DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING

ADVISORY COMMITTEE

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Advisory Committee Conference Room 1066
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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. JUHL: Good morning. We will begin. Welcome to I believe the third meeting of the Pharmacy Compounding Advisory Committee.

Let us begin with the reading of the Conflict of Interest Statement, Dr. Igor Cerny.

Conflict of Interest Statement

DR. CERNY: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

In accordance with 18 U.S.C. 208, general matters waivers have been granted to all committee participants who have interests in companies or organizations which could be affected by the committee's discussions of the five drug products for inclusion on a list of drug products that cannot be compounded because they have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.

With respect to the second topic on the agenda to be discussed today and Friday, July 14th, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no

potential for a conflict of interest at this meeting with the following exception: In accordance with 18 U.S.C. 208(b), a full waiver has been granted to Mr. Welder.

A copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any 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 interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

DR. JUHL: Let's begin by going around the table and having microphone practice and introductions, so that the members of the audience know who we are.

We will start with you, Joan.

MS. LaFOLLETTE: Joan LaFollette, Bristol-Myers Squibb, Director of Regulatory Science, CMC.

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

MR. WELDER: Tony Welder, Community Pharmacist

from Bismarck, North Dakota.

DR. PECK: Garnet Peck, Professor of Industrial Pharmacy and Director of the Industrial Pharmacy Laboratory, Purdue University.

DR. SELLERS: Sarah Sellers, Pharmacist, Greenville, North Carolina.

MR. RUSHO: William Rusho, University of Utah.

DR. McBURNEY: Elizabeth McBurney, Dermatologist, Slidell, Louisiana.

MS. RIFFEE: Judy Riffee, the College of Pharmacy, University of Florida, Gainesville, Florida.

MR. TRISSEL: Larry Trissel, M.D. Anderson Cancer Center.

MS. HOPE: Rose-Ellen Hope, Pharmacist, associated with Public Citizen.

MS. AXELRAD: Jane Axelrad, the Associate Director for Policy, Center for Drugs, and Co-Chair of the Pharmacy Compounding Steering Committee, FDA.

MS. OGRAM: Lana Ogram. I am the Director of the Division of Prescription Drug Compliance and Surveillance, and I am the other Co-Chair of the Pharmacy Compounding Steering Committee, FDA.

CPT SCOTT: George Scott, Regulatory Operations Officer, Office of Compliance, FDA.

DR. ANDERSON: Kathy Anderson, Consumer Safety

Officer, Office of Compliance, FDA.

DR. ROGERS: Brian Rogers, CMC Reviewer, Division of Pulmonary Analogy Drug Products.

DR. JUHL: We will proceed with our agenda. For those of you in the audience who have come in, if you happened to walk past the table without picking up a copy of the agenda, they are on the outer table.

Let me turn it over to Lana Ogram for introductory remarks. Lana.

Introductory Remarks

MS. OGRAM: Good morning. I would like to also welcome you back for the third meeting of the Pharmacy Compounding Advisory Committee meeting and to thank you again for your willingness to participate on this committee.

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Pharmacy compounding is a very complicated and far-reaching area and we truly appreciate your continuing support, your dedication, and your in-depth preparations for each meeting.

I would like now to pause just for a moment and have members of our Steering Committee introduce themselves. They are sitting on the far side.

Rita, would you start.

MS. HOFFMAN: Rita Hoffman, Consumer Safety Officer, Center for Drug Evaluation and Research.

MR. RICHMAN: Fred Richman, Office of Compliance, Center for Drugs.

MS. REID: Kim Keller Reid, Special Government Employee working on a company project in the Office of Compliance.

MR. HOROWITZ: David Horowitz, Office of the Chief Counsel.

MS. MISCAELLI: Andrea Miscaelli, Regulatory Policy Staff in CDER.

MR. MITCHELL: William Mitchell, Regulatory Policy Staff.

