confirmatory and not exploratory, and that would be a lot cheaper.

so, the current thing of $100,000 to $200,000 for a bioequivalence study simply is unnecessary in my thinking. I will not recommend for our budget anything at that level.

I believe that relatively simple confirmatory studies would be possible, being done at a very manageable budgetary level.

DR. LA FOLLETTE: I have another question for the USP. Is there a possibility for some of the compounds that we are going to look at, that are approved in the Japanese pharmacopoeia and the European pharmacopoeia, that they could be harmonized with the USP as has been done with other excipients and compounds?

MR. GRADY: Yes, we would do that. Harmonization is a wonderful thing. It has gotten rid of the word plagiarism.

By that, meaning adopting in total as long as we are basically noblesse oblige, we have confidence in our monographs.

Yes, if there is any reason that somebody recommends that they think we ought to adopt a monograph, we

harmonize where possible, as a matter of policy.

In these cases, there should be relatively little reason why there should be any substantial difference, unless that monograph was very old and they hadn't had a chance to update with, say, modern chromatographic methods or something.

The intent then would be to tell them, hey, here is what we are doing as well. I will be back to the British pharmacopoeia in a matter of a couple of weeks about what we are doing with metronidazole benzoate suspension.

We have already been in contact. That is how I know they are developing a monograph. I talked to one of their scientists last week and they are going to do it.

DR. LA FOLLETTE: I am just concerned about, you know, worldwide supply of drug substances, and the quality of them, so that if they actually end up being harmonized, there is a greater reassurance of the quality of them.

MR. GRADY: At least the consistent challenge to the manufacturers to meet the quality standards. There is a problem in international commerce that everybody faces internationally with supply lines in pharmaceuticals.

There is in international commerce the problem of counterfeit and substandard materials. That applies to everybody and compounding pharmacists are not excluded from that challenge or threat.

DR. JUHL: Thank you. After we get Europe and the United States harmonized, maybe we can go to work on New Jersey and Pennsylvania. Other comments or questions of the committee?

DR. MC BURNEY: I would like to ask Captain Tonelli another question. The chemicals that are proposed, are they currently all available from manufacturers or sources that would meet the criteria that are listed?

In other words, have they been verified? Do we know that they are currently available from approved sources, as such?

CAPTAIN TONELLI: We do not know that at this time. Our purview was just to look at the chemicals under the criteria that I outlined before. We did not look for availability.

However, I believe that if we put them on the list, someone will make them available.

DR. WOODCOCK: The current scheme, though, that I will bring to people's attention, simply requires registration.

That doesn't mean that there will be any, necessarily, vetting prior to shipment of these chemicals. so, if something is on the list, under the current scheme, a manufacturer could manufacture and then ship the chemical,

regardless of whether they have ever been inspected by the FDA. So that people are aware, that is the scheme.

Dr. Juhl, we would like to invite the committee to actually express their view on the criteria. We would really like to know how the members feel about them, in a way that may not be necessarily -- we may not be able to figure out what your thinking is just from the questions that you are asking.

We really would like to hear some discussion among the committee members on their views on the criteria.

DR. JUHL: That may be easier to do after we have looked at the individual compounds, but I would encourage you to provide feedback.

We do have some time before lunch, and you don't look all that hungry.

DR. LIEBMAN: I think you all have done as good a job as you can do with the available information that you have.

I would strongly encourage that any of these compounds that do wind up on the approved list be looked at by the USP and more formalized in their quality assurance.

MS. AXELRAD: Could I ask the committee a question? One of the stipulations in the statute or criteria or whatever is historical use.

I think we have looked very strongly at that,

although, as Bob said, no criterion had a particular overwhelming weight, in looking at this list, from our point of view.

Historical use, we think, is important, given that there is usually no formalized testing that will be submitted.

I would like to hear some comments on that. If you don't have testing, then one assurance of at least safety of the compound would be that it has been historically used and fairly extensively without severe harm ensuing from it.

DR. JUHL: That was the question that I was asking before, if there is something that perhaps has been used in a foreign country and relatively well documented but just not been used here at all, to use the historical use criteria with great weight for a period of time the practice, and not allow new things to be introduced into pharmacy compounding when, in actuality, there may be very good evidence for both safety, and for one reason or another, just has not been used in this country, not been picked up by a manufacturer to develop an NDA on.

I guess I would encourage, as the language states, that no one criteria overwhelms all and they have to be done on a case by case basis with judgement applied.

DR. LIEBMAN: I think the literature probably

gives you a good indication of what has been published. I think as we discuss the various and sundry drugs and the speakers from that side of the table begin to come forth, I have a feeling there is going to be a fair amount of data that comes forth and says, yes, there are a lot of things being used and quite successfully for specific kinds of patients for specific kinds of disease entities, which just didn't show up in the literature, but a fair amount of data saying, yes, lots of patients using these things.

I would hope that if that is the case, we would be hearing that this afternoon.

DR. RODRIGUEZ: One concern that I have, without mentioning the specific drug, in one of these packages over here, I am aware of some drugs that we used 50 years ago and they are listed in here.

Hundreds of people, millions of people were exposed to them. Acute toxicity did not appear to be serious.

Then they started seeing the potential for lymphomatous changes or carcinomatous changes. I was concerned, personally, because I was exposed to one for many years.

That came to my mind. I was not aware of that possibility until I started reviewing the material that was given to me.

I just wonder, prospectively speaking, as we approve the drugs, is that once done and for all, or are we going to be collecting not just acute toxicity, but long term, and what type of criteria are we going to be applying for that.

MS. AXELRAD: I guess I hadn't contemplated that once we put something on the list that we would be launching an extensive evaluation of it.

I don't see how we would be able to obtain that kind of extensive long-term data or toxicity data. We certainly don't have the resources and are not prepared to initiate testing programs on these, unless someone in the private sector was interested in coming forward and doing that. That would be the only way the data would be generated.

Now, we might look at one of the bulk drug substances and decide that we have a sufficient amount of concerns, either about the data that is available or the absence of data, that we would decline to put it on the list and ask people to submit additional data on it.

It seems to me that once something is on the list, unless there was a test or it was tested somehow and we got some kind of negative data, that it would remain on the list.

DR. RODRIGUEZ: In that. regard, it would be

dynamic. What I am trying to say is that once you are on the list, you are not there forever. If something shows up -- that is why this system of reporting has to be looked at in terms of how we are going to make sure that whatever we approve today stands by tomorrow's standards.

MS. AXELRAD: Right. I think if something came up through some system that identified that there was a problem, that we would take it off list.

DR. WOODCOCK: I think we have to be realistic, though, as far as what we are about. We have extreme difficulty getting this kind of information on approved new drugs, once it is on the market. There is very little incentive to do additional safety testing on them.

Unless the National Toxicology Program or other entities take up these challenges, it frequently does not get done.

So, long-term toxicity of agents approved for chronic uses, we don't know as much about that as we would like.

This use would have no known sponsor, in a sense, no one to turn to. I think you have to be realistic about what we are about here, but yes, the list would be dynamic, surely.

DR. JUHL: Let me ask David or Tony or Loyal or anyone else who is of the pharmacy compounding group, what

is the culture for the academy, if you are using a compound that you are the only place in the country that is using it.

Do you collect data? Is that part of the culture of pharmacy compounders, to say, well, I am the only one who has experience with this; I had better at least write these down.

It may not be a double blind placebo controlled trial, but a note in a journal on adverse effects or its effectiveness would. certainly be a useful situation, but I don't know if that occurs.

DR. LIEBMAN: I can only speak for myself. I can't imagine any compounding pharmacist who would, in good faith, make a compound medication for patients who given a negative report back.

What we do -- and I am sure other people do -- you then call your patients and see how they are doing, and if you would talk to the patient or the physician that something terrible was going on, that you wouldn't stop, talk to the physician, tell the patient to stop using the medication while you talk to the doctor.

We have not had an incident where anything -- we have had very few instances where they have taken something and it made them nauseous and we have said, well, maybe you ought to cut back, let me talk to your doctor.

We have not had any disastrous results -- and I am

not stressing disastrous particularly -- where we just ignored it and kept right on going.

DR. JUHL: Nor am I, and the question I am asking is, you have experience after you have had 20 or 30 of those patients.

Do you look back and say, here is what happened; it was very well tolerated or there were three or four out of the 20 who got nauseated or there were seven or eight that it didn't work in, or some kind of clinical report of your experience a particular compounded product?

DR. LIEBMAN: Not that formally. If I were making a compounded medication and I noticed repetitively that they were having nausea or they were having this effect, or this side effect or that side effect occurred on some ongoing basis, I would have some major concerns, then I would talk with the physicians who were using it and I would start looking at it to see if there was something I was doing that was incorrect.

If I got too many reports, I would go back to the physician and say, I am not comfortable doing this any more. There is something about this medicine that I don't understand that is causing some serious problems, and we need to look at what is going on here.

DR. JUHL: The question is -- I think you have answered it -- but do you communicate that with the

compounding community through a note in the journal? That is what I am getting at.

DR. LIEBMAN: Do these go on, where people have kind of show and tell, sharing. You would say, well, I am doing so and so? The answer is yes.

It is not unusual when you go to meetings and people will start saying, well, what problems are you having.

Various pharmacists will say, well, I am making so and so or I am doing such and such and I keep having these same problems. Is anyone else experiencing that, and how are you getting around it.

If and when a problem occurs, yes, I don't think that it is a secret which we hide. I think we share it because we want to know what is going on and what can we do to correct it.

DR. JUHL: My suggestion is, when you have an advisory committee or a regulatory agency who looks over your shoulder, it would be a whole lot useful to write some of these things.

I guess I would encourage that in places where we don't have a lot of information. I would think that you would want to develop information, because you are doing it anyway.

DR. LIEBMAN: Good point.

DR. ALLEN: I might mention on this also, that many of the compounded prescriptions that are written by physicians are primarily practitioners, and not necessarily academically based.

Many of these come from the literature. That is the origination or the source of many of these prescriptions.

Their use generally continues if the product is successful, minimal side effects, et cetera. There is no real incentive at this point in time for them to report adverse drug reactions.

I think it is something that we can look at, very necessary; it is needed. I think that could be easily done.

There are case studies that are reported in the journal. IACP has a publication that they do publish case studies.

So, this is evolving at this point in time. It would be nice to have some, I guess, formal mechanism to start pulling a lot of this together.

We have independent practitioners -- physicians, pharmacists -- throughout the United States. I might also mention, one of the reasons there are not a lot of clinical studies along these lines is that these are not patentable items. So, it is difficult to get a funding source to conduct these studies.

DR. CATIZONE: With regard to the criteria which the FDA has approved, I think the criteria are fair; they are in accordance with the directions to the advisory committee.

I am concerned that we haven't adequately defined historical data usage, and that is going to be left to much interpretation and perhaps some decisions that may not be correct.

We may have a drug that is in wide usage but is not well documented. That may negatively influence the criteria for inclusion on the list.

Perhaps the advisory committee would consider making some references and recommendations to the FDA on how to define historical data and how that data should be evaluated in regard to the criteria as a total.

DR. JUHL: Do you have specific suggestions?

DR. CATIZONE: No, I would like to think about it as we go through the discussions.

DR. JUHL: It was widely known that the earth was flat at one time, too, but that didn't necessarily make it right .

DR. WELDER: I would just like to add that, since I have become involved in compounding, I have found that the pharmacists that do this on a serious basis are the most sharing people in the world about talking to each other

about problems that they have had with particular compounds and chemicals.

While there is no formal way of disseminating that or gathering it all in one place, when we go to seminars, people do talk to each other.

When we dispense a prescription, we strongly advocate that patients come back to us if they have had any problem. We have not had any in the nine years that we have been doing this kind of thing, except maybe minor skin reactions when they have been out in the sun a lot and those kinds of things.

We have noted that, so that the next time we dispense that, we make a note to the next patient that they should probably be aware of the sun sensitivities.

DR. JUHL: I think documentation is obviously very important and it is easier to do with a computer. It also makes it easier to look at the last umpteen patients who took that particular medication. Other comments?

DR. PECK: It is noted that chemical characterization is included. One can document that by means of a certificate of analysis.

I think, in looking at compounds in recent years, there are concerns about physical characterization. As a list is generated of drug substances, the possibility of multi-sourcing comes into play.

The physical nature of that which is generated could be different from a different source. Currently I think we have the situation where probably we are getting a single source of a particular active moiety.

Once we generate a list, I think we will have people interested in preparing that particular material. Certainly that is when some of the other points that were raised this morning about certification of sites and that sort of thing will come into play.

I just want to think about the physical characterization of the material, the degree of crystallinity, polymorph potential, that sort of thing. That arises with multi-source.

DR. WOODCOCK: Can I comment? I think what we mean by chemical characterization is chemical characterizability; that is, ease of characterizability. That, I think, would take into account if there are critical physical chemical characteristics of the product that in some forms it might not be usable.

Then that has to be taken into account in whether or not it is adequate for being on this list.

DR. LA FOLLETTE: I have concerns about that with the certificate of analysis, without the item being monographed.

You can have different suppliers with different

synthetic pathways. There can be different impurity profiles.

I don't think that is necessarily being identified in here with a C of A from a supplier that isn't like a compendia supplier, doesn't have to meet those rigors.

There can also be different solvents used. There are ICH guidelines for what levels of solvents, but if you don't understand or if the FDA or this committee doesn't actually see what the process was to make the drug substance, you are dealing somewhat with the unknown and you are exposing patients to things that potentially could be harmful.

I am probably a strong proponent of seeing things being monographed or at least benefiting by things that are in monographs such as I had already mentioned with the EP or the JP, things that have been recognized by the USP and they work together to harmonize. I think standards have to be put in place.

DR. JUHL: I think that is an obvious point. We have the altryptophan example of an impurity that caused problems, or at least we think is what happened, and we need to prevent that kind of thing from happening here, too, and standardization past the certificate of analysis would be important .

DR. LA FOLLETTE: Also, I think it is obvious, but

even in what I do, we have looked at alternate suppliers of drug substance across the world, and think that they are actually going to meet the compendia requirements.

Until we actually get the item in our own area and test it, it doesn't necessarily or it has other impurities or different characteristics. Again, beware.

DR. JUHL: Seeing no further comments, we will adjourn until 1:00 o'clock, at which time we will have the open public session.

Members of the committee, if you would like to accompany us over to the Parklawn cafeteria, we will lead the way for you there, and we will be back in our seats at 1:00 o'clock.

[Whereupon, the meeting was recessed, to reconvene at 1:00 p.m., that same day.]

A F T E R N O O N S E S S I O N (1:05 p.m.)

DR. JUHL: Our first order of business this afternoon is to have the open public hearing, when people who would like to address the panel on issues that relate to what we are doing, hopefully, come before the panel, and we are happy to have the participation of the public in this process.

Rules of the road here for our speakers include a 10-minute time limit. Also, I would like all the speakers to begin their presentation by identifying themselves and who they represent here at the session.

Our first speaker in the open public hearing is Larry Sasich from Public Citizen. Larry?

Agenda Item: Open Public Hearing.

DR. SASICH: Thank you. Larry Sasich, pharmacist, Public Citizens Health Research Group.

Just a couple of observations about this morning's discussion amongst the committee members, first, particularly, the standard of recognizing a bulk chemical substance because it is approved in another country.

Unless you probably paid a lot of attention or lived outside this country for any length of time, you don't realize that drug standards are not equal around the world.

We have had in this country arguably the best for the last 40 years.

I would like to remind you that in EU countries, and I think every other country on the face of the earth, the drug approval process is totally opaque to the public.

You have no understanding whatsoever, no knowledge whatsoever for the reason that a drug was approved, nor do you have access to any information as to why it was taken off the market.

The only place in the world that you can do that is in this country. A number of researchers from different countries around the world, just to find out basic information about drugs that are approved in their countries, go through our Food and Drug Administration.

I would like to, in particular, bring your attention to drugs approved in Germany, since I did live in that country for four years.

Germany did not have anything that was near the equivalent of our Food, Drug and Cosmetic Act until 1978. Until that point in time, all drugs that were approved in Germany prior to 1978 were grandfathered in.

Just to give you one example, unfortunately this has to do with a natural product, but there may be some similarities between compounding pharmacies and the natural product industry.

This has to do with a drug product for diarrhea. This particular drug product was dirt, from an area near

Frankfurt called Farnheim.

The manufacturer of this drug asked for, made application for approval -- it is called the Bundagasunheitsund (?) , and that is their health regulatory authority. It was denied.

The manufacturer went to court, took the BGA to court in the state of Berlin. The court ruled that the government cannot hold drugs marketed prior to 1978 to the same standards as modern drugs.

The information that was presented for dirt was anecdote from the first world war that was presented in lectures in the 1930s.

Be very, very careful about assuming equivalency between approval processes amongst different countries, even western European countries.

A second observation I would like to make has to do with post-marketing safety surveillance. I seem to get the feeling from the committee that we have an adequate system to be able to identify who is injured or killed from prescription drugs in this country or any other country, for that matter. The fact is that we don't.

You simply cannot use lack of reports of an adverse event as proof of safety.

I know there has been a lot of discussion about our post-marketing surveillance system in this country for

some time.

Some people have held out the fact that the withdrawal of promphynacradurac, the withdrawal of posicor and abiphrodil and the withdrawal of redux were successes of our post-marketing safety surveillance system.

In fact, they were not. For each of these three drugs, there were serious safety questions raised prior to the time that each of these drugs were removed.

We knew about the risk of liver toxicity with romphinac. We knew we had an interim safety analysis for the drug posicor where it was in a large clinical trial being used for congestive heart failure patients.

We had the results, the initial results, of the international primary pulmonary hypertension trial regarding redux, and we had the concerns of 22 neuroscientist who first contacted the FDA two years prior to the time that redux was approved, that they be allowed to do studies of the potential neurotoxicity for this drug.

Overarching all of this, and it is probably not really applicable here, but none of these drugs were innovative drugs.

There were multiple treatment options in all instances. Both patients and physicians have admitted it is a mistake to base your decision about adding a drug to the bulk substances list thinking that if any problems arise,

that it will be picked up by the post-marketing safety surveillance system. We are simply not at that level at this point in time. Thank you very much for your time.

DR. JUHL: Thank you.

DR. LA FOLLETTE: I would like to make some comments to what Dr. Sasich has addressed. For those of you who don't know, the EMEA in Europe actually has a web page and they actually put out why a drug was approved or withdrawn.

I do agree with things that were approved many years ago in individual countries that are part of the EU. If you want to have your product approved in the EU, it has to now go through a decentralized or a centralized procedure, or it has to be mutually recognized.

You can have things that are approved in a European country that do not make it into the EU.

DR. SASICH: You still can't formally request it the way it is done in this country. It is their publication.

Those documents are written by the European agency. If you take a look in last week's British medical journal, there is an article that Andrew Hertzheimer wrote, who is one of the world's experts on drug safety, criticizing the quality of information that is in those EU documents and how much is available from the FDA through the

Freedom of Information that is kept out of the information in the EMEA documents. I forgot the second part of your question.

DR. LA FOLLETTE: You are talking about the EMEA, what is published now today?

DR. SASICH: That is exactly right. The quality of data information has been criticized. The individual citizen cannot make a request to any of those governments for any of the documentation, any of the studies, any of the adverse events that occurred in any of the clinical trials that were used to support the approval of that particular drug.

DR. LA FOLLETTE: I think I just want to make sure that everybody understands -- and maybe you understand -- that there is a difference between products being approved in things like the pharmacopoeias, like the French pharmacopoeia and the Belgian pharmacopoeia and what not in past years, and what they have to go through to be approved by all the member states.