MS. PALLAS: Lou Ann Pallas, Consumer Safety Officer and Pharmacist, Division of Manufacturing and Product Quality, Office of Compliance, CDER.

MR. BROWN: Ron Brown, Regulatory Operations Officer, Office of Compliance.

MS. ORTUZAR: Liz Ortuzar, Executive Operations Staff.

MR. JONES: Mike Jones, Office of the Center Director.

MS. MILLE: Yana Mille, Operations Staff.

MR. LENISH: John Lenish, Office of Policy, Planning, and Legislation.

MS. OGRAM: Thank you. I would like to thank each of these individuals who has really been working diligently

to implement the provisions of Section 503A of the Act.

It has been almost a year since we met last, and before we proceed with our formal agenda, I would like to bring you up to date on some of the issues that have transpired.

I will briefly talk about the status of the lawsuit, the bulk drug substances list, the Memorandum of Understanding between FDA and the States, and our general compounding regulations.

As we mentioned during our last meeting, the day before Section 503 went into effect in November of 1998, seven compounding pharmacies sued FDA in the Federal District Court of Nevada. They challenged the constitutionality of two provisions of the law based on First Amendment grounds as an abridgement of the right to freedom of speech.

As you may recall, the law exempts compounded drugs that are produced under specified conditions from three key requirements of the Food, Drug, and Cosmetic Act, and those requirements are: that the drugs are produced under current Good Manufacturing Practices, that they are labeled with adequate directions for use, and that drugs undergo agency approval of New Drug Applications and Abbreviated New Drug Applications.

The two provisions that were challenged in the

lawsuit state that in order to qualify for the exemptions provided for by the law, the compounded drug may not be based on a prescription that has been solicited by the compounding pharmacist, pharmacy, or compounding physician, and that the pharmacy, pharmacist, or compounding physician may not advertise or promote the compounding of a particular drug, class of drug, or type of drug.

It is important to remember, though, that the law always permitted the advertisement of compounding services.

On December 18th of '98, the court issued a temporary restraining order which enjoined FDA from enforcing these two provisions of the law.

On September 16th of '99, the U.S. District Court of Nevada decided that the two speech-related restrictions of Section 503A violated the First Amendment of the Constitution.

In addition, the Court concluded that the advertisement and solicitation provisions can be severed from the remainder of the law, and this means that for the moment, Section 503A is fully operative as a law, but without the restrictions on advertisement and solicitation of prescriptions.

In June of this year, FDA filed an appeal in the Ninth Circuit Court of Appeals, and that appeal is pending.

As you may remember, Section 503A restricts the

universe of bulk drug substances that may be used in compounding and qualify for the exemptions. In addition to certain other requirements, only bulk drug substances that fall into one of three major categories may be used in compounding.

Each bulk drug substance must comply with an applicable current USP or NF monograph and the USP chapter on pharmacy compounding. If a monograph does not exist, then, it must be a component of an FDA-approved drug, and if neither, it must appear on a list of bulk drug substances published by FDA in the Federal Register.

FDA originally solicited nominations for this drug from the public in April of 1998, and after reviewing candidates for the list, in January of 1999, we published a proposed bulk drug substances rule, and we received a number of additional nominations for the list.

We have discussed each nomination with this committee at the first two Pharmacy Compounding Advisory meetings in October of '98 and May of '99.

USP, with whom we have been consulting in the development of this list, has agreed to develop standard monographs that will establish the identity, strength, quality, and purity of bulk drug substances that will appear on the agency's published list.

They are working quickly to develop these

standards and have already developed seven monographs for drug which were nominated for inclusion on the list. Final monographs now exist for bismuth citrate, iodoform, sodium butyrate, diloxanide furoate, myrrh topical solution, tinidazole, and ferric sulfate hydrate.

Ferric sulfate will most likely stay on the list because USP's monograph is for ferric sulfate hydrate solution, and since the substance is available as both a solution and a powder, listing the ferric sulfate will clarify that either the solution or the power form may be used in compounding.