DR. SASICH: But we still don't have adequate access to what data were used to support the approval of those drugs, nothing that comes anywhere close to the United States.

DR. LA FOLLETTE: In your opinion, okay.

DR. JUHL: Thank you. Our next speaker is Bob

Scarborough of Abrams Royal Pharmacy.

DR. SCARBOROUGH: Good afternoon. My name is Bob Scarborough. I am a compounding pharmacist from Dallas, Texas.

I have been a compounding pharmacist for about 30 years. Ever since I got out of school, that is all I do, is compounded, basically.

I first would also like to tell you that my patients, as are the majority of patients of everyone who has pharmacies, are your aunts and your husbands and your cousins and what have you.

They are people, but more importantly, they are my friends. Not any one of us would do anything to harm these people.

It is our intent only to help, and I think that is the feeling of most compounding pharmacists. The issues of monetary or any other issues are not really an issue.

We try and endeavor so hard to get a product that an individual can tolerate and can take and improve their health.

A large part of my practice involves a huge amount of people who are environmentally ill. I have to compound medications that are free of dyes, fillers, preservatives, and various things that are very toxic to a huge amount of the population.

I have a huge file of letters from patients who have all sorts of problems with just these things. I have to clean up all the medications that are dispensed for these patients.

It is okay for a certain percentage of people, I am quite sure. For my patients, they cannot tolerate a dye. They become seriously ill.

I had a patient last week who was hospitalized for the fourth time because she inadvertently got a substance that she was allergic to in the form of corn starch.

In my pharmacy, I only have capsules, for instance, that are dye free and, in many cases, vegetable caps. Those are criteria that the physician and the patient have dictated to me.

I think it is the feeling of most all of the compounders that our issue is to take care of the patient, in trying to give them a superior quality of life.

That is all that we have the desire to do, is to take care of the patient, and we have our triad in place, which I am constantly in communication with the physician, talking about the patient, how we can help, what is their best need, and how we can prepare a dosage form and mechanism to get it into the system.

That involves rectal, troche, buccal, any form that is necessary in order to get a patient to receive some

medication for comfort or the ability to survive in this world.

In leaving yesterday afternoon, a patient stopped me at the door and presented me with a letter of thanks, because she wanted to tell me that she was a semi-invalid and had been for many, many years until she found the source of her problem and I was able to compound certain medications so that she can survive. We have many, many of those types of stories.

I would like to address one of the substances, DMPS, which is dimercapto-1 propane succinate, and a very fine substance.

We have to prepare that for a large segment of the population because they have mercury poisoning, essentially.

Basically, this is due to amalgams that they have in their teeth. I prepare this for them so they can remove and chelate some of the mercury out of their body.

I, too, am a victim of just that thing, so I am very interested, of course, in that particular entity.

These are some of the example. If I may talk about another substance called hydrazine, which we dispense to many, many of our patients who are seriously ill and have only a short time to live, perhaps.

We have improved the quality of their life and hopefully we have extended their life by giving them a

substance that they no way could get in any other form or fashion.

Those are some of the things that I would like to tell you about what I see in my day-to-day practice. These people are very real to me and I spend lots of time on the phone consulting with the patient and the physician.

We are only trying to achieve a situation in which they can survive and they can live in this society and in this world today.

They are not just numbers. They are people. I can't get past that point. You must know that we do care, and that is our utmost and most important thing that we do, is to give them a quality product that is something that they can ingest and not cause harm to the patient.

With that, I think that I have nothing more to say except to perhaps tell you once again about what we do do. This is the most important and rewarding thing of my life, is to take care of patients. I hope that I have conveyed that to you. Thank you.

DR. JUHL: Thank you. Our next speaker is either Kate Duffy Mazan or Jeffrey Gibbs.

MS. MAZAN: Good afternoon. My name is Kate Duffy Mazan and I am an attorney with the law firm of Hyman, Phelps and McNamara in Washington, D.C.

DR. JUHL: Are you representing a firm or a

client?

MS. MAZAN: No, our firm represents several pharmaceutical and trade associations, pharmacy trade associations, and my comments today are supported by those clients.

Over the next two days this committee will discuss two components critical to the implementation of the pharmacy compounding provision of the Food and Drug Administration Modernization Act of 1997.

The committee's selection of drugs for inclusion or exclusion on either the positive list of bulk drug substances that may be used in compounding or the negative list of drug products that may not be used in compounding will have a significant impact on the practice of compounding in the United States and patient care in the United States.

If the practice of compounding is to be preserved as Congress intended it to be preserved in the modernization act, it is critical that the committee understand and utilize the criteria for the selection of those compounds as established by Congress.

This morning, FDA presented the criteria it has proposed using for evaluating the candidates for the positive list.

We have not had an opportunity to evaluate these

criteria in detail. We are concerned, however, that an overly stringent application of these standards could freeze in time the addition of new compounds.

We are also concerned that the widespread but unpublished use of compounded drug is not recognized.

We also want to respond to comments this morning that essentially oppose the formation of the positive list. That approach would disregard the Congressional intent of the compounding provisions and the bulk drug list, as recognized by FDA in its proposal.

I want to address, first, the positive list. In establishing the criteria for inclusion of bulk substances on the positive list, it is clear that Congress did not intend to impose the safety and effectiveness standards that have long been applied in the new drug application process.

Rather, the statute provides that FDA consider the historical use of the product, reports in peer reviewed medical literature, and other criteria as identified by FDA.

Moreover, the legislative history reveals that Congress explicitly recognized that drug substances that would be eligible for the positive list lack safety and effectiveness data comparable to that contained in a new drug application under section 505 of the law.

In finalizing section 503, the conference committee specifically provided, "where evidence relating to

an approval under 505 does not exist, the Secretary shall consider other criteria."

Congress applied a different standard precisely because compounded drugs, by virtue of being compounded for individuals, are not susceptible to the well-controlled trials done for NDA studies.

Although we have not had the opportunity to review the FDA's Federal Register notice in detail, we do applaud FDA's decision not to apply rigorous NDA standards.

However, it is critical that the advisory committee members understand that the adoption of more rigorous standards would exceed the authority granted to FDA by Congress to regulate the practice of pharmacy compounding.

It would, as you have also heard, hamper the ability of patients to get the medication that their physicians have prescribed.

In evaluating whether an individual bulk drug should be included. on the positive list, this committee is not being asked to consider whether an NDA should be approved.

The NDA criteria have no role to play in this committee's deliberations in deciding which drugs to recommend for inclusion on the positive list.

Thus, the committee should use the more flexible

criteria set out by Congress -- historical use, journal articles and other reliable information.

Moreover, the committee should apply that criteria in a flexible manner. Restrictions which Congress did not impose by statute should not be imposed by FDA or by this advisory committee in implementing this statute.

Next, I want to talk about the negative list. Last week FDA published a list of over 50 drugs that it says have been withdrawn for safety reasons. We have not had a chance to research those drugs.

In the development of the negative list, the advisory committee should clearly distinguish between drugs that have been withdrawn for safety reasons and those drugs that have been withdrawn solely on the basis of a lack of effectiveness data.

For those drugs withdrawn for efficacy reasons, the committee should carefully consider whether withdrawal from use in the general population, based on a failure to demonstrate efficacy in well controlled clinical trials warrants withdrawal of the drug for purposes of patient specific pharmacy compounding.

Inclusion of such a drug on the negative list could eliminate the use of a drug that physicians and pharmacists have found efficacious for their patients.

The failure of a drug manufacturer to conduct two

adequate, well-controlled, randomized, blinded trials that provide evidence that a drug is effective in a large population does not mean that the drug is ineffective for particular patients.

This committee should proceed very cautiously in depriving patients of access to medications that the physicians and pharmacists have determined to be efficacious.

DR. CATIZONE: Dr. Juhl, I have got two questions, one for Captain Tonelli and one for our speaker, if I may.

Bob, in preparing the unpublished preliminary draft report, were safety and efficacy the only factors, or the predominant factors, in making a decision to distinguish what drugs appeared in what categories?

CAPTAIN TONELLI: Safety was considered as one of the factors. Efficacy was not considered as one of the factors at all, except tangentially.

I mean, we looked at if there -- efficacy standards, basically, were not applied. We saw if there was an efficacious use of the product, and that was actually used. We did not actually rate it on an efficacy standard.

DR. CATIZONE: My question to the presenter, if I may, your recommendation to the advisory committee used the guidelines from the statutory language of the historical data and other information.

Is the supposition correct that if that information is lacking, that that drug should not be approved or put on the positive list, if that is the only basis for the committee or the FDA to make a decision?

MS. MAZAN: If that information is lacking entirely, that there is no information available?

DR. CATIZONE: Correct.

MS. MAZAN: If there is no information available, then I think it would not be appropriate to put it on the positive list.

DR. CATIZONE: Thank you.

DR. JUHL: We received a request from Samuel Moser from New Carlysle, Ohio to speak. We have not seen that he has arrived. Is Mr. Moser present? Not seeing him, then we will go on.

Our next speaker is Sammie R. Young of Silver Spring, Maryland, who has asked to speak for 10 minutes. Could yOU, for the record, state your name and your affiliation, if any.

MR. YOUNG: My name is Sammie Young. I was an FDA employee between 1963 and 1992, the final phase of a 41-year government career.

DR. JUHL: You are representing yourself, I presume?

MR. YOUNG: I will have some comment on that at

the end, if you please.

DR. JUHL: I would like it for the record. You are not here at an organization's request? You are speaking for yourself?

MR. YOUNG: I am speaking for myself.

DR. JUHL: Thank you.

Having listened to the morning session, I wish to depart from the written submission before you, which I would like included in the record, and proceed with some comments on today's session.

As the chairman said in his opening statements, the presentations will give you an insight into our views, and the fine print on the front of my statement will give you a clue as to where I am coming from.

I thank you for the opportunity to speak before you today. I had perhaps the dubious distinction of being deputy director of the office of compliance in the Center for Drug Evaluation and Research and being at least one of the people who, after years of inattention, brought the so-called compounding issue to a head.

In my wildest dreams, however, I never envisioned that such a simple issue would result in such a monumental undertaking.

Having been enlightened this morning by the CDER people, it looks like you are well underway, and I think it

looks good.

I am, however, thoroughly shocked that a representative of a law maker and a senator would stand before you today or at any time, and if I heard her correctly, cloud the important health and safety issue by quibbling over the definition of manufacturing versus compounding, and then suggest that separate standards be developed for new drugs, compounded and so forth.

I wish the lawyer who just spoke would tell Bob McNamara that I am disappointed by his law firm's attitude on the same issue. I knew Bob many years ago in FDA.

It reminds me of perhaps current attitudes on the parts of some people, that if you can't meet the standards of quality or whatever, you lower the standards, or you cloud the issue.

This is a new drug issue, and that is precisely what it is. There is only one standard and that standard includes the preparation of drugs under current good manufacturing practices, or CGMP.

Before my retirement in 1992 from FDA, Mary Pendergast, a distinguished attorney and distinguished assistant of FDA Commissioner Kessler, in conjunction with discussions on the compounding issue said to me, Sammie, everyone knows what the law is. They -- referring to the compounders -- don't want to go to court, because it is a

new drug issue, and they know they will lose.

I also don't wish to get into a one-upmanship discussion on certain issues, but Mr. Gans, I don't believe, is here, but he spoke earlier this morning.

I agree with much of what Mr. Gans said, despite the fact that he was the recipient of one of my venomous letters that I wrote to him and his group while I was employed at FDA.

I don't agree with him, that government intervention has been responsible in any way for pharmacy, or erosion of the practice of pharmacy.

The world has changed. Health delivery system practices have changed. I have been involved in it since 1951.

In substance, I also agree with the comments made earlier this morning by Mr. Bruce Roberts. I don't know if he is here or not, from Virginia, who is a compounding pharmacist.

If I understood him correctly, what he says he is doing and practicing is practicing the legitimate pharmacy compounding, has been for a long time, and is currently sanctioned under FDA's discretionary enforcement policy.

I wish to state that pharmacy compounding as defined in FDA's policy documents has long been recognized as a legitimate practice.

Neither I, nor anyone in the agency, to my knowledge, ever advocated, number one, banning, sanctioned new drug compounding by a licensed pharmacist, or interfering with the day-to-day practice of pharmacy. I can say that with 30 years of experience.

So-called pharmacy compounding is a term which I think I coined. It involves engaging in any of the nine acts identified in the FDA's old compliance policy guide, 72-31.6, dated back on March 16, 1992. A copy of this is attached to the submission that is before you.

That compliance policy guide was introduced by Commissioner Kessler before a pharmaceutical manufacturers association out in California.

I was involved with some of the preparations, some of the follow up and dissemination of information that occurred at that time.

It was a legitimate, reasonable policy. If yOU look at it carefully, you will find that it doesn't prevent legitimate pharmacy compounding activities.

I would like to move this issue into one of ethics and so forth. We have heard since World War II -- and I am a military member who has seen a lot of death; my wife saw a lot and I tagged a lot of toes in my duties.

The advisory committee on human radiation experiments recently submitted a document to the President.

The authors argue over timeless principles, principles such as that one ought not to deceive others, which predates the discipline of medical ethics.

The response proceeds, although there have been changes in ethical values in the United States between the mid-1940s and the present, it is implausible that these changes involved in the rejection or affirmation of principles so basic as that it is wrong to treat people as mere means, wrong to inflict harm, or wrong to deceive people.

In continuing the advisory committee's evaluation of the human radiation experiments, in light of these basic principles, it is based on a simple, we think, reasonable assumption that even 50 years ago, these principles were pervasive features of moral life in the United States that were widely recognized and accepted, much as we recognize and accept them today.

In a brief summary, the practice of so-called pharmacy compounding is not a states right issue. It is a new drug issue, and its safety record is completely unknown, since compounding pharmacists are not required to comply with adverse drug reaction reporting.

Dr. Woodcock mentioned this morning that they aren't required to, and I understand that. As director of compliance for the office of compliance from 1975 to 1983,

there were not mandatory requirements for reporting adverse reactions for biological products.

It is only within the last few years that this requirement has been imposed through the normal rule making process.

This deprives FDA and/or the public of knowledge necessary to determine safety and efficacy status of drugs and to facilitate recall or withdrawal from user patients when defects occur.

Further, compounding pharmacists are not likely to test their products or comply with the strict testing of products or current good manufacturing practices required of conventional manufacturers.

All of these public health protective measures are circumvented or ignored in the case of the illegally operating or so-called pharmacy compounder entity that I have isolated.

Newt Gingrich gave the Democrats 15 seconds to summarize their report.

DR. JUHL: I will give you 30.

MR. YOUNG: The minimum requirements of keeping with these basic principles and so forth are, one ought not to deceive others, and we hear often, first, do not harm. Risk must be minimized and informed consent must be imposed.

You have a series of documents attached.

As a final pitch, this astute committee has an opportunity to put this entire issue in proper perspective. I hope you will do that.

No one has the right to kill or injure people. The agency has within its records deaths and injuries due to compounded pharmaceutical products. I don't think that you ought to be identified with the Neuremberg treatise. Thank you .

DR. JUHL: Thank you, Mr. Young. Our final speaker is William Pitlick from Pathogenesis Corporation. Dr. Pitlick?

DR. PITLICK: Thank you very much. I am Bill Pitlick, vice president of regulatory affairs for Pathogenesis Corporation in Seattle. I will abbreviate the text of my remarks. I submitted my remarks for the record, but would like to address a few issues this morning.

I think the committee ought to recognize, when the Pharmaceutical Manufacturers Association, the Generic Drugs Association and the Health Research Group all agree on a policy, then you ought to sit up and take notice of that.

I take particular exception to the remarks that were made by Kate Mazan this afternoon. It sounds like what she is advocating is that pharmacists should be able to toss aside any body of scientific data and use anecdotal evidence to allow a drug to be compounded. I feel very uncomfortable

with that, as a citizen and as a consumer. That is very uncomfortable.

On December 22, 1977, the FDA approved the Orphan Drug Product tobramycin solution for inhalation, or TOBI, for treatment and management of CF patients for pseudomonas aeruginosa.

Up until this time, pharmacists had been preparing tobramycin for inhalation using products approved for parenteral use.

Despite the approval of TOBI, some pharmacists are continuing to compound tobramycin solutions for inhalation using parenteral products.

From what I gather today, there are two lists being promulgated or proposed for promulgation by the FDA, a positive list and a negative list.

I think we are already on the positive list, since tobramycin is a compendia product. I don't want to be on the other list, because we don't want to be withdrawn from the market because of safety or efficacy.

However, I do think that the committee ought to consider -- in the text of my remarks -- that that list ought to be expanded to include -- and I believe that is the intention -- products for which there may be safety and efficacy issues arising as a result of difficulties in compounding the product.

As you will see in my remarks today, I believe tobramycin solution as an aerosolized product solution for inhalation falls into that latter category.

My remarks here are intended today to ask this committee to include tobramycin in a list of products which are not suitable for exemption from the requirements of the act .

In many cases, pharmacists are reformulating tobramycin because essentially it provides a significant cost savings to patients when substituted for TOBI.

The issue today posed by Pathogenesis is we believe that reformulating other tobramycin products into a formulation that patients can use for inhalation is prohibited by federal law.

We believe there are four valid arguments under the FDA Modernization Act, and two strong policy arguments for advocating that pharmacists' reformulation activities are not compounding.

I believe there has been considerable time spent this morning on many of these, so I won't go into great detail on them.

The first argument is that reformulation violates Congressional intent. It is clear from the language in the act that Congress intended that products be available for a medical need for individual patients.

It is also very clear in that language that compounding for purposes of financial reasons is not an appropriate activity.

Thus, compounding orders filled by pharmacists at the request of a payer or because of a reimbursement policy to save money would fail to fit within the compounding exemptions contemplated by Congress.

The second argument is that reformulation fails to meet the statutory requirements for exemption described in the Food and Drug Modernization Act.

We have already talked about these, about the fact that there must be an identified individual patient, and it must be an unsolicited receipt.

When a pharmacist goes back to a prescriber and asks them if they would substitute a generic or a compounded product using parenteral tobramycin compounded into a solution for inhalation use, it is no longer an unsolicited prescription and, therefore, falls outside the exemption.

There are a couple of other alternatives, but none of the alternatives within the modernization act have been discussed at great length this morning meet the definition required for compounding, for solutions for inhalation in general, and for tobramycin in particular.

Now, the third argument, that reformulation would fall outside the exemption because of the regular

compounding of a commercially available product, reformulation is an attempt to make a copy of a commercially available product, and it provides no beneficial difference of the patients beyond lower cost, and therefore, meets the statutory definition of being essentially a copy of a commercially available product.

If the pharmacist typically reformulates IV tobramycin for all patients, or for all patients in specific health plans who present TOBI prescriptions, such conduct would constitute regular compounding.

The fourth argument is that safety and efficacy concerns, if reformulated tobramycin qualified TOBI as a drug that the FDA should list as unsuitable for compounding.

I guess that means that we would like to be added to the negative list of drugs that are unsuitable for compounding because they present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on safety and effectiveness of drug product. TOBI is certainly such a drug. I would like to elaborate on that a little bit for a minute.

CF patients have very sensitive airways because they have a chronic lung disease, and they also have very localized infections.

Aerosolized antibiotics for those infections is an ideal treatment because it localizes the treatment to the

area of infection and it reduces systemic availability.

Nebulization of drugs is a very tricky concept. You hear people saying, this isn't rocket science. Well, nebulization of drugs for inhalation is rocket science.

The physics of nebulizing a drug so that you get a defined particle size within a very narrow range is, in fact, a very difficult situation.

Particles that are too big impact on the nasopharynx and are swallowed. Particles that are too small go into the alveoli and are absorbed systemically. That is good for a lot of products but it is not good for an antibiotic for CF disease.

So, particle size is very important. We have spent a lot of time and effort in cooperation with the FDA to develop a formulation which is designed specifically for CF patients.

It is 300 milligrams of tobramycin in a quarter ml of saline. The gauge is 6.0. It is sterile, preservative-free and non-pyrogenic.

Each of the characteristics of this formulation is designed for CF patients. If you want to have a solution of proper osmology and proper chloride concentrations so that you don't cause bronchospasm in these patients, you also need to have a solution with proper osmology and proper pH so that it nebulizes properly, again going back to the

characteristics of nebulization.

The development priority review and expedited approval of TOBI by the FDA was the result of several years of cooperation between the CF community, the FDA and Pathogenesis.

All these groups recognized that aerosolizing parenteral tobramycin was unacceptable and the FDA required us to do two well-controlled clinical trials. If yOU pUt Up the next slide, I will show you the results of those clinical trials, where we measured pulmonary functions in patients, in 520 CF patients, after taking TOBI or placebo.

On the left-hand axis, there was a lead-in period of six months prior to the study in which patients were allowed to receive aerosolized tobramycin using parenteral product. So, that is the zero baseline.

At time zero, patients were put onto the TOBI product which we prepared, or continued on placebo, which was standard of care for whatever they were receiving.

This is the difference in efficacy that you see with a well-controlled and scientifically prepared product.

To ignore this data is simply, to me, unconscionable and probably unethical. To continue to reformulate product which has not shown similar efficacy, to me is unconscionable.

I would contend that given the amount of effort

that the FDA has put into approving this product, that they would want to consider the reformulation of this product by compounding by pharmacists would be unacceptable.

It was unacceptable before we submitted the application and it is still unacceptable.

The second policy issue relates to the orphan drug status of TOBI. TOBI was granted exclusivity under the orphan product act, and reformulation of product violates that orphan drug exclusivity.

The practice of pharmacists reformulating tobramycin IV for inhalation does not qualify as a compound of the group that was exempted by the FDA.

Reformulation of tobramycin for inhalation is not what Congress intended, does not meet the FDA requirements, and it violates the orphan drug exclusivity provisions. Thank you very much.

DR. JUHL: Thank you. We do not have any other speakers who have asked to address the committee. I would at this point ask if there are those who came here to address the committee but have not registered with us, if they would like to identify themselves now.

Seeing none, I think we will move on, then.

DR. CATIZONE: Dr. Juhl, a question for you. Earlier, representatives of the FDA had asked for the committee's comments on the criteria that Mr. Tonelli had

used as the basis for differentiating the drugs to be considered on the bulk drug substance list .

In light of that request, in light of the fact that those individuals who presented comments during the open hearing, and only one individual spoke to the criteria, I would like the committee to consider two assumptions as we deliberate toward a final report of recommendations to the FDA .

First, there seems to be a positive acceptance of the criteria from committee members at this point, unless we have further discussion.

Secondly, except for the one presenter, there doesn't seem to be negative criticism of the criteria as proposed by the FDA.

Of those groups and individuals represented here, when the materials are submitted for comment, or the FDA should not be criticized about the criteria or the use of that criteria, since there seems to be some tacit approval for the criteria as submitted.

DR. JUHL: Comments on the comment? I would ask, by the way -- our audio technician has asked that we move ourselves closer to the microphone when you speak. They should be about four inches, plus or minus USP 10 percent from the microphones. They aren't designed to pick up your speech when you are leaning back.

Are there any comments on Carmen's comment? I suspect the criteria may come alive as we have to apply them and we may not be as comfortable then as we are now. I think I do sense a recognition of the general acceptance of the broad nature of the criteria.

I think we are readying ourselves to move on, then, to the presentation on the bulk list.

I have one other piece of housekeeping, if you would allow me to take care of it. Earlier in the discussion this morning, Dr. Sasich had raised the issue of the selection of the consumer representative to this committee. I wanted to take just a second to address that.

There are issues of consumer representation on all FDA committees, and I think there are valid arguments and discussions going on about that particular topic.

I did not want his comments to reflect specifically on this committee or on our consumer representative for this committee and wanted to state for the record how the selection for a consumer representative went forward.

The FDA Consumer Consortium is a group of individuals convened by the FDA to provide nominees for such committee membership.

The consortium did provide us with the names of three candidates, who were given alphabetically, and said

that any of these would be very good representatives on this committee.

One of those was Anna McClain, who was selected to be on our committee, and I am happy that she is here. I think she will represent the consumer view quite well.

Copies of this letter are available for any of you who want to verify the process through which our consumer representative was selected. Thank you. Captain Tonelli?

Agenda Item: Introduction of Bulk Drug Nominations.

CAPTAIN TONELLI: Thank you. I am going to do a little housekeeping, too. In this morning's presentation, I said there were 38 nominated substances. That is actually what we saw and reviewed and looked at.

I was notified yesterday that there was actually another nominator who, for some reason, did not get to us.

I will just present that there was another nominator, the American Academy of Dermatology, and they had four substances on their nomination list.

One of them will be considered because it was nominated by another nominator, and that is cantharidin.

A second, diphencitrone, was not considered and would have been a candidate for the list, and will be considered probably after this meeting, and anybody who wants to may address that particular substance. We will not

be addressing it.

A third substance, myrrh chloroethamine, was looked up and found to be in an approved product. Therefore, it is already available for compounding outside the list, so it wouldn't have been considered as a nominee for the list.

The fourth, squeric acid dibutyl ester would have been considered for the list and probably will be considered after this meeting for the list, but will not be discussed with this list.

In my presentation this afternoon, I will be explaining the process used to review the submissions for the bulk drug substances, and the sources of the information used to assess each substance.

The nominated substances have been divided into four groups and each group will be presented separately.

FDA did an assessment of each of the 29 substances nominated for the list. The nomination packages received varied greatly in the information provided for the bulk substances.

In no case was a rationale for use of the bulk provided by the nominee. That is, why should the compounded substance be used in place of any commercially available product.

In most cases, a brief bibliography of journal

articles was provided for each bulk nominated.

FDA did a search of several data bases, including Medline, Toxline, IRIS and International Pharmaceutical Abstracts, for each of the bulks under consideration for the list.

From these searches, a bibliography for the substances was produced.

To evaluate the safety of the nominated substances, then, the agency evaluated the limited information available about each substance's acute toxicity, repeat dose toxicity, pharmacokinetics, and other reported toxicities, including mutagenicity, teratogenicity, and carcinogenicity.

The agency also considered reports and abstracts in the literature, as well as its own data bases about adverse reactions the substances had caused in humans.

In some cases, such as where the toxicity of a substance appeared to be significant, the FDA further considered the availability of alternative approved therapies.

The existence of alternative approved therapies, in those cases, weighed against inclusion on the proposed list, because the risks of using the substances were more likely to outweigh the benefits.

The source of the information assessed by FDA

under each of the evaluation criteria was obtained through journal reports and abstracts from reliable medical sources, including peer reviewed medical literature.

Some of this information was submitted in support of the nominations, as had been requested by FDA. The remainder was gathered by FDA through independent searches of medical and pharmaceutical data bases.

The amount of relevant information available about the nominated substances, including their uses and safety, varied considerably. In some cases, there was very little data.

For one of the nominated substances, thymol iodide, the agency found only two journal articles. For other substances, such as taurine and sodium butyrate, reports in the literature were more plentiful and sometimes comprised hundreds of articles.

In those cases, the agency reviewed a limited sample of the available literature. The review was not exhaustive of all possible articles.

I would like to point out that, based upon the criteria previously described and in our review of scientific literature, we proposed placing limits on the route of administration; that is, like topical use or for rectal enema use, for six of the substances that are likely to appear on the list being developed. I will discuss this

in greater detail when I address the individual bulk drug substances nominated.

I would also like to emphasize that the assessment of the nominated substance, limited as it was to a sampling of literature sources, was far less rigorous than the ordinary evaluation of drugs as part of the new drug review process.

Even the most thoroughly reported of the nominated substances have not been the subject of any adequate or well controlled clinical investigations establishing their safety or effectiveness.

For these reasons, the inclusion of a drug substance on the bulk drugs list must not in any way be equated with an endorsement or a recommendation of the substance by the agency.

Nor should it be assumed that the substances on the proposed list have been proven to be safe and effective under the standards normally required to receive an FDA approval.

In response to this proposed rule, FDA is specifically seeking comment on whether the substances on the list should remain on the list, and whether the substances that have been rejected should remain off the list.

Additionally, FDA seeks public comment on the

economic impact associated with any of the nominated bulk drug substances.

In particular, the agency requests public comment and data on the current level of pharmacy compounding of the bulk drugs proposed for inclusion on the bulk drug list.

We are seeking this committee's recommendations for each of the 29 nominated substances. After evaluating all comments, the FDA will issue the list as a final rule, which will be codified in the Code of Federal Regulations.

The final rule may include all, or maybe only some of the substances proposed for inclusion on the list in this proposal, depending on the comments received.

Individuals and organizations will be able to petition FDA at any time after the final rule is published to amend the list, by adding or removing one or more bulk drug substances.

Group 1. FDA is proposing that the following drug substances, which are neither the subject of a current USP or NF monograph, nor components of FDA approved drugs, be included in the list of bulk drug substances that may be used in compounding under the exemptions provided in section 503A of the FD&C act.

When a salt of ester of a particular moiety is listed, only that particular salt or ester may be used. Neither the base compound nor other salts or esters of the

same active moiety will qualify for the compounding exemptions, unless separately listed.

This is because such a change could cause a difference in the effect and safety of the substance, as it was evaluated for inclusion in the list.

The bulk drug substances have been divided into the four groups that I would present separately.

In group one, FDA has identified the following substances as likely candidates for inclusion on the bulk drugs list, because at doses reported in the literature, for the indications listed, these substances appear to be relatively non-toxic and severe adverse reactions associated with their use have not been commonly reported.

Agenda Item: Presentation and Discussion of Bulk Drug Nominations, Groups 1-4.

CAPTAIN TONELLI: Bismuth Citrate. Bismuth citrate is well characterized chemically. It has been used extensively in compounded products for short-term treatment of several gastrointestinal disorders, including helicobacter pylori-associated ulcers.

Caffeine Citrate. Caffeine citrate, which is a mixture of caffeine and citric acid, is well characterized chemically.

Caffeine citrate stimulates the central nervous system and has been used extensively, and for many years, in

compounded products to treat apnea in premature infants.

Glutamine. Glutamine, the most abundant free amino acid found in the body, is well characterized chemically.

Glutamine is involved in a wide variety of metabolic processes, including regulation of the body's acid/base balance.

For years, glutamine has been used in compounding as a supplement in parenteral nutrition regimens in adults.

Guaiacol. Guaiacol is chemically well characterized and has been used for decades in compounded products as an expectorant.

Mild Silver Protein. Mild silver protein is chemically well characterized. It has been used extensively and for many years to treat conjunctivitis and by ophthalmologists as a preoperative chemical preparation of the eye.

If mild silver protein is administered internally, however, it can be an extremely toxic substance and is the subject of a Federal Register notice concerning argyria caused by silver products.

For this reason, FDA is proposing to include mild silver protein on the bulk drug list for ophthalmic use only.

Sodium Butyrate. Sodium butyrate is a short chain

fatty acid that is chemically well characterized. It has been used rectally in an enema formulation to treat ulcerative colitis and radiation proctitis.

However, because the literature is limited to the use of sodium butyrate rectally in an enema formulation, FDA is proposing to include it on the bulk drugs list for use in this dosage form and route of administration only.

Taurine. Taurine, an amino acid with several important physiological functions, including a role in bile acid conjugation, is chemically well characterized.

It has been used for years in compounding as a component in parenteral nutrition solutions for infants and adult patients.

This concludes group one and I would like the committee to discuss this group before we move on. I will leave that slide up for discussion purposes.

DR. JUHL: We have a number of ways that we can proceed now. The agency and the committee have also asked that the nominators of the drug substances be allowed to make presentations about those products to the committee. Gina Ford of the Academy is here to speak on most of these agents.

I think what I will do, if it is okay with the committee, is to ask her to make her comments on this group of drugs.

One of these also has been nominated by MD Anderson, and Larry Trissel will do that from the podium when we get to that point. Then I think we will engage in the discussion of the agents one at a time, as you wish.

So, Gina, if you would, please?

MS. FORD: Hello, my name is Gina Ford. I am the executive director of the International Academy of Compounding Pharmacists. I am myself a compounding pharmacist. I practiced in a retail setting for about two years, two and a half years, and worked as a consultant in the field for an additional two and a half.

In reference to some of your questions earlier, the International Academy of Compounding Pharmacists is, and would much like to move forward to the professionalism of compounding pharmacy.

Some of the concerns you addressed as far as how do we document adverse drug events, I think I can speak on behalf of our organization, that we would like to develop some type of mechanism to be able to do that, maybe in conjunction with USP if possible.

The only other thing that I would like to dispel at this point is that thus far we have covered significantly that patients have needs and that we are all here to meet individualized patient needs.

Pharmacists are looking to meet those needs

through their compounding practice. What I think that we also need to remember here is that pharmacists aren't out just digging these chemicals up to meet patient needs. They are being requested by physicians, and patients are requesting of their physicians that they be able to receive these therapies.

I would just like to emphasize that point, that we are here to meet physician need as well as patient need.

The substances that are here in front of you, we feel very excited, very glad to have those as far as no controversy.

The safety and the patient population that they will reach is certainly encompassing. I can answer any questions. I will move on so that we will have time for some of the other more important issues.

DR. RUSHO: Prior to coming to this meeting, I had a consultation with one of my faculty members in pharmacy practice.

She gave me a memorandum from Proctor and Gamble. They state that they have a patent on all bismic preparations for "gastrointestinal disorders."

They further go on to say they have already had one lawsuit where a manufacturer was offering to sale bismuth, in this case bismuth citrate, metronidazole and tetracycline for h. pylori.

I guess my question actually goes to Dave Horowitz over there. Are we going to get into deeper trouble if we approve this particular drug?

MR. HOROWITZ: I am sorry, I don't have an answer for you on that question. We are interested in comments that you may have, and that people in the audience may have on that subject, and we will take it all into consideration before we issue the proposed rule.

MS. AXELRAD: I would say that we are not approving the drug. I mean, we are putting it on a list, which I think we have indicated is very different from approving the drug.

It is certainly not the same as approving a new drug application for a new drug substance. That may affect what action we may take, or the action we take may be affected by the patent.

DR. JUHL: I am sure that is an important point for compounding pharmacists, but probably outside the jurisdiction of the committee. I think we just need to move forward and look at the information we have. I am sure if that would be the case, that Proctor and Gamble will be in touch, but not with us. Other comments or questions?

Let me ask Dr. Trissel if you would like to make some comments. Sodium butyrate was nominated by MD Anderson.

Dr. Trissel, who is a member of the committee, for the audio record, has removed himself from the table and is speaking to us from the podium, to avoid the appearance of a compound.

DR. TRISSEL: Thank you, Dr. Juhl. Lawrence Trissel from MD Anderson Cancer Center.

In preparation for this and to try to comply with the new FDAMA rules, we went through a review of our formulary looking for potential products that would fall under this rule.

It is our intention to use commercial products wherever we can. After a review of our entire formulary, we came up with three products that did not fit this category. We have gone ahead and submitted these to FDA for consideration for this list.

This first one that is up there, sodium butyrate, is obviously the sodium salt of butyric acid. It is a white powder with a very unpleasant odor and is not fun to compound.

It has a specification of about 98 percent, but we usually get significantly better than that on our certificates of analysis, usually 99.5 or better.

It is one of the components of short chain fatty acid enemas, along with sodium acetate and sodium propionate. Both those other components have USP

monographs.

Once again, I would encourage USP to consider this one as well for a USP monograph.

It is an ester present in butter, which surprised me. I did not realize that, at about five percent, and is also a product of fermentation of carbohydrates.

Short chain fatty acids, including sodium butyrate, are major fecal solutes in the normal colon. They are produced by bacterial fermentation of dietary fiber in the gut.

Short chain fatty acids are also readily absorbed by the colon with simultaneous stimulation of water and sodium absorption.

The FDA was able to come up with about 140 articles dealing with various aspects of butyrated sodium butyrate.

Animal studies have shown that short chain fatty acids may enhance epithelial cell proliferation and provide better colonic and astomodic strength.

Clinical use has centered around the treatment of several inflammatory bowel conditions, including ulcerative colitis and diversion colitis, particularly in our institution, diversion colitis associated with surgical removal or resection of the bowel.

The diversion colitis characteristics include

tissue erythema, friability, edema, nodularity, ulcerations, exudates and bleeding from the affected intestine, when the condition is possibly aggravated by adding antibiotics for use after surgery, reducing the normal flora in the bowel.

Short chain fatty acid enemas, as I said, have also been used to treat ulcerative colitis and proctosigmoiditis, including patients who have failed conventional therapies, such as steroids and mesalamine -- 5ASA as we call it.

It has also been used in radiation proctitis.

Short chain fatty acids is a group that may play a critical role in preventing, eliminating or ameliorating the unpleasant symptoms of these conditions.

In human treatment, short chain fatty acids are given typically as a 60 ml enema to the patient, with the patient remaining supine for 30 minutes after the administration, given twice daily for a period extending sometimes into weeks, if necessary.

A representative enema formulation would include sodium butyrate 40 millimoles, along with sodium acetate 60 millimoles, sodium propionate 30 millimoles in 60 mls with sodium chloride added for isotonicity.

There are few reports of side effects in the literature that we have been able to find from the use of the material.

It has a low order of toxicity. The LD50 orally in rats is 8.79 grams per kilo. The material safety data sheet indicates that the pure powder can be irritating to mucous membranes, eyes and upper respiratory tract, which would require a compounding pharmacist to take some protection, perhaps.

As I said, there is very little notice of side effects or toxicities that we have been able to find in the published literature.

In summary, sodium butyrate is one of the components of short chain fatty acid enemas, along with acetate and propionate.

It is relatively non-toxic with little or no side effects, and it is used to control the unpleasant symptoms of ulcerative colitis and diversion colitis. Thank you.

DR. JUHL: Let's proceed through the list and I will ask for comments. Please, we want comments. This will be a good warm up for the ones that are more controversial.

I have the tab numbers for our big books. The tab numbers don't mean anything to the audience, but we received this 10-pound book of information that we will be referring to occasionally here.

The first thing on the list is bismuth citrate, which was found in tab 3 of your book. Comments or questions about bismuth citrate?

Hearing none, caffeine citrate? My observation is the committee is quite familiar with caffeine.

Tab 14, glutamine.

Tab 24, mild silver protein.

DR. RODRIGUEZ: I have a question. I saw the safety but I wasn't convinced much of effectiveness from what I see from the data supplied to us.

I know that silver preparations have been used extensively in burn units as silvadine where it has been shown to be very effective.

My question is, in the case of the silvadine preparation the data doesn't seem to support much effectiveness. It appears to be safe. That was my question.

DR. JUHL: Bob, could I have your comment on the consideration of effectiveness in your deliberations for the proposed list?

CAPTAIN TONELLI: I don't want to speak to the effectiveness of silver per se. What we did try to do was limit its dosage form to ophthalmic, because that was the only thing that we could find in the literature which would not produce the argyria, which would seem to have a real bad effect from any oral use of silver.

We thought that even topically, over large portions of the body, argyria is a possibility.