Once a USP standard monograph is published, a bulk drug substance no longer requires listing within FDA's regulation, so these drugs will not be included in the final rule.

Several months ago, FDA approved a drug containing caffeine citrate as an active ingredient, therefore, this substance may be used in pharmacy compounding and it also will not appear in the final rule.

USP is also tackling monographs for eight other drug substances listed in the proposed rule, and these include betahistine chloride, choline bitartrate, cyclandelate, levoglutamide, metronidazole benzoate, phenindamine tartrate, and phenyltoloxamine dihydrogen citrate.

These proposed monographs are in the very early stages of development and have appeared in the U.S. pharmacopeial form as preview proposals. Monographs proposed as previews must then be reproposed as in-process revisions before they can be made official.

A monograph for taurine has also been published as an in-process revision.

The bulks final rule is currently undergoing agency review, and after clearance, it will go to OMB and then publication.

This regulation will continue to evolve as substances are recommended for addition to, or removal from, the list through the petition process.

It is also important to remember that the list is not intended to interfere in any way with the agency's investigational New Drug Program, and that drug substances that are excluded from this list may still be available under an IND protocol.

Since our last meeting, we received a petition to amend the bulk drug substances list to include one more drug - D-ribose. The nominator intends to supply the substance as a powder and as a sterile concentrated solution for IV injection.

Unfortunately, we didn't receive this nomination in enough time to review and present it at this meeting,

however, as part of our deliberations on this substance, we will in the future consult with the USP and this committee as required by statute. We will go through the formal rulemaking process before we take a final action on D-ribose.

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At our last meeting, we discussed the Memorandum of Understanding that FDA is developing in consultation with the National Association of Boards of Pharmacy. The MOU is designed to address the interstate distribution of compounded drugs, and a compounded drug may qualify for the exemptions of 503A that I mentioned before if, among other conditions, either of these two conditions apply, and that is, that it is in a state in which the drug is compounded, and that state has entered into an MOU with FDA.

If this is the case, then, the MOU must address the distribution that inordinate amounts of compounded drug outside of the state and the MOU must provide for the appropriate investigation by the state of complaints related to compounded drugs which are distributed outside of the state.

On the other hand, if the state in which the drug is compounded has not entered into an MOU, then, the amount of compounded drug products shipped out of the state by the licensed pharmacy would not be permitted to exceed 5 percent

of the total prescription orders dispensed or distributed by the pharmacy and still qualify for the exemptions from the law.

One of the elements that must be defined in the MOU is guidance on the meaning of "inordinate amounts," and also a safe harbor in excess of 5 percent which would not be considered to be inordinate.

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We have been working with NABP to develop the draft standard MOU as required by the law, and although the law did not require it, because of the complicated nature of this provision, FDA did publish the draft standard MOU in the Federal Register in January of 1999, and we made it available for public comment.

The MOU generated a tremendous amount of interest and we wound up reopening and extending the comment period t twice, in March and again in June of 1999. By the end of August, we had received over 6,000 comments from a variety of sources, from trade associations, from compounding pharmacies, prescribers, as well as 13 state boards of pharmacy.

A large proportion of the comments that we received were as form letters from customers from several large compounding pharmacies.

To kind of put the volume of comments received

into perspective, we received a little over 200 comments on the bulk drug substances proposed rule and approximately 30 comments on the withdrawn and removed proposed rule.

Most of the comments that we received on the MOU centered around the definition of the term "inordinate" although we also received some comments on the portion of the MOU that deals with the investigation of complaints.

We have reviewed the comments and we understand and we are sympathetic to many of the concerns voiced, so we have continued to consult with the National Association of Boards of Pharmacy, and we are revising the draft standard MOU in the areas which were the primary focus of comments.

We intend to republish the revised draft MOU and again solicit comments from the public. After we consider those comments and we revise the draft, we intend to finalize the MOU and make it available for signature by individual state agencies.