Ophthalmologically, such a small amount in the eye didn't seem to have that problem. That is why we did it for ophthalmological use only.

DR. JUHL: In terms of effectiveness, that was not a large component of your consideration?

CAPTAIN TONELLI: Absolutely not.

MS. AXELRAD: Can I speak to that for a minute? We decided at the outset -- and you will notice that it is not in any of the criteria that we used -- not to use efficacy per se.

We understood that we were not to use the standards that we usually use for efficacy, which is adequate and well controlled clinical trials.

There was no alternative efficacy standard provided. So we felt that by looking at the factor that was described in the statute of historical use, that we would essentially get a feel for the fact that there were people out there who felt that these products were useful for something, or they wouldn't have been using them for a long period of time, and it would also give us a feel for the safety of it.

We did not look at the efficacy at all, for any of the substances.

DR. LIEBMAN: We have got an ophthalmologist who uses mild silver protein and has been using it for years and

was pleased that he found a source for it, and continues to use it. Obviously, it is part of his armamentarium.

CAPTAIN TONELLI: The silver part that I believe he was referring to is an approved product, actually. It is a topical for burns; is that what you are talking about?

DR. LIEBMAN: Yes.

CAPTAIN TONELLI: That wouldn't be a problem, obviously. It is an approved product. This particular silver protein or this complex, we only had it ophthalmologically.

DR. RODRIGUEZ: My concerns here were in the data supply. We have a number of abstracts available to us. That means that there is at least some degree of published information. Whether that it peer reviewed, I have questions in my mind.

Anyway, there is a question about whether it is efficacious or not. In fact, all the abstracts raise the question. Some of them even compare it to a povidone type solution or an iodine containing solution, where there is a decrease in the bacterial counts when compared to the preparation. It may be better than water, in one of the abstracts.

DR. JUHL: Although efficacy wasn't considered per se, I do believe that the existence of known to be effective products in the category was a consideration?

CAPTAIN TONELLI: Absolutely.

DR. JUHL: So, in that regard there was some consideration of efficacy, with whatever was the gold standard, if there was one.

CAPTAIN TONELLI: When we mainly considered the alternative approved products was when we had a toxicity that we were really questioning. Then it came into play much more prominently.

Just because there was another product possibly available, if the toxicity wasn't something that we were particularly concerned about for this particular product, then we didn't look beyond that.

DR. JUHL: The primary standard is safety.

CAPTAIN TONELLI: Safety.

DR. JUHL: I looked through -- and perhaps some of you did, too -- the legislative record to see if, outside of the act itself, there was discussion of this topic.

There really wasn't much. There was, however, one piece of conversation from the floor of the Senate where Senator Kennedy, in asking for clarification from Senator Jeffords says, it is my assumption that these compounded products will have -- I think I am quoting directly here -- a reasonable assurance of safety and quality. Senator Jeffords says, yes, it is.

That is the nearest I could find to a standard by

which the products would be evaluated, with the pieces of information that we get from the literature and historical records.

DR. WOODCOCK: I think Dr. Rodriguez, though, is raising a reasonable point, which gets to our criteria. If the existing literature mainly raises questions about the effective of the product, I guess we are asking your advice on what do you think of that.

In this case, that is the case. It is not that we have a lot of anecdotal reports saying it is great. We have some studies that raise questions about the effectiveness of the product. What do you think about that? That is what we want to ask you.

DR. JUHL: The committee may have opinions, but I would suspect you would get a better range of opinion from 18 ophthalmologists rather than 18 scattered individuals. I would certainly be happy to entertain any comments that the committee has on the effectiveness of silver protein solution.

DR. WOODCOCK: That or on our approach when this is the case, and what we find is studies that are actually negative for any product, where there are studies and one might conclude from those studies that a product is ineffective.

That is different than a situation where there are

a lot of anecdotal reports of success of using a product.

DR. JUHL: Would they then, by necessity, need to be well controlled double blind studies to show that they are not effective as well, or are we willing to look at the bulk of the evidence?

DR. WOODCOCK: That is what we are asking you. Obviously, we are not using a standard -- this seems to be a whipping boy. This is actually the basic scientific method of evaluating whether or not products work, is to do double blind trials simply to eliminate bias. It is not some kind of regulatory hurdle.

The question is, when you don't have that kind of evidence, you have lesser evidence, are you going to look at the totality of the evidence and how would you advise us to do that.

DR. RODRIGUEZ: Some of the studies were actually done by ophthalmologists and published in the ophthalmology literature.

That is what came to my eyes as I was going through the thing. When some of the members of the profession happen to be convinced of it -- I happen to me a microbiologist, too, in my other life, and I am not impressed with what I see over there.

I will be honest with you, if somebody asked me whether silver was effective, I would have said yes off the

top of my head.

So, I was a little bit surprised by seeing these "negative reports."

MS. FORD: Mr. Chairman, if I might, some of the data that we have, we do polling of the various chemical suppliers that are throughout the country as well as our members and the usage of this.

I can speak to mild silver protein. Around nine kilograms of this substance was sold in the United States in the last year.

In terms of your talking about effectiveness and talking with pharmacists and the chemical suppliers, this is repeat business.

This is not just one pharmacist ordering it, did it work on the patient or not, no, it didn't so now it is sitting on their shelf. They are getting repeat business for patients who are finding effectiveness with this substance.

DR. JUHL: They are using it in what conditions?

MS. FORD: The majority of the pharmacists used -- or all of them that I polled -- are just ophthalmic use. That is all that they are interested in, is ophthalmic use.

DR. LIEBMAN: Which is what I think the FDA would say, that is the reason to include it in the list, is for ophthalmic use only.

DR. WOODCOCK: Certainly that is what is proposed.

DR. LIEBMAN: So, this data supports the FDA position that it should be included for ophthalmic use.

MS. AXELRAD: We proposed including it only for ophthalmic use because there were definite safety problems associated with any other kind of use.

DR. ALLEN: I believe argyrol used to be commercially available as a product and was probably withdrawn due to economic reasons a number of years ago.

Some of the other silver nitrate products had become available. But I remember for years it being commercially available.

DR. RODRIGUEZ: For painting of tonsils trying to get rid of strep, and the question was whether it really worked on that or not.

DR. JUHL: Other comments on either the general question or mild silver protein? Lana?

MS. OGRAM: Yes, I would just like to reiterate Dr. Woodcock's question and see whether we do have a consensus about not paying attention to negative efficacy data. Is that the consensus of the committee?

DR. ALLEN: I think it might be a little difficult, since we don't have all the articles; we just have a representative sample.

Without having access to the complete files of

some of these things, even though these may be actually representative, you know, it might be a little difficult.

MS. OGRAM: I think that is one of the processes that we are going through today, and that is to determine whether we do have enough information to make a definite conclusion on these.

I think that is a valid point. Do we need additional information on this.

DR. JUHL: Can we hear from some we haven't heard from? Anybody on the left, geographically speaking, not politically speaking.

DR. SELLERS: I am not comfortable ignoring data that shows that a product is not effective. I am not comfortable with that.

DR. WOODCOCK: Would you recommend that we do a more thorough evaluation of the literature in this case?

DR. SELLERS: If, in fact, there is literature suggesting that it is not efficacious, I think that further research needs to be done, whether it is more anecdotal or more based on unpublished data on something I can evaluate.

I am very uncomfortable is there is published data indicating that it is not efficacious.

DR. RUSHO: I would like to add one other thing, too, and how is this being sterilized. We are talking about a protein that looks like it is being denatured. I would

think that would be very difficult to push through a two micron filter.

If it can't be made -- this gets into the difficulty of something being made -- can it be made and made sterile on an extemporaneous basis.

DR. JUHL: Can anyone comment on the preparation of this product? Any of our compounders used this?

DR. LIEBMAN: Let me try to respond to Sarah's comment about the literature. The facts here, I think, are that argyrol, the silver products, have gone off the market because there are sexier things.

That means that I don't think you are going to find a lot in the literature when you go looking now, that it is terribly effective.

Again, it is not sexy and has not been used a whole lot in the last 10 years, 15 years. You all may have trouble in trying to find efficacy data that is reasonably current that is not at least 10 to 15 years old.

It may place upon them a burden which may be difficult for them to try to do.

The fact that the IACP, Gina says that the membership that is using it and the chemical companies that are selling it have repeat business says that, for at least a body of physicians and patients and compounding pharmacists, there is a market.

Again, it would seem to me, were it not efficacious, people would not reuse it. They would not reorder it.

They would try it; it would fail. They would say, well, I am not going to use this any more; let's go on to something else.

That they continue using it, I would assume that it means that they are getting satisfactory results.

DR. JUHL: I think the fact that it is being sold means that there is a market for it. I think it is difficult to interpret very far past that, but it is one piece of information.

DR. SELLERS: I was thinking more also just in general, ignoring any data that suggests that any of these compounds is not effective.

I know in the case of silver protein it was used in hospital settings for newborns, and it was replaced by erythromycin, because it not only covered -- the erythromycin came in and it covered more potential pathogens than did just the silver nitrate, for example, chlamydia, which is now one of the major problems associated with newborns.

It was phased out in that setting. It may still be effective for other cases, but we are not talking about specific organisms here as well.

We are talking about a general application. So, I guess I just have some reluctance in approving something for the list, if we don't have enough data to suggest it is effective.

DR. JUHL: If you raise the question of whether or not this is being used as a routine or being used as we envision, for a patient who for some reason can't use an existing product, I guess I don't have a handle on the common usage to know how that would apply.

DR. MC BURNEY: I realize that efficacy was not one of the criteria in selecting these drugs, and I appreciate that.

However, I also share the concern that has been voiced about putting a drug on the list that we have, in the data presented to us, information that it is not effective, for two reasons.

One is because it will be given, so to speak, the imprimatur of the FDA. Although we are not saying that this is a new drug application or approval, the public's perception of that would be that this is a drug that is approved for usage and has efficacy, although that is not technically what we are saying.

I think the perception of that, public-wise, could come forth and that makes me concerned as a person, as a physician, as a patient, a future patient, hopefully.

The second thing is, I don't think in considering medications that we can completely throw aside the efficacy issue.

I think that goes against our whole scientific training that we have, and I am uncomfortable with that.

I certainly do not want to see double blind controlled studies to be provided on all of these drugs, but I would like to see some body of information that would show efficacy.

DR. RIFFEE: I share your concerns, Elizabeth. I am wondering if efficacy is considered here, can we glean any pattern for a look at efficacy from the OTC review process.

We had a similar situation, in that efficacy had not been considered in a number of OTC products that had been on the shelf for a long, long time.

Were any of you involved in that process, and what was considered there? Was historical data solely what was used there? We certainly weren't looking at double blind scientific studies in all those cases.

DR. WOODCOCK: In some cases. Probably the closest relationship to what you are talking about was the desi review, where the available body of evidence for different drugs was evaluated when the efficacy standards went into effect for the Food, Drug and Cosmetic Act, and

their older studies were being looked at.

I understand your points about effectiveness and desiring effectiveness data. I think the point we want to raise is that for none of these drugs is the kind of evidence that you would usually see, even generally at a desi review level.

What I was asking is what Dr. Rodriguez raised, when there is actually affirmative evidence that the drug doesn't work; should that raise some further investigation on our part.

We don't think it would be possible, because looking at the studies that have been submitted, there really wasn't the kind of evidence that you would be able to evaluate efficacy.

DR. RIFFEE: So, you are saying that you don't even have as much information as you had in the desi review, then; it is less than that?

DR. WOODCOCK: That is right.

DR. JUHL: I think, too, the conundrum we are dealing with here is that pharmacy compounding is intended for that fringe of non-responders, the ones that don't show up in the efficacy trials to be responsive.

As we were talking this morning, maybe if 10 or 20 percent don't respond, then some small fraction of that 10 or 20 percent could be helped by some other product or some

other dosage form, that is the population we are choosing to look at.

Any kind of an efficacy study that has been done to this point looks at the entire population and we are just looking at the wrong end of the spectrum, to be able to evaluate efficacy.

I suspect you all went around the circle several times on this whole thing and that is why the decision was made to evaluate safety in the main.

I think we could set a standard that probably everybody could agree to. If there was incontrovertible evidence, that this drug was not effective for nobody, nowhere, nohow, no time, in the literature and we are comfortable with that, then we could say, no, that probably should not go on the list.

I don't mean to speak for the group, but I think we could agree on that. The problem is we are going to have to be somewhere in between on that.

We can choose to make a recommendation on that ourselves. We could choose to recommend that the agency use its advisory committee in the area of practice that it would be most knowledgeable.

That, too, may not necessarily address that fringe of the 10 percent. There may be mor knowledge outside of this committee on this particular product from a group of

ophthalmologists perhaps.

DR. ALLEN: If I could also add, in a situation like this, where it may be difficult to get a lot of definitive studies, we also need to ask ourselves, what is going to happen to the core group of patients and physicians that are continuing to use the product, whether or not that would be in a sense some sign of positive use of the product and what is going to happen if it is not available to them come next month at this time.

It is a difficult situation. Like you said, getting some of these study subjects that are reported in the literature has a lot of variability.

DR. JUHL: Well, did we clear that up for you?

Does anybody have a recommendation to make?

DR. RODRIGUEZ: The concern that I have in thinking about a small percentage if that if you are applying it to the small percentage, fine. If you are using that to apply to a whole group, then that is another story.

For people who are allergic to iodine containing solutions or whatever it is, then I could say fine. If you say all the population, then I have problems going from one stage to the next.

DR. JUHL: Additional comments? I don't feel like we have provided much in the way of helpful review on this subject, but I think that is the issue that we have.

Carmen?

DR. CATIZONE: Dr. Juhl, maybe continuing what you began to say, if we are considering a drug for inclusion or exclusion on the list, and if efficacy is one of those considerations but not the primary consideration in accordance with the statutory direction, if there are no data or conflicting data, then I would suggest that there be more study or more literature review done on that drug prior to inclusion or exclusion on the list.

If there is favorable data or information that goes beyond study, it could be information submitted to various journals where patients or physicians or pharmacists have used this product, this drug efficaciously, that drug should be included, or the consideration or the recommendation would be positive in regard to the efficacy.

DR. JUHL: Comments?

DR. WELDER: My feeling is that although there are concerns about the effectiveness of certain drugs we are considering, being in the field of compounding and knowing that there are a select few people who do benefit from drugs that probably in the broad scope of things are not widely used, I think we would do a disservice in taking a drug off that might possibly be effective for that select group.

DR. JUHL: I guess, too, that we have to keep in mind that having a USP or a NF monograph doesn't necessarily

confer effectiveness, if we would use the same kind of standard.

I guess, Tony, you are suggesting to consider the consequence. What is the consequence of an ineffective drug being used, and what is the consequence of people not having access to something that in their minds is effective.

There are both ends of that, and I don't know that we have an answer to that question either.

Well, shall we move on? I don't think we have a summary judgement on this.

DR. ALLEN: If I could just bring up one philosophical question, I suppose, that is, if there is a period of time that we are requesting additional data, what is going to happen as of November 21 when the product is no longer available.

The physicians would have to basically cease prescribing those products until the information was gathered, as opposed to continuing to let them use them while the information is gathered, and then the decision being made as to whether to place it on the list or not.

I know the regulations don't really speak to that, or the legislation doesn't really speak to that. I would hate to go out and pull some items and then put them back on the list -- I mean, not approve them at this point and then approve them at a later time.

It is going to disrupt some of the patient care, if there is no significant danger or toxicity that is occurring at this point with these products.

DR. MC CLAIN: That sounds reasonable to me because the idea is to do no harm. That seems like a good route to go.

DR. JUHL: I suspect this question will rear its ugly head once again as we go further on.

MS. AXELRAD: First of all, we may see if we can frame the questions perhaps a little mor precisely or say something about this later on as we go on in the meeting and we get to some of the other drugs.

With regard to the issue of what happens on November 21, there are several parts of the statute and implementation of the statute that are not going to be in place by November 21.

Certainly, we won't have the final bulks list in place by November 21. We won't have the final list of products that have been withdrawn or removed from the market in place by November 21. We won't have an MOU in place by then.

We intend to issue a guidance document that will tell everyone basically what our posture is going to be in regard to that.

We will probably not be enforcing those specific

parts of the statute and exemptions that are not in place, or which we have to do something that isn't in place yet.

DR. JUHL: There will be some flexibility until we get the act together, but at some point we have to recognize that once it is done, it is the law of the land.

MS. AXELRAD: Right, and we will have to deal with the question of the evolving nature of these lists. We will have things in various different status categories.

For example, we will have things on the proposed list. We may have things that we have specifically reviewed that we think should be excluded from the list.

We will have other things that may come in after this meeting. We have two already that we haven't really evaluated for this.

There may be other things that come in after the meeting that will be between meetings when we won't have had a chance to discuss with you.

We will have to discuss what the status of those different categories of products is going to be when we determine what happens after November 21.

DR. RODRIGUEZ: Why can't we have so-called under review. Essentially, if this was a fellowship application, for example, it could be approved or it could be under review.

You could still enroll fellows in the program

because there is nothing evil in your thing.

For example, if we uncover something of horrible health, et cetera, I can see you taking it out. Here, to go back to the previous example, on collecting more data on efficacy, et cetera.

You would have that under review. That would not take it out of commission, and would allow the continued use until you complete the review, whenever you set up the deadline.

MS. AXELRAD: I think we have to think through all the implications of the various different scenarios. I think that is a possibility.

We proposed this as a likely candidate. We didn't have significant questions, based on our review of the literature, with regard to this particular substance.

We, in fact, had proposed in the document that we would include it on the list in this first go round which presumably would allow people to continue to use it.

We will evaluate or re-evaluate that in light of the discussions here and make some determination. I think what we were originally proposing was consistent with what you were suggesting.

DR. JUHL: And what you had decided upon as consistent with your criteria. The broader question that has been raised, then, is when there is a large body of

evidence suggesting something is ineffective for what it is being used, how does that factor into the consideration.

MS. AXELRAD: Or any body of evidence suggesting that it shouldn't be used. I mean, we have various levels of evidence.

First, there is no real evidence, just anecdotal reports. Then there may be actual studies or something that are reported in the literature that are either positive or negative. There may be one, there may be two, there may be ten.

I think we are going to have things that fall into various categories, including no evidence one way or the other.

DR. JUHL: I think evidence of ineffectiveness can be viewed different than evidence of effectiveness. At least I am viewing it differently now.

CAPTAIN TONELLI: When we were considering that, one of the considerations that at least the bulks committee looked at was, that is going to be used on a very individual patient basis.

On a compounded product for an individual patient, even if we did have good controlled studies, there is so much patient to patient variability, we are talking about a one patient basis here.

Under that consideration, that is one of the

things that deterred us from looking at an efficacy standard.

The other thing that I wanted to bring up, in my first proposal we talked about limiting dosage forms or routes of administration. I would like the committee's comments on that, because that was the first that you have heard that.

DR. LIEBMAN: An observation, and that is that while a drug like mild silver protein may not have great efficacy for most of the patient, the mere fact that it was proposed by somebody, or some group of bodies, says that for a certain, maybe very small, but for a certain critical group of patients, this is a drug which they feel is important to their well being.

While it may not be efficacious in macro, in micro it might be very important. So, efficaciousness in and of itself is a kind of a tenuous sort of thing and it needs to be looked at very carefully in light of a very small patient population who may not have many other choices.

DR. JUHL: Captain Tonelli's question about limiting products for external use or topical use only, for in office procedures only, and there are a variety of limitations that may or may not serve the purposes of the data, and may or may not serve the purposes of the committee or compounding pharmacists.

Your comments on that general category of classification on the list with reservations, I guess.

DR. ALLEN: If I could just mention one thing, I guess philosophically, if we limit a product to a specific dosage form, what we are doing then is almost stating to physicians and pharmacists, you should not use this for any other route of administration or prepare another dosage form.

The question then comes, are we then stifling creativity, new therapies. As I understand it, then the only way that an alternate route of administration could then be approved would be to come back to this committee. Then you don't have any data to support revisiting the application.

Even though you could understand why you would want to do it, it almost is going to limit potential new therapies in the future.

So, that would be one of the down sides, I think, of doing that, even though I understand why because that is all the data that is currently there.

DR. JUHL: I think your reason for at least doing that in this case, I think the other is a matter of toxicity via other routes of administration.

CAPTAIN TONELLI: In one of these cases. In others, it was the only evidence that we had to evaluate.

The literature only proposed it in those single routes of administration uses.

It wasn't evaluated beyond that. We couldn't make a safety evaluation beyond what we saw.

MS. AXELRAD: Nor was there any evidence of historical use in any other dosage form. For cases like this where there was actually toxicity data associated with other dosage forms, our choice was to either not put it on the list at all, because of that, or to put it on the list limited to the route of administration or dosage form that we felt was safe.

DR. ALLEN: I think my comment on that is I understand that. If we look at the future, though, there will be no such thing as historical use in the future, as of the dates that these lists are in effect.

DR. JUHL: Other comments? Carmen?

DR. CATIZONE: A question to Jane, and perhaps this is something that we have to decide later. If there is a product and it is approved on the list and there is a new indication or a new dosage form for that drug, would the system provide a mechanism for a pharmacist or physicians to submit that drug for consideration and information to the literature to document the use of that product or that drug in a new way or in a new dosage form?

For instance, for a particular product, if it is

limited to topical application, that doesn't exclude future applications for other dosage forms or other uses, does it, or doesn't it?

DR. JUHL: I will attempt an answer. Let's say we are down the road how many ever months or years from now and the law is what the law is.

There would be no way to gather that information without submitting an IND on that product and gathering that information unless it was perhaps in the foreign literature where something came up.

I suspect that individuals are always able to petition the agency to request most anything, and the agency will deal with it in whatever way seems appropriate, which may include coming to the committee or not.

DR. WELDER: I may be confused on this. The limitations is topical and rectal only. Does that refer to all the drugs or just this specific one?

CAPTAIN TONELLI: Just this specific one.

DR. LA FOLLETTE: What are the mechanisms that the committee or the FDA, if these were the routes of administration and we limit it to those routes of administration, I have concern.

We talked earlier today about not having a mechanism, a formal mechanism or process for reporting adverse drug events.

I understand what you are saying about, you know, having the creativity to go and do other things. If there isn't a process in place -- and I really don't believe that pharmacists having a network and talking is a process; that is the dynamics of the personality of the individual. It is not a set process that things are going to be reported and acknowledged to the public and to the FDA.

So, you know, I think -- this is my opinion, but I think we need to take some serious steps or recommendations here. We are treading uncharted waters here. I feel a little uncomfortable.

DR. LIEBMAN: I apologize for talking so much. In terms of what Loyd Allen said, I looked at the next drug, taurine, which is used primarily for parenteral nutrition solutions.

Well, we have a physician who uses it orally. If we don't take Loyd's approach which says, in a sense, trust the physician and the pharmacist to do no harm, and to make up or to recommend a dosage form which is most appropriate for a particular patient under particular circumstances, if we limit it to what is historically available -- i.e., injectable -- then I have got to stop treating my patient.

My physician has to stop treating his patient, simply because it doesn't fall under the aegis of what was.

I have kind of got to trust my physician and

myself and my patient to meet a unique need.

DR. LA FOLLETTE: If you open it up to whatever dosage form that you choose to compound, I think there has to be a formal mechanism to report adverse events. I very strongly feel that way. I don't think we have that right now.

DR. JUHL: I don't think we do and I think we are going to and I think we have to accept that as a given. We can encourage all we want.

Take your hospital setting where, several years ag, our medical center had two adverse reactions in a whole year. It is a better program, but it is not just unique to pharmacy compounding.

Let me challenge you, David. If there was very good evidence in the literature that the oral route was toxic and caused great harm, wouldn't it be right for us to point that out in some fashion?

DR. LIEBMAN: Absolutely, and if I became aware of that, I would certainly go back to my doctor and say, I have got some real problems with what you are doing in terms of the route of administration. There is an ample amount of data which supports that the way you are doing what you are doing, while it may be very good for your patient, there is a lot of data out there that says this is not the best way to go. Can we re-think this position.

Absolutely; I think it becomes incumbent upon the compounding pharmacist, if he or she knows that there are problems that the physician may not be aware of. Absolutely you have got to feed it back to the doctor; absolutely.

DR. JUHL: Others who would like to comment on the listed with restrictions comment, either listed with restrictions because of well-known safety problems or listed with restrictions because there is a lack of information about any other route of administration? I think there are two levels.

DR. CATIZONE: Dr. Juhl, I would support restricting the use of a drug on the list if there are severe toxicity problems.

If there are severe toxicity problems, if the drug is approved, it should be allowed to be used for other purposes, other routes, other dosage forms.

Toxicity should automatically allow exclusion or recommendation that that should be excluded for any other toxic routes or dosage forms than it has been approved of.

DR. JUHL: It would seem to be a prudent consideration of the safety file. This will come up again, as well.

Moving off mild silver protein, any questions or comments on sodium butyrate, or general issues arising therefrom?

DR. LIEBMAN: I would support its inclusion. We use it, because the physicians at Hopkins write it for the short chain fatty acids, either plain or in combination with some other things.

It has been a good drug for those patients who just don't respond to anything else. I would support its inclusion.

DR. JUHL: Number 27 in your tab, taurine? Comments or questions raised?

It is now 3:00 o'clock as if we planned this. I think now would be a good time to take a 15-minute break, if I could ask you to be back in your seats at 3:15.

[Brief recess.]

DR. JUHL: If I can attempt to summarize our review of the group one drugs, I am presuming, because of the absence of objections on all but mild silver protein, that the committee is comfortable with recommending that the agency include those on the list.

Seeing no heads nodding one way or another, I am taking that, and in the instance of mild silver protein, I think the topical administration people were comfortable with the safety profiles on that, but there were general questions raised, and you have heard our discussion on those general issues for that topic.

Now, let us move to something more difficult.

DR. SELLERS: Dr. Juhl, before we move on, the group one includes several drugs that are administered intravenously and some that I have compounded myself in infusion settings.

I think this group -- now may be the time, it may not be the time to discuss or at least bring to the committee just what type of not necessarily restrictions, but in the formulating of these products from a bulk drug chemical that may contain pyrogens, what type of measures should be made to ensure that they are non-pyrogenic, that they are sterile.

A .22 micron filter is not a sterilizing filter. We need to ensure that these products are sterile, that there is apyrogenicity, and that they are at a proper pH and osmality for intravenous infusion.

DR. JUHL: I think that is a very good point. I believe, and correct me if I am wrong, that in the act there is a requirement that these drugs be made with not only everything we have talked about so far, but also according to the USP chapter on compounding. That, I believe, has those kinds of requirements in it.

DR. SELLERS: Specific requirements, though, relating testing for pyrogens, testing for sterility. In the settings that I am familiar with, we did test for sterility and for pyrogens.

I think that needs to be understood and that needs to be ensured for safety.

DR. TRISSEL: I am not sure and maybe Loyd can address the chapter of compounding, but I am not sure it addresses all the specifics of sterile product compounding to a degree that would be appropriate for an injection from a bulk powder.

DR. ALLEN: There are actually two different chapters in the USP, the one on good compounding practices and the second on sterile drug products for home use, which does cover this in quite some detail.

Since the chapters in the USP are living chapters, in essence, there will be some revisits made on some of those in order to bring those into conformance with what we discuss here.

I suspect that there is nobody going to argue against having these standards. The question is how do we put them into effect. Would the revisions that USP does on the chapter on compounding be a better way to proceed than the FDA trying to develop additional regulations? I ask that as a question, I guess.

DR. LIEBMAN: I would think so, as a member of that committee. I would think so.

DR. TRISSEL: I would certainly encourage the USP to broaden the scope of that sterile product compounding

chapter to include settings other than home use. It clearly could be made to apply to that.

DR. RHODES: I think there is an additional point here. The USP, I think, does an excellent job, but they are propounding general statements.

We are talking here about certain individual substances, certain individual products.

As I recall, the people who submitted the data for some of the substances that would be used by the parenteral route, when they indicated what standards they would propose for those drug substances, did not even indicate that the materials should be pyrogen free.

Turning to your point, which I think is a very important one, surely it is essential that any drug substance which is going to be given by the parenteral route, must have a requirement that it be pyrogen free.

I think this issue is an important one. Some of the speakers this morning talked about the general category of parenteral products, and whether they should or should not be included for products that can be compounded.

I don't want to take up too much of the committee's time now, but I think that some of the points that were made this morning are important, and perhaps we should return to look at some of the inclusion or exclusion criteria generally that have been put forward.

CAPTAIN TONELLI: In putting these on the list, we did not look to the final product in actuality. We only looked to the ingredient and what we could find in the literature per the ingredient.

There is another section of the act on demonstrably difficult products that I am sure will address some of the issues you are bringing up. I don't want to like supersede it, because that is not the purview of the committee at this time, but I think those will come up at that time.

DR. JUHL: Again, I don't think there is any argument from anyone on the committee about the importance of these things. Have you considered the regulatory approach to do this.

It would seem the Congressional intent, by suggesting USP as a way of developing these standards would be one approach.

Another approach would be to do it drug by drug, which would seem to be less efficient. Have you talked about that, as the most effective approach to take.

MS. OGRAM: We are going to be prepared to address that at a future meeting. It is one of the things we are looking at in the demonstrably difficult to compound drugs.

I think it is probably premature to speak about it in detail today.

DR. RHODES: Jane, I fully accept that. The only reason I spoke on this topic was just to make sure that people were aware of that problem. I certainly don't want to preempt time on that right now.

DR. JUHL: We will put that on the list of to dos. Other comments stemming from early afternoon discussion before we go on to group 2? Captain Tonelli, if you will.

CAPTAIN TONELLI: Now that we have taken care of the easy ones, in group two, FDA considered the following bulk drug substances as likely to be included on the list because of the doses reported in the literature for the indications listed.

These substances appear to be relatively non-toxic and serious adverse reactions associated with their use have not been commonly reported.

However, FDA has questions concerning the historical use in pharmacy compounding. Specifically, FDA needs information on the medical conditions they have been used to treat and how widespread their use has been.

The group 2 drugs include:

Choline bitartrate. Choline bitartrate is chemically well characterized. It has been used to treat Alzheimer's type dementia. It has also been used to treat infantile colic.

Additionally, FDA has established that choline

bitartrate is generally recognized as safe as a dietary supplement when used in accordance with good manufacturing processes.

Diloxanide furoate. Diloxanide furoate is chemically well characterized. It has been used to treat parasitic diseases such as intestinal amoebiasis.

Dimercapto-1-propanesulfonic acid, or DMPS. Dimercapto-1-propanesulfonic acid, a chelating agent, is chemically well characterized. DMPS has been used to treat heavy metal poisoning.

Ferric subsulfate. Ferric subsulfate is well characterized chemically, has been used topically as a hemostatic agent to control bleeding, including cervical bleeding.

However, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Ferric sulfate hydrate. Ferric sulfate hydrate is well characterized chemically. It has been used topically as a hemostatic agent to control bleeding in dermatological and dental procedures.

However, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Iodoform. Iodoform is chemically well

characterized. It has been used for the control of acute epistaxis and as a paste for dental root fillings.

Iodoform has tested positive in in vitro mutagenicity assays and in an in vitro transformational assay mammalian cells.

However, in two-year bioassays conducted by the National Toxicology Program, iodoform was found to be noncarcinogenic in rats and mice.

Because the literature is limited to topical and intra-dental use of this substance, FDA is proposing to include it on the bulks drug list for topical and intra-dental use only.

Myrrh gum tincture. Myrrh is a gum resin obtained from the stem of the camphora species.

Myrrh is a mixture of many substances and has not been well characterized chemically. Myrrh has been used in its natural form and as a tincture to treat inflammatory disorders of the mouth and pharynx. The preparation reviewed by FDA is a tincture.

Phenindamine Tartrate. Phenindamine tartrate is chemically well characterized. It is an antihistamine that has been used to treat hypersensitivity reactions including urticaria and rhinitis.

Additionally, in developing the over-the-counter monograph for antihistamine drug products, FDA previously

established that phenindamine tartrate is generally recognized as safe and effective for over-the-counter use.

Phenyltoloxamine dihydrogen citrate. Phenyltoloxamine dihydrogen citrate, chemically well characterized and has been used as an antihistamine.

Piracetam. Piracetam is chemically well characterized. It has been used to treat children with dyslexia and patients with Alzheimer's disease, among other cognitive disorders.

Thymol iodide. Thymol iodide is chemically well characterized. It has been used as a topical agent for its absorbent, protective and antimicrobial properties.

FDA notes, however, that it was able to identify only two articles in the literature concerning thymol iodide.

FDA is soliciting public comment on additional information about this substance generally, including how long it has been used in pharmacy compounding and how widespread that use has been.

Additionally, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Tinidazole. Tinidazole is chemically well characterized and has been used often in conjunction with diloxanide furoate, which also appears on the proposed list,

to treat parasitic diseases such as amoebiasis and giardiasis. That is the conclusion of list 2.

DR. JUHL: Thank you. Any questions? Good; let's move to list three.

MD Anderson was the nominator of ferric subsulfate and I would like Dr. Trissel to got to the podium and make his presentation on that. Then, committee, we will discuss that.

When we are done with that, Dr. Trissel can come back to the committee. I don't want to lose his expertise for the rest of group 2.

DR. TRISSEL: Thank you. Lawrence Trissel, MD Anderson Cancer Center.

The second drug that we found in our review of our formulary that we have used for some period of time is ferric subsulfate, or Monsell's salt.

Ferric subsulfate salt is a yellow to brown odorless powder, but as an aqueous solution, it is a dark reddish brown in color.

It is prepared by oxidizing ferrous sulfate in aqueous solution with nitric acid, in the presence of sulfuric acid and boiling to release the nitric oxide. It contains about 25 to 30 percent ferric iron.

Ferric subsulfate was originally described in 1857 by Leon Monsell, and the salt and its aqueous solution are

still termed Monsells today, giving him a certain degree of immortality.

The salt is freely soluble in water and is most often used clinically throughout the country as a 20 percent aqueous solution. It was cited previously in NF-11.

Now, Leon Monsell described ferric subsulfate in his original article as being a powerful topical hemostatic agent. Its clinical use today is also as a topical astringent hemostatic agent in minor surgical procedures, to check bleeding, and to check bleeding from small cuts and abrasions.

Its hemostatic action results from the ability of ferric ions to denature and agglutinate proteins, thereby mechanically sealing small bleeding vessels.

Ferrous salts don't have that ability.

In animals, Monsell solutions, and 3.8 molar ferric chloride solution exhibit similar degrees of hemostasis, showing it is the ferric ions.

Ferric subsulfate is described as more effective, however, as a hemostat than alum or silver nitrate, and it is less irritating than silver sulfate, possibly because of the lower amount of sulfuric acid that is present.

Although throughout the country the most common form of this product is as an aqueous solution, in our institution it is actually used as a gel.

The gel was formed by combining ferric subsulfate salt with propylene glycol.

The gel is used as a hemostatic agent vaginally in patients having minor gynecologic procedures, the gel form helping to maintain the medication in place after its application.

As I said, the aqueous solution is the most common form that is used clinically, and it is also used in minor gynecologic procedures involving the cervix.

It may also be used topically at biopsy sites and other minor surgical procedures.

The FDA was only able to come up with eight published articles citing Monsell's solution, which probably reflects the length of time this product has been around -- its antiquity -- and also the fact that it is neither a patentable item nor something that would be of interest for research.

As far as toxicities goes, certainly this is a good drug to restrict to a topical application. Its LD50 in rabbits intravenously is 7.2 milligrams per kilo, so you certainly wouldn't want to make an injection out of this.

Ferric subsulfate powder can cause skin and eye and mucous membrane and upper respiratory tract irritation.

In the case of contact, the MSDS recommends soap and water washing. Eye contact is similarly just flushing

with water.

Application to skeletal muscles or deep tissue injuries have caused inflammatory reactions.

Ferric subsulfate may also cause ferrigination of tissue resulting in skin pigmentation. That has to be watched for.

In summary, ferric subsulfate is a relatively non-toxic topical hemostatic agent in use since at least 1857. In our institution, the gel has been used for a couple of decades, but no one has been there long enough to know how far back it goes.

Its current use is to control bleeding from minor surgical procedures, biopsies, and minor gynecological surgery involving the cervix. Thank you.

DR. JUHL: Questions for Dr. Trissel or comments on this particular agent.

DR. MC BURNEY: I am quite familiar with this agent, using it a good bit in minor surgical procedures. The main problem with this has been the iatrogenic tattooing of the skin that can result from using the Monsells; it leaves a discoloration.

Other than that, there is not a problem. I would not have a problem with it as it is proposed.

DR. JUHL: Does intravaginal and cervical use fall within the agency's topical use definition?

CAPTAIN TONELLI: Yes.

DR. ALLEN: I have one. I believe I have heard of this being used, believe it or not, as an oral solution for the treatment of esophageal areas that are bleeding in a dilute solution. I am not sure that the topical would cover that.

CAPTAIN TONELLI: Is it swallowed?

DR. ALLEN: It is swallowed, because esophageal bleeding varies.

CAPTAIN TONELLI: I can honestly say that we didn't assess it for that, because all the articles we had were topical only. That is how we assessed it and that is how we planned on limiting it, not as an oral preparation.

DR. JUHL: Other comments? It would appear from Dr. Trissel's presentation that this does have historical use behind it. Are there others who can comment on that?

DR. LIEBMAN: It was in NF-14 you said?

DR. TRISSEL: NF-11.

DR. LIEBMAN: Does that not automatically grandfather it in based on things that are in the USP or NF?

DR. JUHL: It has to be in the current.

DR. LIEBMAN: Okay, thank you.

DR. JUHL: Okay, let's move on, then. Gina, if you could speak on behalf of the Academy for any one or all of these? Perhaps if you have them one at a time, why don't

you go one at a time, or however.

MS. FORD: Sure, that is fine. You have all the information in front of you and I know FDA has provided you with the summaries as far as how chemically well characterized they are, their safety profile.

The statement seems to be repetitious in what you are looking for in this particular group, public comment on how long the substance has been used in pharmacy compounding, how widespread that use is.

To begin with, choline bitartrate also did appear in NF-9. As far as use in actual compounding practice, we know that has been going on since before 1987.

In polling pharmacists and chemical companies as far as the amount of choline bitartrate they are supplying, there are probably less than 1,500 patients on this substance on a yearly basis.

This may or may not be something ongoing. Probably the majority of those patients take it for a limited time and then come off the therapy.

A smaller number, probably 500, would be on this continually. One of the uses that is not listed in your packet there is as a biosalt. That is what choline bitartrate is, and that is why it possibly would be used on a routine data.

So, the historical data, we know it has been used

since before 1987 in compounding practice. It has been in the literature since before or around 1955.

DR. JUHL: Other comments on choline bitartrate.

DR. LA FOLLETTE: Could you please explain to me, it has been removed from the NF, and why? Is that my understanding?