We plan to continue to exercise our enforcement discretion and will not normally take regulatory action regarding this requirement until at least after 90 days after the standard MOU is finalized and made available for signature.

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I would like to talk just a little bit about our general implementing regulations. In addition to the three

specific regulations which list drugs which may or may not be compounded, and the MOU which I just described, we are continuing to work on a proposed rule which will address general regulations necessary to implement certain provisions of the pharmacy compounding law although most of the provisions of 503A are self-implementing.

In our proposed regulations, we will define what it means to compound regularly or in inordinate quantities, copies of commercially available drug products that will not qualify for the exemption from the Act, and the regulation will also address such things as supplying of compounded drugs to physicians for office stock, the labeling of compounded drugs, and elements of the certificate of analysis which is required to accompany bulk drug substances.

The regulations will, of course, go through notice and comment rulemaking, and we hope to publish something in the near future.

Before we begin our in-depth discussions of the two topics which are the subject of this meeting, the additions to the list of the drugs that have been withdrawn or removed from the market and may not be compounded under the exemptions of 503A, and our preliminary thoughts on the list of drugs that are demonstrably difficult to compound, I would like to turn to Jane Axelrad, who will discuss some

additional recent development in the bulks drug arena.

DR. JUHL: Before we move on, are there questions for Lana about any of the topics that she covered?

[No response.]

DR. JUHL: Any rough idea of how long it will be before the MOU will be available?

MS. OGRAM: It will be reproposed, republished, and I would say that is months away.

DR. JUHL: Sometime before the end of the year perhaps?

MS. OGRAM: Yes.

DR. JUHL: Okay. Has there been any activity at the state board level with regard to enforcement of any of the provisions that you are aware of?

MS. OGRAM: There has been some state activity. As you know, we do have a final rule in the area Withdrawn and Removed Drugs, so pharmacies that are compounding those types of drugs are going through a warning process. Since the law is fairly new, we are making sure that compounders that are working in that area are being advised, and then we will take action if there is a continuation of compounding of drugs that are on that list.

DR. JUHL: Are the state boards taking the lead on this and consulting with you? How is that working?

MS. OGRAM: We are working with the state boards,

it's a partnership. Information has come to us, and we are sharing information with the state boards and working together.

DR. JUHL: Okay. Good. Thank you.

Jane.

3,4-diaminopyridine and 4-aminopyridine - Updates to the Committee

Introduction

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MS. AXELRAD: We, at the meeting a year ago, when we were discussing the bulks list, we discussed two compound that had been nominated for consideration on the list - 4-aminopyridine, which is being used to treat a spinal cord injury and multiple sclerosis, and 3,4-diaminopyridine, which is principally used to treat Lambert-Eaton's disease.

Those were two of the compounds that we had originally indicated that we had concerns about and that we were consulting with the committee, and we were not proposing to put them on the list because we had concerns about the toxicity profile with those drugs, and we had presentations by two firms at the meeting who indicated that they were studying those drugs under INDs.

At the time, the Advisory Committee asked us to give them an update, and this is the first time we have met since then, so we wanted to provide you with an update on

where we stand in terms of working with the companies on making those drugs available under open label trials.

As you will recall, the committee voted against putting those drugs on the bulk drugs list, but we wanted to provide you the update about where we were. I spoke with Dr. Jacobus from Jacobus Pharmaceuticals who produces 3,4-diaminopyridine and who is involved in studies in that, and Dr. Jacobus has authorized me to tell you that they have submitted a protocol to us for an open label trial and that they believe, and we also believe, that we can work out the details of that, and that they will be able to supply any of the patients with Lambert-Eaton's disease with 3,4-diaminopyridine.

We have representatives here from Acorda Pharmaceuticals who will address the situation with regard to 4-aminopyridine.

DR. JUHL: We have Dr. Andrew Blight, Vice President of Research and Development from Acorda, and Dr. Veronica Mallon, Vice President of Intellectual Property and Government Affairs.

I presume you are Dr. Blight.

DR. BLIGHT: Yes.