MS. FORD: The majority of substances -- and we may take a response on that -- that have been removed from the USPS, they did not have a widespread use any more.

If USPS or NF kept on every substance that they had ever put into the NF or the USP, their book would be this big.

DR. JUHL: Loyd, do you have a comment on what the process is that results in removal?

DR. ALLEN: In basically every edition of the USP there are additions and deletions, largely based upon what new products have come on the market, what has been submitted by the various manufacturers, et cetera.

Then if the item drops below common usage and there is no longer a great need to have standards published, then it can be removed from the USP. So, the USP is a living, ongoing document.

DR. LIEBMAN: So, being dropped is not negative; it just means it is not in widespread use any more.

DR. RHODES: Mr. Chairman, I think that is

extremely helpful. As someone who has served on USP for many years, there is something else you should know.

At the time, NF was owned by the American Pharmaceutical Association. They definitely had a criteria that it was use, how commonly the material was used.

My understanding is that our current USP requirement is not just use. A drug substance doesn't necessarily have to have a huge market to be USP.

The fact that it is not presently in USP doesn't necessarily mean that it could not come back into USP. The reason it was taken out of the old NF was, I believe, that the previous owners of NF did have that policy. It is not designed to stand the current USP policy.

MR. GRADY: Medical merit.

DR. RHODES: Medical merit is the term; thank you, Dr. Grady.

DR. LA FOLLETTE: I agree with Dr. Rhodes. I would love to see this put back into the compendia, again, for reasons that I had talked about earlier, about just making sure that the quality of the bulk drug substances we use meet certain standards.

MS. AXELRAD: I would like to request that IACP submit for the record the data that they are citing for this.

We had asked originally, in our original request

for nominations, for data on this. Although certainly the statements that are made at the meeting will be in the record, I think that to the extent that people were talked to or articles were pulled or it was identified in an earlier version of the USP or NF, I think it would be very useful if copies of that material could be submitted for the record.

DR. JUHL: Realizing that there were some time constraints in getting your monographs in, if you would like to update those, we would appreciate having the additional information.

MS. FORD: Sure.

DR. JUHL: We will move on to diloxanide furoate, tab 9 if you are scoring at home.

MS. FORD: Diloxanide furoate, as you all know, is antiamoebic. Physicians that are using this particular substance are most likely infectious disease physicians who are treating those with the HIV or the AIDS virus who have come up with strange bugs of some sort.

It is usually dosed at 500 milligrams three times a day, but it can also be given on a one-time basis. This is something that might be done for a one-time shot or maybe 10 days at a time.

It has been used in compounding since the early 1980s. We estimate, as far as dosage, and polling those

particularly who work in the infectious disease area, that it is possibly less than 100 patients a year are on this current therapy.

DR. SELLERS: I would also like to just state for the record that it is a recommended agent. Even though it is not approved, it is a recommended agent in Sanford's Guide to Antimicrobial Therapy, because we don't have very many therapies for this condition. So, it is widely recognized.

DR. RODRIGUEZ: I would like to state that, again, from the pediatric point of view, we are recommended to call CDC at this moment if we want to get it, because of the small amount of it.

One of the abstracts that we were given had a little bit of negative on efficacy again. But the majority and the general thing, as you go through the literature, it is more supportive than in one of the abstracts, 44 versus than 99 something percent, and therefore they wouldn't recommend it.

The majority of people said, if you need an anti-alluminicidal(?) in a symptomatic, for example, this could be another option.

DR. RUSHO: Also, it says in Micromedics that the product is available from CDC at no charge if the physician will just call.

DR. JUHL: I believe there is another drug in the same category, tinidazole.

MS. FORD: Certainly. Tinidazole is used in combination with diloxanide. It is an antiamoebic used by infectious disease conditions.

We approximate the use on that will somewhat be a little bit higher. It is also used in giardia, 100 milligrams twice a day for seven days, or a two-gram one-time dose.

Polling pharmacists and knowing what we do about the use there, approximately 5,000 patients on this substance in a year's time.

DR. RODRIGUEZ: There is a commentary that it can be better tolerated than metronidazole. So, it is a positive commentary that I am making, at least from the literature.

DR. JUHL: Other comments on either of these two items?

DR. TRISSEL: Certainly looking at the brief number of articles that have been presented to us here today, the overwhelming number of those show positive benefit, at least in some categories of patients.

DR. JUHL: I am sensing a consensus toward a positive recommendation here as well.

Dimercapto-1-propanesulfonic acid, number 10 on

your program.

MS. FORD: We call it DMPS. DMPS, as you all have read there, is used to treat mercury poisoning. We had the poignant story earlier today.

It can be used orally, but we don't feel it is quite as effective orally. The main route is through injectable.

It is oftentimes a one-time treatment. They will do urinalysis to determine if the levels are acceptable. If not, they may repeat it twice or three times.

DMPS has been used in compounding since the mid-1980s. We approximate 1,000 to 2,000 patients receive this therapy every year.

DR. JUHL: Is usage for this drug for well-documented heavy metal toxicity, or is this something that kind of causes all the ills of your life and therefore this cures all the ills of your life?

I have seen, not this promoted, but heavy metal poisoning promoted in a different fashion.

MS. FORD: Sure, there is a difference. When we specifically talk about DMPS, that is mercury poisoning. It is not just heavy metal toxicity, but mercury poisoning. There is no other agent available -- BAL or DSMA -- that will pull mercury out like this particular substance.

DR. JUHL: From where does mercury poisoning

arise?

MS. FORD: Fillings; teeth fillings is the biggest cause.

DR. JUHL: That is a very controversial area, as I understand.

MS. FORD: If you live on the coast, it is those oysters we eat all the time.

DR. JUHL: Other comments or questions?

DR. TRISSEL: Would this material have application in industrial poisonings from mercury? Wasn't there a case in Japan some years ago of widespread mercury poisoning?

DR. JUHL: I know I have read something in the last year or two of some kids playing with some mercury of some sort, the pure element, and mixing it with something and ending up with mercury poisoning.

MS. FORD: This is another instance where I don't think people are going out and grabbing people on the street and saying, let me test your mercury level.

It is one of those things where a physician who is practicing in this particular area may, after doing blood levels or mercury levels especially, find a particularly high level of mercury.

If they have other diseases that they feel mercury is disabling them in treating those other diseases, that would be a cause for removing the mercury out of their body.

In the instance of an accident, if they could document those high levels, I think we could use this as well.

DR. TRISSEL: I would think that industrial exposures might be the largest causes of really severe mercury poisoning and it might have application in that setting.

DR. JUHL: In terms of safety again, could you remind us of the findings?

CAPTAIN TONELLI: Actually, we didn't have any adverse events related to the DMPS itself. I mean, mercury poisoning, its diagnosis, I don't know. The incidence of mercury poisoning, I certainly have no indication of how widespread that is.

DR. JUHL: Other questions or comments? Am I sensing passive acceptance on this as well?

DR. TRISSEL: Once again, looking at the articles that have been presented, most of the results have been very positive in treating mercury poisoning.

If it is true that there are no alternatives, this may be a good candidate for inclusion on this list, particularly for the industrially poisoned individual.

DR. JUHL: Ferric sulfate hydrate, number 13?

MS. FORD: ferric sulfate hydrate is possibly an alternative to therapies where sulfate is simply used as a

styptic, just like we would use Monsell's.

Perhaps another indication for ferrous sulfate hydrate would be in the dental area. You would find many dentists using it, once again, as a styptic in the mouth after they have done some type of extraction.

Ferric sulfide hydrate has been used in compounding since around the early 1990s, 1990.

It is difficult to say, as this is probably a one-time use in a dentist's office. As far as the data goes in the research, there may be approximately 100 to 200 patients who receive this therapy every year.

DR. JUHL: Is there a reason a dentist would choose this over an alternative?

MS. FORD: It is his favorite. As far as what he has found and what he has used in his practice, he likes this best. That is the only thing I could add.

DR. JUHL: I certainly think that compounding for the purposes of procedures makes sense. We have had some others of these before.

How does that fit in with what now is the federal definition of pharmacy compounding, which includes this triad between the pharmacist and the physician and the patient or the prescriber and the patient, in these cases where the pharmacist and the patient have no relationship at all?

DR. LIEBMAN: Gina, is that usually used for the patient or you would compound it for a doctor to have in his office?

MS. FORD: It depends on what the physician might want. He might possibly have this for a procedure in his office, or he might send some home with the patient to use if they felt like it. Either one would apply.

The legislation, as it is written, does not exclude compounding for office procedures or for office use. In looking at the Congressional intent, they wanted that to be a part of our practice, to be able to supply physicians with those needs that they might have in their regular day to day practicing.

DR. JUHL: It doesn't exclude, but I don't know that it includes either -- I am hoping that it should and it would. Is the assumption that all the other limitations apply to those kinds of products, limited quantities and so on and so forth?

MS. FORD: Since it hasn't been specifically addressed in the legislation, I can't answer that. Some states, in their compounding rules and regulations, address for office use compounding.

They address in their rules, you know, how much you can supply, whether that be five percent of your total prescription business or compounding business. At this

point, it is a state issue. I just can't speak federally. It has been addressed.

DR. JUHL: Do pharmacists compound things that physicians resell?

MS. FORD: I hope not.

DR. JUHL: I think the Act, being silent on that, it would seem that that would be another one of those to-do list things, to make sure that that be allowed, but also be subject to the same kinds of limitations.

DR. LIEBMAN: Mr. Chairman, we do office compounding for physicians and/or dentists for use in their office.

I would think that most of the office compounding is because a physician wants something to use on a patient in the office then. They may give him something to take home.

In my practice, I don't think I have any physicians who are selling stuff that we made for them. They use it in the office as part of a procedure.

DR. JUHL: I understand that. What I am saying is that we ought to make sure that the same kinds of allowances and controls apply there and I don't know that necessarily - -

DR. LIEBMAN: I don't think you can make something for resale. That is manufacturing.

MS. AXELRAD: We need to address -- we are looking at this issue of office use in developing our general regulations.

Frankly, the language of the statute raises some legal questions about that. It says it has to be by a licensed pharmacist for an individual patient based on a written prescription order, or in limited quantities based on sort of an anticipation of having a prescription for a patient and that type of thing.

In this case, you don't have the three things that you normally need under either of the sections of the statute.

We are looking at that to see how that will work in our general regulations.

DR. JUHL: I think there are several of the drugs that we are talking about here that are being used for procedures that would have that difficulty in meeting the language.

MS. AXELRAD: Right. We are sort of not taking that into account in determining whether the drug should go on the bulk drug list.

However, if we think the active ingredient is appropriate for inclusion of the list, it would be included, regardless of how that analysis comes out.

DR. JUHL: I presume it is the agency's intent to

find a way to make that work, so that things can be prepared for office use?

MS. AXELRAD: We are going to try and do that.

DR. JUHL: I think the committee would recommend that.

MS. FORD: Just to use this substance as an example, it is not realistic for the physician to yank out a tooth, write a prescription, and have the patient go pick it up. I mean, it is simply a matter of office procedure.

DR. JUHL: I wish you ran my HMO.

DR. ALLEN: I might mention one other thing, too, concerning the quantities that are prepared. Inherent in the USP chapter on good compounding practices are some guidelines on beyond use date.

Products should not be prepared with dating beyond what is listed there, unless there are specific stability studies that support that.

So, inherently, some things are going to be limited in quantities that can be provided to doctors' offices based on the USP beyond-use date.

DR. RODRIGUEZ: Just looking at two items, number one the safety, number two the use and efficacy, we have two groups that are listed in the abstracts submitted to us.

One of them says about control of occious hemorrhage, which is a general term, and the other one is

mostly in dental surgery, still controlling occious hemorrhage.

Then it tells us that there can be side effects such as liver and kidney damage. The concern that comes to my mind when I hear that is, if you were to handle a localized dental type thing, I can see that would not be a problem.

I don't know how often it is used in orthopedic surgery, for example. When the time comes to -- if we are going to limit, I would like us to consider where are these liver and kidney damages reported from. I doubt it was from the dental surgery.

MR. OSTERBERG: That information came from the material safety data sheet, which was a general statement of toxicities which have been observed, without respect to dosage.

DR. JUHL: Is that a general toxicity that they list for general products, or was that something specific for this one?

MR. OSTERBERG: It was just specific for this particular product, the two iron salts here.

DR. JUHL: No further comments? Iodoform, number 17.

MS. FORD: Iodoform has been specifically used in compounding practice since about the mid-1980s. Its use has

been limited to a topical application simply as a protectant or to help in healing. On rare instances, you might see iodoform used in oral surgery.

As far as the number of patients using this on a yearly basis, it is probably less than 500.

Once again, the reason why a physician might choose this over some other product, it would simply be physician preference.

DR. JUHL: There was a product or a preparation of iodoform gauze. Was that an official preparation or was that a product?

PARTICIPANT: It was a product, if I remember correctly.

DR. JUHL: I guess that would speak someone of the historical use of the compound, anyway, if not the preparation. Comments on iodoform?

DR. LIEBMAN: Correct me. If it was part of a recognized FDA product, iodoform gauze, would that not again mean that it was acceptable; ergo, it was okay.

DR. JUHL: Was iodoform gauze an approved, FDA-approved product?

PARTICIPANT: It was over the counter, I believe, wasn't it?

CAPTAIN TONELLI: We didn't have a current NDA approval for any iodoform products.

DR. JUHL: So, it may have been grandfathered or just there without notice?

CAPTAIN TONELLI: It is possible. As a gauze, it might even have been a non-drug device. It would have been a device.

DR. TRISSEL: Its use seems to be earlier than that. It was included, according to this, in NF number 7 in 1942. It must go back a long way beyond the 1980s.

DR. JUHL: Can anybody remember NF-7? Okay, I sense a consensus on that. Tab number 19, myrrh gum tincture.

MS. FORD: Myrrh gum tincture, I think we all know, has been used in compounding or pharmacy compounding since biblical times.

It has been included or listed in formulations in the early 1900s, mid-1900s, and continues to be used in pharmacy compounding today.

Most of it is limited to a topical application, once again, as a protectant. It has been used by dentists but, once again, most a topical application.

DR. JUHL: I presume in terms of chemical characterization of this one we don't do too well, but the consequences of such lack of information is unremarkable; is that accurate?

MS. FORD: That is right.

CAPTAIN TONELLI: That is correct. USP has offered to help in getting a characterization done for this also.

DR. RIFFEE: The recommendation on here, however, is not for topical use only?

CAPTAIN TONELLI: I wouldn't have any problem extending it to that.

DR. RIFFEE: To topical use only, to limiting it to topical use.

DR. TRISSEL: Does topical use include dental topical use in the mouth?

CAPTAIN TONELLI: Yes, it does.

DR. JUHL: Other comments or questions?

DR. LA FOLLETTE: Just a question. How many suppliers are there of this?

DR. JUHL: I think the international house of myrrh is the only one. [Laughter.]

MS. FORD: Do you really want to know? I am sorry. I have two that I know of for certain that are supplying that.

DR. LA FOLLETTE: Where are they located?

MS. FORD: Houston, Texas and Amarillo, Texas. Spectrum, I have heard, carries it also.

DR. JUHL: Okay, let's move on to tab 21, phenindamine tartrate, PT. It is an antihistamine that has

been generally recognized as safe and effective under the OTC monograph process.

MS. FORD: Exactly. Phenindamine tartrate has been used in compounding practice since about 1994. The reason for that is because the product was removed from the market in 1993.

It is generally used at a dosage of 25 milligrams three times a day for two to four weeks to clear up symptoms. Probably less than 100 people in a year's time would use this substance.

DR. JUHL: The removal was for reasons other than safety and effectiveness?

CAPTAIN TONELLI: We didn't have any safety reasons -- it was probably economic. We didn't have any reason that it was removed. We didn't remove it from the market. They probably just quit making it as an OTC.

DR. JUHL: Comments?

DR. TRISSEL: This also seems like a good candidate for inclusion for meeting all the criteria that we need for compounded bulks.

DR. JUHL: I suspect its use in pharmacy compounding would not come before 1993. Was that when it was removed?

MS. FORD: Exactly, right.

DR. JUHL: Simply because of that?

MS. FORD: Simply because of that, yes.

DR. JUHL: Okay, let's move on to tab 22, phenyltoloxamine dihydrogen citrate.

MS. FORD: What he just said, in polling some of my pharmacists that have been doing this for a lot longer than I have, the response I got was, oh, Gina, that is an old, old antihistamine.

As an approved product, it was used as a number of years. It has only been used in pharmacy compounding since about the mid-1980s.

Once again, a two-week course of there. Probably less than 300 patients are using this in a year's time. They simply liked the product, it worked for them. They wanted to continue it.

DR. RIFFEE: I know that in the OTC review it was originally a category III. Was there any safety, efficacy ruling on that or did you find anything?

CAPTAIN TONELLI: The OTC review said that there was not sufficient evidence of effectiveness to add it to the OTC monograph.

DR. RIFFEE: So, it is another one that sort of died for lack of interest.

CAPTAIN TONELLI: That is correct. No one actually submitted the evidence.

DR. JUHL: Having been a real pharmacist back when

that review was done and some products were removed because of that, I remember people like Ms. Penningroth becoming exceptionally angry, and no double blinded study was going to convince her that the antihistamines that we had to give her now were as good as the ones we used to have. I understand that. Other comments? Tab 23, piracetam.

MS. FORD: Piracetam. I just have to use it to repeat the statement that was made earlier, that there is no compelling medical need.

Piracetam has a very distinctive compelling medical need, and that is for use in children who are suffering from Down's syndrome.

I can speak of personal anecdotal information for those of you who care. I had a patient of my own who was Down's syndrome, did not speak.

We put her on piracetam, just a simple 100 milligram a day dose, and within a week's time she had spoken a sentence, that she had never spoken before, and continued to progress.

It is not that her disease was cured, but certainly her parents received some communication between them and their child.

Estimated use in the United States, probably somewhere in the range of 800 to 1,000 patients that receive this per year.

I am not discounting that there are those patients who are going to request this from their physician for cognitive enhancement; I could use a little right now. It has been used in pharmacy compounding since about 1990.

DR. JUHL: Is this a drug that has had an orphan classification or has anyone pursued that in any fashion?

CAPTAIN TONELLI: It has been given orphan designation.

DR. TRISSEL: How does that impact what this committee does?

CAPTAIN TONELLI: It probably should have no impact, probably. Giving a substance orphan designation dose not attest to anything except that there is a small population that may have some derived use for this particular product.

DR. JUHL: Comments?

DR. LIEBMAN: They use it at Kennedy Krieger and at Johns Hopkins. They are using it. They like it. We see more and more new patients going on to it.

CAPTAIN TONELLI: I will ask a question of the committee. Since this one has only popped up, our articles probably go back into the 1990s at the earliest. Is that sufficient historical use for pharmacy compounding? I would like the committee's opinion on that.

DR. TRISSEL: 1980, it looks like the earliest one

in that cognitive situation in children. Actually, there is one in 1976.

DR. RIFFEE: David, has it been used in Hopkins primarily in adults or children?

DR. LIEBMAN: Mostly in the kids at Kennedy Krieger.

DR. TRISSEL: It seems exceptionally non-toxic in rodents with an oral LD-50 greater than 10 grams per kilo.

DR. JUHL: Okay, thymol iodide, thin tab number 28.

MS. FORD: Information on this, thymol iodide is used as a disinfectant most times, in some type of foot powder. It may be used with other ingredients.

It is most often used in compounding as a topical preparation. It is then difficult to say how many patients might be using this on a yearly basis. It has probably been used in pharmacy compounding since the pre-1980s.

DR. JUHL: Any idea what the attraction is for this?

MS. FORD: I don't. I have never used it. Anyone else?

DR. ALLEN: I believe it is used somewhat in dentistry also. Thymol iodide has been around for years and years. I know it dates back to what, at least the 1960s, 1950s?

DR. RODRIGUEZ: I have some problem with the definition of topical. Essentially, I see in one of the abstracts they were applying it intrapleurally. To me, that is not topical; that is systemic.

I think that if we go that way, we had better make sure that we limit this, particularly because there is toxicity there.

The safety ratio looks pretty good. You have to have like 30 grams plus and the maximum was three. Given the situation, someone with kidney failure, et cetera, god only knows what the levels might be.

CAPTAIN TONELLI: In looking at this product, we didn't find a lot in the antimicrobial properties. We thought that its absorbent and protective properties seemed to have some effect. That is why we said topical only.

DR. JUHL: Okay, and we have already discussed tinidazole. Are there any other comments on category two?

Very good. Let's take a run at category three.

CAPTAIN TONELLI: Group three. The following substances have been identified as possible candidates for inclusion on the bulk drugs list.

FDA has specific concerns about the historical use as well as the toxicity of these substances, and is soliciting advisory committee input regarding these and any other relevant issues.

I would like to point out that, if these substances are excluded from the bulk drugs list, they may still be available for use under an investigational new drug provision, so they wouldn't be taken completely out of use. Luckily, there are only five on this list.

4-aminopyridine, or 4-AP. 4-AP, which is well characterized chemically, is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals.

It has been used to treat several neurological disorders, including Lambert-Eaton myasthenic syndrome, multiple sclerosis, and Alzheimer's disease.

It has also been used to reverse the effects of non-depolarizing muscle relaxants.

The toxicological properties of 4-AP have not been thoroughly investigated in animal studies.

At doses reported in the literature, the side effect of 4-AP for most patients do not appear to be serious. However, there have been some reports of seizures associated with the use of 4-AP.

Until more information is available about the historical use and safety of 4-AP, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

3,4-diaminipyridine or DAP, is well characterized

chemically, is a potassium channel blocker. It may enhance the release of acetylcholine from nerve terminals.

DAP has been used in the treatment of several neuromuscular disorders, including Lambert-Eaton myasthenic syndrome, myasthenia gravis, amyotrophic lateral sclerosis, and multiple sclerosis.

The toxicological properties of DAP have not been thoroughly investigated in animal studies.

At doses reported in the literature, DAP appears to be well-tolerated and its toxicity appears to be dose related.

There have been reports of seizures with its use, however, and DAP is contraindicated in patients with epilepsy.

Until more information is available about the historical use and safety of DAP, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

Dinitrochlorobenzene. Dinitrochlorobenzene, DNCB, has been used in the treatment of recurrent melanoma and as a skin sensitizer to estimate immune system competency.

Chemically, it is well characterized.

DNCB is highly toxic in doses as little as five to 50 milligram per kilogram, and may be fatal if inhaled, swallowed or absorbed through skin.

High concentrations of DNCB are also extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes and skin.

Until more information is available about the historical use and safety of DNCB, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

Hydrazine sulfate. Hydrazine sulfate is chemically well characterized and has been used to treat cachexia in cancer patients.

The substance, however, is extremely toxic. Multiple exposures to hydrazine sulfate have caused liver and kidney damage, gastrointestinal damage, convulsions and coma, among other conditions.

Hydrazine sulfate is also considered by the International Agency for Research on Cancer to be a potential carcinogen in humans.

Until more information is available about the historical use and safety of hydrazine sulfate, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

Metronidazole benzoate. Metronidazole benzoate is well characterized chemically. It has been used to treat periodontitis and amoebiasis.

FDA assumes that the toxicities for metronidazole

benzoate would be the same as the toxicities of metronidazole itself, which is an FDA-approved drug.

Serious adverse reactions associated with the use of metronidazole benzoate have not been commonly reported.

However, FDA has questions about the effect of the benzoate salt on the dosing and bioavailability of this substance.

Literature reports that metronidazole benzoate is approximately 1/100th as soluble as the metronidazole in water, in that the metronidazole benzoate does not significantly hydrolyse to free base when tested.

Metronidazole benzoate is used in place of the metronidazole base in solutions because of the bitter taste of the base.

FDA could not find any information to support the dose relationship between the metronidazole benzoate and metronidazole base.

FDA is soliciting public comment on these issues. FDA is also soliciting public comment on how long metronidazole benzoate has been used in pharmacy compounding and how widespread that use has been.

Until more information is available about the historical use, the safety, and the bioavailability of metronidazole benzoate, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

That is the third group.

DR. JUHL: Again, I would like to have Dr. Trissel, whose institution nominated DNCB, to make a presentation and answer questions about it.

DR. TRISSEL: Lawrence Trissel, MD Anderson Cancer Center. My presentation will be brief.

We proposed DNCB based on our institution's use of it as a research diagnostic in an FDA approved clinical trial of a separate biological agent.

I have since been advised that the agency has interpreted and clarified the rule, so that any compounded material or drug used under the aegis of an FDA-approved clinical trial does not require nomination to this bulk drugs list.

Consequently, our need has been obviated, and I withdraw our nomination of this compound.

DR. MC BURNEY: I would like to speak to the DNCB. This compound, I know, is used topically in a number of situations as immunotherapy for warts, recalcitrant warts, in which the patient is sensitized to the DNCB and then very low concentrations are applied to the wart to induce an immune response and hopefully cause eradication of the virile infection.

It is also used by a small number of physicians with a disease known as alopecia areata, in which they lose

some or all of their hair.

Once again, the same process is used as with the warts, to induce an immune response to hopefully stimulate the hair growth.

There have been numerous reports in the literature. This has all been topically applied. It is not given systemically.

I would suggest that consideration be given perhaps to just limiting to topical preparations.

DR. LIEBMAN: Dr. Juhl, we had a dermatologist at Johns Hopkins who was involved very much in occupational medicine. He used it the same way and only topically, in very low concentrations, either in acetone or in vitrolatum, very, very weak concentrations to build up a tolerance, and then used short-term therapy and that is it. But he used it.

DR. JUHL: Other comments? I guess technically we would need another nominator for the compound.

Oh, can we consider it ad hoc?

MS. FORD: Can I ask, are they giving it to the patient to take home in those instances, or applying it in the office?

DR. MC BURNEY: I cannot answer that because I don't use the product personally, but I am aware of other people using it.

The sensitization process, where the higher concentration is applied on the forearm is usually done in the office by the physician or the physician's assistant.

I suspect in some cases this is applied usually once or twice a week, depending on the reaction to the patient. Perhaps a very dilute solution would be given to be applied at home.

More often than not, I would think it would be applied in the office. I do think there are cases where it is given to the patients. Most of these are children, because this is a non-painful way of treating warts and alopecia areata.

It would be given to the parents to be applied, once the procedure had been explained to them.

DR. JUHL: It would be the diluted?

DR. MC BURNEY: The markedly, diluted, the .01.

DR. JUHL: Do you have comments on it?

MS. FORD: If we could get you information in the morning on its use as far as in office or taken home. I have the small statistics as far as how long it has been used and approximately how many patients, but I could get you usage information, if that would be helpful.

DR. JUHL: I think that would be helpful. I think the agency is also soliciting comments through notice. I would perhaps alert more in the dermatology community and

the AIDS community. If it is in common use, we need to know about that. The literature just is too old to be reported; is that what your guess is? I remember it being used 25, 30 years ago myself.

CAPTAIN TONELLI: The question here is, it is such a strong sensitizer, we had some real concerns about just having it being used generally, in general pharmacology.

DR. LIEBMAN: My doctor only used it in the office because it had the potential for problems. He always applied it in the office, very clear about that.

DR. JUHL: Would you be comfortable with that limitation on a drug that was listed?

DR. LIEBMAN: I think so. We have never made it for a patient to come in and get. It was always we would make the product -- actually, he supplied us with the medication.

We made it into a useful dosage form and always returned it back to his office. I don't have any problems with that.

DR. JUHL: I guess that wouldn't jive with the way you are familiar with it being used.

DR. MC BURNEY: It is my impression that more often than not it is applied by the physician. I can see that if someone was going on vacation or something and required it and the parents received it and it had been

given many times in the office, that the physician could theoretically give a small quantity to the parents. I suspect that it is more often than not in the office.

DR. RUSHO: We make it up in a one percent solution in acetone and dispense it in a five to seven ml applicator bottle. The patient actually does take that home.

DR. JUHL: The use is for warts?

DR. RUSHO: Yes.

DR. RODRIGUEZ: Are those bottles child safe?

DR. LIEBMAN: No, they are not. If it was going home, you could dispense it in a child-proof prescription vial, or 40 or 50 dram vial.

DR. JUHL: Other comments? If we had to have a yay or nay about this, I am having a hard time telling how the group feels about this one.

DR. LIEBMAN: For me, this falls into the same category as some other things. There is a very small patient population, but it is a necessary population.

As long as I think most times it is used in doctors' offices or very clearly explained by the physician if they take it home, it would seem to me it is necessary, a medical necessity.

DR. RUSHO: My impression is this is a last resort. After they have failed salicylic acid and

glutaraldehyde, then this is the one they use. The usage in our institution is not great, but we do use it.

DR. JUHL: And for some length of time, I presume, from a historical basis?

DR. RUSHO: Actually, we started using it, it was probably back in the 1970s, as a stimulus when we were first doing renal transplants. Then we transferred it over to the wart removal.

DR. RODRIGUEZ: Are we limiting it to the wart removal? There are some statements about its use as a stimulant in leprosy, too. Are we thinking of a broad thing or are we thinking of a narrow application?

DR. JUHL: I don't think we have tried to limit indications of any of the other.

MS. MC CLAIN: Are we specifying one percent or just leaving that open?

DR. JUHL: No, just availability.

DR. LIEBMAN: When we used to make it, it started out like .01 or .001 percent, and then made it progressively stronger and they would start and just use upward. Dr. McBurney, is that about right?

DR. MC BURNEY: Initially you sensitize them with a one percent. Then when you next apply it, you will use the lowest dilution possible to get a reaction, to minimize the chance of allergic contact dermatitis, which is a rash

that can occur in the site of the application. That is correct.

DR. WOODCOCK: Any comments on the carcinogenic potential of this compound? This isn't something that you would detect in ordinary clinical use, even if it were occurring.

DR. LIEBMAN: Excuse me. Again, I think the physician who uses it is fairly aware of what he is dealing with. It is not widely used.

A very few physicians use it because it is the drug of last choice and they have experience with it. I have only one or two derms who are using it.

We would say to other people, you know, we are doing such and such for Dr. so-and-so. Do you have need for, or what else have you done for other people, and we would tell them and they would say, well, I don't have use for that.

I think it is very specific and the physician has a full awareness of all the possible ramifications. I think it should be included for that small number of people who need it.

DR. JUHL: Anybody disagree with that premise? This is a powerful piece of equipment and I guess we have others sitting on shelves here and there.

I think I agree, too, that it seems to be accepted

in many areas and is being used. To not put it on the list would be difficult for us to justify.

I would certainly hold out for other information that may be forthcoming regarding either use, misuse, carcinogenicity or any other problems that people have seen with the drug.

DR. MC BURNEY: Just to comment, it would be my understanding that this would be for topical use only; is that correct?

DR. LIEBMAN: That is all we have ever used it for.

DR. MC BURNEY: That would be my recommendation, if it was put on the list.

DR. JUHL: Any sentiment for limiting it to office use? It seems to be used outside the office now.

DR. LIEBMAN: I don't think you want to do that, simply because you have a facility where it is given to the patient under careful instruction, to take home and how to use it.

You don't want to say to them, you can't do what you are doing any more.

DR. LA FOLLETTE: Just a comment, and maybe it is covered, but since this is a compounded drug that is toxic and that could possibly be going home, I would hope, as you already said, that it is in a child resistant container and

properly labeled with the proper auxiliary labels. Maybe that is understood, but this seems to be a little bit different than the other drugs we have looked at.

DR. JUHL: This would be one that it would be nice to have a USP monograph on, that would stipulate those things in greater detail than we would be able to do on the list. Okay, thank you, Larry.

Let's take the aminopyradines as a group, 4-amino and 3,4-diamino.

MS. FORD: Both of these substances, 4-aminopyridine and 3,4-diaminopyridine, have been used in pharmacy compounding since the early 1990s.

3,4-diaminopyridine, the usage appears to be less. There are approximately 1,000 patients on this particular substance in the United States that are using it for multiple sclerosis.

3,4-diaminopyridine seems to have more effect directly on the muscle and the fatigue factor that MS patients experience from their disease.

4-aminopyridine is also used in multiple sclerosis. It is also effective on the muscle fiber, but it also is effective in improving conduction between the nerves. It has been used in compounding since, like I said, 1990.

There are an estimated 10,000 patients across the

United States on this particular substance. These patients all belong to, or I would hope that they belong to, the society that benefits MS patients, being the Multiple Sclerosis Society.

This is a particular substance that, if cut off, will disrupt patient management and patient care. This is one of these substances where they are at their last resort.

They are using this because everything else they have tried has been unsuccessful and they have found success using these particular products.

The toxicities are somewhat of a concern. One of those is particularly addressed as far as seizures. This would be an instance where a compounding pharmacy engages in his skill and knowledge to exercise pharmaceutical care.

We would emphasize and hope that through interview with the patient and then subsequent evaluation of the patient, that if they did have a lower threshold due to some other disease state, that 4-aminopyridine would not be appropriate in that particular patient.

Some of the studies you have compared dosages. What we recommend, what all compounding pharmacists do when they initiate this therapy, is start at the lowest possible dose, and that is about two and a half milligrams.

That 2.5 milligram dose is given once a day for approximately three to five days, twice a day for three to

five days, and three times a day for three to five days, on a 2.5 milligram dose.

If at any point during that period of time they have found success in the therapy, the dosage is stopped.

The dosage can rise from there to five milligrams bid, five milligrams tid and very rarely as high as 10 milligrams bid or 10 milligrams tid. Most patients are finding success in the 35 to 50 milligram dosage range.

The one particular study that you have where a patient did present to an ER with convulsions, I want particularly to point out that normal protocol was followed in the emergency room to control this event and they were successful. Almost immediately the patient made a full recovery.

Why there are concerns with this, there is also a very large section of the population, those dependent upon this particular substance, for management of their disease process.

We would hate for these patients to be cut off. This is important to them. This is important to their quality of life as an MS patient sufferer.

Once again, this is not something that a compounding pharmacist drags you off the street and says, let me give this to you.

This is an instance where a physician would have

tried and evaluated other therapies without success, and would then contact the appropriate resources within a compounding pharmacy to be able to provide this medication.

DR. RODRIGUEZ: I am looking at the doses and I am looking at the LD50 in the only animals where they have been tested.

Obviously, the patients are responding and they are not dying. You are pretty close to the LD50, at least the species that were treated with the 3,4 anyway.

Any major problems, per se? I am sure that this is a chronic type treatment that patients have.

MS. FORD: In my experience with this particular therapy and using some of our members who use this quite extensively, no, there are not major concerns.

There are signs that you can look at as far as when you might be getting to a toxic level, just as we would look at any other manufactured product.

If nausea or vomiting or diarrhea are noted, then we may need to back off of therapy, contact your physician, reevaluate where we are. There are ways to monitor this therapy.

DR. TRISSEL: could I get a clarification on what the dose is you said?

MS. FORD: Generally it started about 2.5 milligrams.

DR. TRISSEL: Per patient?

MS. FORD: Per patient.

DR. TRISSEL: Then I am not sure it is close to the LD50.

DR. RODRIGUEZ: 3,4-diaminopyridine, 20 milligrams four times a day is actually the recommended doses. I am told they are taking both of them together. The LD50 in rodents is less than 100 milligrams per kilo.

I was getting a little bit concerned about the weight of the patient, of example, and things like that. Essentially, I just wanted to be reassured.

DR. JUHL: I received a letter dated October 6. I think you have it somewhere in your packet. This is from Dr. David Lacomis. He is associate professor of neurology and pathology at the University of Pittsburgh, division of neuromuscular diseases.

He had heard that I was on the compounding committee and wrote a letter to me that says that he specializes in neuromuscular diseases and has several patients with Lambert-Eaton myasthenic syndrome and 3,4-DAP, in his experience, is the drug of choice for this disorder.

Prior to its availability in the Pittsburgh area from a pharmacy, he had to send his patients to Duke to get the medication.

He is quite emphatic about the necessity to

continue the availability of this drug.

I called him and asked him about the differences between the diaminopyridine and the single amino compound. His take on it was that the single amino was better at penetrating the CNS and that is why it probably the reason that it has the higher propensity for seizures, but also has more ability to affect things centrally than the diamino does, which apparently works more peripherally. Other comments?

DR. TRISSEL: Could I get a discussion of the use in spinal cord injury, which was cited in some of the literature and, in fact, is used in some of the hospitals and the medical centers. It is not my area. I wonder how you get some discussion on that.

MS. FORD: Very few of the pharmacists that I polled were using these drugs in that particular way. I don't have numbers across the country. I couldn't tell you if it is 100 patients or 1,000 patients.

I know it has been tried for spinal cord injuries. That brings us to the situation it is of last resort and the patient is just looking for something to improve their condition.

DR. TRISSEL: I would assume it is probably because it is mostly used in hospitals, that you haven't seen it in the outpatient setting.

DR. PECK: There have been studies done in Canada, and they are continuing on, in terms of the spinal cord injury.

There is a faculty on my campus who is participating in -- well, he is trying to get a grant to continue his work. There have been human studies done in Canada for the spinal application.

It has to be given by injection and they are looking for an oral route. That is what the current desire is for studies, giving it orally.

MS. FORD: Does he need any compounding pharmacists to help him with that?

DR. PECK: Would you like the names of some compounding pharmacists in Canada?

DR. JUHL: I don't believe that would be an unsolicited request.

DR. WOODCOCK: I just have a question. These are extremely serious neurologic diseases here, not most of the topical treatments and everything that we were previously discussing.

Is there a manufacturer for these products, and how did they come to be used in this manner without being studied.

If they are actually effective, they are being used in a very small number of people compared to the number

of people who actually suffer from these conditions.

It actually sounds to me as if their dosage recommendations are anecdotal.

DR. JUHL: It would seem to be ripe for an orphan development program.

MS. FORD: As you look at the studies, we once again get into this as far as what population base is served by this.

The studies that were done perhaps did not find usefulness in those particular patients studied. One has indicated that there is a particular subset of the population that this is used for, that it is effective for.

There were early clinical trials that I can give you in the 1990s. I cannot give you the details of those, but we know that there were some trials that were set forth.

DR. JUHL: I think we can probably do better justice to this by spending a whole morning on this topic with experts in this area.

So, we may run into some others that would warrant the same kinds of attention. Unfortunately, we have neither the time nor the expertise to give that level of evaluation to this, and I think we have to make kind of a supposition based on that information that we have.

I guess alternatively, we could suggest that we would like to spend additional time on something like this.

I agree, this is serious stuff for serious illnesses. Either putting it on the list or taking it off has serious consequences as opposed to something for foot powder.

DR. TRISSEL: I would certainly concur with that. This has dramatic consequences either way you go with this, and I think it would warrant serious attention by specialists in the field, if this has use in a very limited population like spinal cord injuries.

DR. RUSHO: Both of these drugs are listed with an orphan drug classification on the FDA web page.

DR. JUHL: I don't know that anybody is actively developing them under the orphan drug program. That may not be true. I guess I am not aware of an active program. Did you run across anybody who is --

DR. WOODCOCK: We probably couldn't reveal it if we had, due to the confidentiality requirements.

DR. JUHL: Aren't orphan grants that are given public record?

DR. WOODCOCK: There are no orphan grants that we know of.

DR. LA FOLLETTE: Due to the toxicity and the side effects, I really feel that this is a drug that should follow an IND route.

DR. JUHL: The question is what do we do with the 10,000 patients that are on it, or whatever that number is.

DR. LA FOLLETTE: If you have that large a population of people, I mean, it doesn't address the people who are on the drug.

I really feel that there is a medical need for this drug and there is probably some type of forum that could solicit pharmaceutical companies or whatever, possibly the clinical studies that Dr. Peck mentioned in Canada.

FDA has done reviews of drugs with Canada for approval; I have been involved with those. There are different avenues to do things, and they could be pursued; not by this committee.

Just for us to approve it with just the information that is presented, I have concerns. If there is a medical need, I think there are other ways to get drugs out there in the market.

DR. JUHL: I couldn't agree more, but by November 21, I am not so sure.

DR. LIEBMAN: Mr. Chairman, it would appear to me that we have 10,000 patients who are currently on an unusual medication, which appears to be helpful to them.

The question that we are kind of faced with is, that while I would agree with you that it would appear that this certainly is a drug which could be looked at by one of the drug companies -- there are 10,000 patients who are taking a drug that appears to be effective, it appears to be

a medical necessity, it is the drug of last resort for most of them, otherwise they would be on other kinds of things.

I think that if we exclude it, what we have suddenly said to 10,000 patients, plus or minus, is sorry, guys, you will have to stop taking your medicine and you will have to go back down to where you were before.

It would seem to me that, given the low incidence reports that we have heard, based again on anecdotal information, there doesn't appear to be a lot of them.

I don't know how in good conscience we can say to 10,000 people, sorry, you can't have your medicine any more.

DR. RHODES: I appreciate that argument. It has, I think, considerable merit. Of course, we could apply that to any drug that comes before this committee which is presently being used.

If we take that argument wholesale, it means we might as well sign off on anything that is presently being used.

I would like to concur with the speaker who said, whatever else this is, it certainly isn't foot powder. Was it you, Mr. Chairman, a very apt choice of phrase. The chairman always makes appropriate comments.

DR. JUHL: Let the record note. [Laughter.]

DR. RHODES: Quite seriously, this is a serious condition. It may well be that perhaps it is justified.

I feel very uncomfortable about approving it based upon the information that we have at the moment.

Is there some mechanism by which we can delay implementation without requiring the patients who are presently using it to be removed? Is there some middle way that we can deal with this?

I don't like giving approval now based upon this very limited information.

DR. JUHL: First, there are a couple of options. First, we have to recommend and the agency has to make the decision.

We could recommend that we, at our next meeting after the first of the year, spend half a day and ask for experts in the field to provide us the assistance that we desire, and perhaps give us the level of comfort we desire.

That may or may not address the need to have things done by November 21. I am assuming the policy of regulatory flexibility may enter in here.

MS. AXELRAD: Dr. Juhl, I really want to sort of take away the sort of feeling that people have to do something by November 21.

For drugs that the committee feels they need to do a fuller evaluation to make a decision yes or no, especially drugs like this where 10,000 people are actually taking it now and who have been taking it for however long they have

been taking it, for some extensive period of time, we are willing to allow them to continue to take it, and to give the committee an opportunity to do a fuller evaluation of these.

I think we will need to identify which of these fall into that category, obviously these two and any other ones that we identify, and then take those up at the next meeting.

In the meantime, we would put out something that indicates that it would be okay to continue using them until the committee and the agency makes a final decision on them.

DR. JUHL: If you are comfortable with that, I think that would be the thing most comfortable with the committee.

MS. AXELRAD: I think that we can definitely do that. I think we should identify a list of the ones that you feel fall into that category.

DR. JUHL: Other comments on these two agents?

DR. ALLEN: I might do one request. That is, if we do exactly that, then in line with what was suggested earlier, we also need to look at the feasibility of what is out there, what company is out there, who would be willing to put out the money for basically a nonpatentable item, to support the clinical studies, so that these patients can continue throughout this project.

If we come up and say yes or no, that no, we are going to have a company do it, but we don't know that someone would be willing to, then we have done the patients probably a disservice.

DR. JUHL: Okay, let's move on to a non-controversial one, hydrozine sulfate.

MS. FORD: This just gets easier and easier.

DR. JUHL: Tab 16.

MS. FORD: First off, I want to go ahead and emphasize again the particular use that the patients and the physicians are using this for, and that is cachexia or wasting in a cancer patient.

This has been used in pharmacy compounding since about 1988. The approximate number of patients on this in the United States is probably between 5,000 and 10,000.

Once again, these patients do go through a dose titration and they are started at 60 milligrams every day for three days, 60 milligrams twice a day for three days and then three times a day thereafter.

This is once again a situation where a patient is seeking a last resort. Their disease is progressing anyway and it becomes a matter of quality of life.

You have heard the stories already today, how we treat the severely terminally ill, those who have already been placed on hospice care.

Shouldn't those who are not at that hospice level still be taken care of and managed appropriately so that their quality of life continues.

Most of these patients and their physicians agree that the benefits of this substance far outweigh the risks. The majority of patients would probably stand here and tell you that the drug risk itself is no worse than the disease process that they are currently going through.

DR. JUHL: Questions or comments on hydrozine sulfate?

DR. LA FOLLETTE: Just reading what has been provided here, it is still a compendial item in USP; 23; is that correct?

CAPTAIN TONELLI: It is not a compendial item.

DR. LA FOLLETTE: So, this is in correct, the information? It never was?

CAPTAIN TONELLI: It is not in the present USP.

DR. LA FOLLETTE: Okay, so when you see the document I am looking at --

CAPTAIN TONELLI: No, I don't.

DR. LA FOLLETTE: The first page, it says USP 23, Indian pharmacopoeia, third edition.

CAPTAIN TONELLI: That is an Indian pharmacopoeia, not the U.S. one.

DR. LA FOLLETTE: That is called the USP also?

CAPTAIN TONELLI: That is the pharmacopoeia from India, the continent.

DR. JUHL: The first item, USP-23.

DR. LA FOLLETTE: The first item says, USP-23.

CAPTAIN TONELLI: It is not in USP.

DR. LA FOLLETTE: That is what I wanted to clarify; thank you.

DR. TRISSEL: This is a compound that, unlike most of them, have actually had double blind placebo controlled clinical trials, two of them, both published in 1994 in the Journal of Clinical Oncology, by Costi et al and LaPrinzi, et al.

Both were findings where there was, at best, no effect, and in one the patients worsened faster than placebo. I would like to call those well controlled, double blind placebo controlled clinical trials to the attention of this committee.

DR. JUHL: I went to my trusty internet and did some looking on this, too. This is a drug that is promoted -- for those of you who do not know, this is a quest of a scientist over many years to have this drug approved.

He truly believes and has followers who are true believers as well. His response to the clinical trials is that they were not properly designed, did not eliminate alcohol and barbiturates and other sedatives which he thinks

interfere with these drugs.

This is a drug that the science has been, in many instances, obliterated by the battle between scientists and people in the non-scientific community. It gets real difficult to evaluate what is what.

I did find a recent article -- this is from the Canadian Medical Association's journal in May of this year -- where they are, in a series of articles, reviewing unconventional therapies for cancer.

Number four on their series was hydrozine sulfate, and they detailed much of this.

To our point here, quoting from the article, the product is available legally in Canada and physicians can obtain information about its availability by contacting the Health Protection Branch of Health Canada.

This is a sentence that I find interesting. The Health Protection Branch does not object to the use of hydrozine sulfate, as long as the patient is under medical supervision.

So, it is available in Canada; it is available in Europe. They also say that it is available through the IND program in the Food and Drug Administration.

I am not exactly sure that you provide that yourselves, but apparently someone has an IND that that provides.

I think this is also a very difficult article to evaluate, a very difficult set of circumstances. I don't know if anyone has found any more information on that, or experience at your sites that might be useful. Dr. Rhodes?

DR. RHODES: I think this is a drug about which some people on both sides feel very strongly indeed. Clearly, there is a lot of emotion involved in this.

I know the criticisms of the clinical trials. Perhaps those criticisms may be valid; I don't know.

The fact remains that they are the only clinical trials that we have got at the moment. They do not support the idea of efficacy.

We know that the drug substance potentially, at least, are toxic. On this particular drug, I would have great reservations for the committee to approve it.

DR. JUHL: Agreements or disagreements?

DR. LA FOLLETTE: I would concur with Dr. Rhodes' comments. Efficacy aside, I think from a safety issue, which was one of our criteria, I would have great difficulty accepting this on the list.

DR. ALLEN: Could this not be one, since we do have a fairly large patient base, that we need to look at it and possibly obtain additional information for the next meeting?

DR. RHODES: Surely, Mr. Chair, if we don't

approve a drug at this particular meeting, that doesn't mean that that drug is damned from now to eternity.

Presumably, what it means, if the sponsor wants to come back, address some of the concerns that some of us have raised, dig up additional information, I would hope that this committee would look at the situation again.

DR. LA FOLLETTE: I agree with Dr. Rhodes.

DR. TRISSEL: Also, this is a situation that is different from the previous compounds, where we have an absence of information, and we are looking for a specialist to have input on the efficacy or not of those products.

This, there does exist a data base of a number of studies, and two well-controlled, placebo controlled, double blind trials. It is not the same thing and it is a toxic compound.

I am not sure that interim category, awaiting further information, I am not sure what kind of information we would be hoping for other than another well controlled, double blind placebo controlled clinical trial which would show a different result.

DR. JUHL: Which is outside the criteria that we require.

DR. WOODCOCK: I would point out, this relates to the discussion we had in the morning where, instead of just contradictory or other data, the data we have on

effectiveness, the affirmative data, is negative.

DR. JUHL: And there are safety concerns.

MS. FORD: Just to clarify the previous, the pyridines. I just don't want basically to flood this office with 15,000 names because those names did not appear on a list.

Is there going to be some inclusion so that we can let people know publicly that the pyridine group especially, the committee wants more information before they make a decision.

DR. JUHL: Again, the committee recommends. The list that was released either Friday or on Monday, will be sent out for public comment.

I believe that is etched in stone. They will be listed as they are listed with requests for different information based on the category that they are in.

I think the word through the official Federal Register will be that more information is needed, and I presume that any information in the trade press that comes out of this meeting will reflect the committee's desire for more information on the two pyridine compounds.

DR. LIEBMAN: Just a question. What do we do with the patients who are currently on it?

MS. AXELRAD: Well, we leave them on it until a final agency action is taken on it, to decide whether it is

or isn't on the list.

DR. LIEBMAN: Is there anything that the physicians or the pharmacists and/or the patients who are currently involved in the usage of this product can do?

I don't want people to feel kind of helpless. Is there something they can do so at least they can say, we at least did something.

DR. JUHL: The thing to do is respond to the call for information.

DR. LIEBMAN: Okay.

DR. JUHL: I need to know. Do we want to defer on this? Do we want to have an additional half day's worth of discussion on this? Do we want to say no? Do we want to say yes? I have heard most all of those options expressed in one way or the other.

DR. LIEBMAN: Yes, that is exactly what we want to do.

DR. ALLEN: I would like to see -- we have got 5,000 to 10,000 terminal patients wasting. I would hate to, in their latter days, all of a sudden come up and say, no, you can't have it any more, until we have a chance to really make sure.

Whether it is effective or not, it is going to adversely affect some of these patients. I would like to be double sure before we make a decision on that one.

DR. JUHL: So, your suggestion would be to defer or schedule for our next meeting a half day's worth of discussion on this topic?

DR. ALLEN: I would like to see more data on it basically, for further discussion.

DR. RODRIGUEZ: We talked about efficacy in those two double blinded trials. Does anybody know the toxicity? That is the concern that we are having.

In other words, was there more toxicity in those that received it other than the control?

We all understand the placebo effect and we understand that these people are really at the end. So, we are worried about toxicity, too. That is the other question that may help us in terms of decisions.

DR. TRISSEL: In one of the studies, I believe it was Costi, that the lines for survival for the placebo and for the hydrazine were very close.

However, in the LaPrinzi article, the survival line actually shortened and their line was worse than placebo considerably.

DR. LIEBMAN: Are we talking about toxicity in terminally ill patients?

DR. TRISSEL: We are talking about survival, duration of survival.

DR. LIEBMAN: Question. Do patients have the

right to choose? I don't mean to play devil's advocate, but if a patient says or feels or the patient and physician say, there is nothing more I can do for you. Would you like standing on your left foot? Are we going to say, no, you can't do that.

DR. JUHL: I think we are at the point to try to decide whether the scientific literature supports the rationality of the decision.

I don't think we have that information. I think with regard to toxicity, it is very difficult to ferret out what is toxic and what isn't in the last few months of life, as opposed to no treatment or a different treatment.

DR. LIEBMAN: I think we need to give great credence to what Allen is saying. You have got a body of 10,000 patients.

I am not saying that we should do A or B. I think we should carefully think of what we are going to do because there are 10,000 patients out there.

DR. JUHL: We can go ahead and designate another time for discussion. I can tell the committee, what we are going to get is more of what we have got.

This will not be easy and it will have some overlay of some very emotional issues having to do with end of life choices and whether or not the drug is effective or whether it isn't, outside the realm of science.

Be prepared to deal with that in its entirety. Even though this is a scientific advisory committee, we are going to have other information given to us on this topic.

Ready to move on? Metronidazole benzoate, tab 18.

MS. FORD: I started to bring samples and let you taste the bad one first and let you taste the good one, but I didn't know how you would feel about me at this point in the day, so I didn't do that.

Metronidazole benzoate is used for giardia in children. There are probably 2,000 to 5,000 children who receive this over an annual period.

This has been in use since before 1987. What makes this compound tasteless is the salt form that has been added on there, which renders the component insoluble, so it doesn't directly fit on those tastebuds and make you go yuck.

There is information supplied in your packet that comes from the Indian pharmacopoeia, that 125 milligrams of metronidazole base is equivalent to 200 milligrams of metronidazole benzoate.

Compounding pharmacists can take that information and make an equivalent dose of the benzoate salt.

This is probably from one particular supplier, the number one overnight shipment that takes place in this country.

Despite their best efforts, if they try to crush up that metronidazole tablet and supply it to that client, undoubtedly they are back before the end of the day and they want something else so the child can't taste it.

This is not a continuous therapy in children. Usually it is a 14-day course of treatment.

DR. JUHL: How was the equivalency determined? Could you refresh my memory?

MS. FORD: I believe it is from the Indian pharmacopoeia.

DR. JUHL: How did they come up with that?

MS. FORD: I don't know that information.

DR. WOODCOCK: It might just be a mass equivalent, not a bioavailability question.

DR. JUHL: This, to me, is an easier question because it has to do with solubility rather than humanity. The reason you can't taste it is because it is insoluble and because it is insoluble, it may not dissolve any place and get into the system.

I guess that is the information that is lacking to be helpful. I wonder if there are other indirect ways to get at that.

MS. FORD: My question is, would physicians continue to use this product if it wasn't effective, if the children did not have the same result on the benzoate salt

as they do on the base, within 14 days time. They do.

DR. LIEBMAN: We make it in our practice a lot. Repeatedly we get calls saying, if you couldn't make it tasteless, I don't know what I would do.

DR. JUHL: I really understand and appreciate that part of it.

DR. LIEBMAN: Again, the point that I think she makes is a good one and that is we get the same physicians and more and more physicians from hospital based practices and in the community, asking us to make the solution of metronidazole that their patients can take. It works.

DR. RODRIGUEZ: One question that I have is, how frequent is the disease, so that people can develop a -- I am asking a very mean question because I am in infectious diseases and I take care of these.

How frequent is the disease so they can actually base one versus the other? I can tell you, that I agree with you, that I have some patients who will not touch metronidazole.

People say the base is working on the basis of what, one patient today, two patients tomorrow?

MS. FORD: I don't have that information. I think that would also depend on the population base. In my practice as a compounding pharmacist, I was in a small north Texas town of 10,000 people, upper middle class.

We probably had a case for metronidazole benzoate once every two weeks.

DR. RHODES: I believe that USP is doing some work at the moment examining the solubility of this and the rate of dissolution. That is what USP is doing.

I don't know -- Tim, have we got any data here for people on the solubility?

DR. JUHL: Can I ask you to come to a microphone? Any one you can find will be fine.

TIM: It is poorly soluble, but you can get about 230 milligrams into a liter at 37 degrees, which is the temperature that matters.

We are looking at the dissolution rate from suspension. That would be also relevant. But you are within the ball park where you can't just presume it is completely insoluble. It may well have sufficient solubility to be an active therapeutic agent.

DR. JUHL: Is the hydrolysis of the benzoate pH dependent at all?

TIM: Under the conditions you are looking at a typical dissolution experiment, you won't be getting any hydrolysis. You will be looking at water or a slightly pH 5 buffer, and most esters are pretty stable under those circumstances.

The dissolution, we are going to take a look and

see if it meets first case, and it is basically not a particularly relevant thing at that point.

Then the conversation would probably switch over to whether or not there is any evidence of different systemic absorption of the drug, as to whether it has a higher systemic absorption than trimetazole would have.

I haven't seen any data about that. I did report earlier today that the British pharmacopoeia has been asked to develop a monograph of the suspension.

I will correspond with them to find out who is behind that.

DR. RHODES: This is an ester, Mr. Chairman. Therefore, esterases being ubiquitous in the GI tract, I would suggest that it will hydrolyze rapidly in the GI tract to give the free alcohol, the free drug. I don't know that for a fact, but it seems very likely.

DR. JUHL: It would seem to make sense.

DR. TRISSEL: Another consideration is that one of the most common sources of failure of medication to work is patient non-compliance. If we can do something to help patient compliance, that may help therapy.

Taste is certainly of considerable importance to children in particular but, with this particular one, to anyone.

DR. JUHL: I didn't use to think so, until I had

kids. Other comments?

I think the issue is clear. It is certainly a preparation that I can understand the usefulness and the need for.

If there is more information that we receive that would make us more comfortable with the systemic availability of it, that would make it an easier call.

I sense at this point the committee in general looks favorably on the inclusion, although we would like to have more information? Is that fair?

DR. RODRIGUEZ: I have a question. We have an application for gingivitis here, too. Is that something that we are thinking of?

In thinking of fighting a microbial infection in the gum, we are not talking only about anti-parasitic activity, but we are also talking about its anti-bacterial activity.

MS. FORD: Sure. Of the six, nine pharmacists that I polled, they are all using it for giardia in children. I got no other information.

There possibly is that use but, once again, the subsection of people is much smaller for that.

DR. JUHL: Other comments? How many would like to take the rest of them and go straight through to tomorrow? Ah, we have unanimity. I have been looking for that all

day.

Well, we will pick this up tomorrow morning with category four. It is my hope that we will be able to address the list proposed for withdrawn because of safety and efficacy reasons.

Perhaps we would be able to finish tomorrow and we could all go home tomorrow. I think we will use that as our goal, if that meets the committee's approval.

Before we close, I want to thank those who came to make presentations to us today, and to also thank the staff of the agency.

This has been a great deal of work for a lot of people on all sides, and I appreciate the diligence with which everyone has participated today and look forward to more of it tomorrow. We are adjourned.

[Whereupon, at 3:45 p.m., the meeting was adjourned, to reconvene the following day, October 15, 1998.]