DR. JUHL: Welcome.

Acorda Therapeutics

DR. BLIGHT: I am, in fact, Andrew Blight. I am

here today to answer any questions that you may have regarding Acorda Therapeutics and the proposed expanded access program.

I know we were not originally on the agenda, therefore, I will keep my statement brief and leave details to questions should you have them.

As you know, at the meeting in May of '99, Acorda agreed to initiate an expanded access program that would make its sustained released formulation of fampridine available to patients who are currently taking compounded formulations, and it's with sincere regret that I have to report that Acorda does not feel it is possible to initiate an expanded access study of fampridine at the present time.

This is a difficult position for us, as you will realize, because we took our commitment very serious and expended a great deal of effort towards that goal. The reasons for the change in our outlook are quite straightforward.

As intended following the 1999 meeting, we planned extensively for the study. We retained a specialize clinical research organization and put together two protocols that were submitted to the FDA in December of last year.

In the process of doing this, it became clear to us and to our board of directors that such a program would

constitute a much larger drain on our resources and capital than we initially envisioned when we met with you last year.

In trying to assess the actual costs of undertaking this kind of study, we found that it wasn't possible to obtain sufficiently detailed information about the numbers of patients already taking compounded fampridine, the doses that they receive, or the proportion of cost recovery that we might reasonably expect.

Without such information on which to base a detailed plan and budget, we believe it would be irresponsible for a small company like ours with no current revenue stream to initiate such an open-ended study.

This is particularly because, of course, it would threaten our ability to proceed in a timely manner with a clinical development program designed to bring fampridine to regulatory approval.

So, in summary, I repeat that we regret our inability to provide an immediate solution for people currently taking this drug, however, I will add that our development program is on track with active Phase II studies in both MS and spinal cord injury, and plans for entering Phase III in the next calendar year.

Our primary concern as a company must be to complete our development program for fampridine in these two indications, so that everyone who may benefit can have

access to a well-characterized drug with demonstrated efficacy and safety.

I would be happy to answer any questions that you may have.

Thank you.

Committee Discussion

DR. JUHL: Questions from the committee?

MR. TRISSEL: Maybe this is more directed to the agency. Where does the situation stand with the implementation of 4-AP on to any list?

MS. AXELRAD: We haven't published the final list yet, but I don't think it is any secret that we really changed our position since we proposed it to the committee. You know, we are considering the comments, but we had some fairly serious concerns about the drug.

We indicated that although we would try to work with the company to make it available under an open label trial, our decision on whether to put it on the list did not depend on whether it would be made available in that situation.

We felt that since this was a drug to treat a serious life-threatening disease, and it had a significant toxicity profile, it was only in very early trials, and we really did not have any sound evidence that it would work, that we did not feel that it should go on the list.

I don't think that the fact that it won't be made available is likely to change that decision.

Also, we, too, have been trying to get a better handle on how many patients are out there. The only thing that we have are the representations from IACP of the numbers of patients that are actually on the drug. We have talked to people with the Multiple Sclerosis Society and some of the other organizations, and it may not be that there are that many patients on it.

We are having the same difficulty that the company has in trying to estimate how many patients are actually taking this and how many would be affected, but I think that we agree that the best thing to do is to get this drug studied under an IND and if it shows that it is safe and effective, then, it can be made available to everybody who needs it under an approved application.

DR. JUHL: Could I ask, then, the reason that this would be not be financially feasible for the company is that the access would have to be expanded to too many patients for you to afford?

DR. BLIGHT: No. Really, the issue is one of needing to be able to plan for it, so that the cost recovery could make this self-sustaining. As a small company, we don't have the resources obviously to undertake this based on existing capital because that would derail our

development program.

DR. JUHL: So, what are your estimates of the number of patients that would be involved in such a possibility?

DR. BLIGHT: As Jane said, we really don't have an estimate that we can put any reliance on. Originally, I think we had estimates that were in the range of 10- to 20,000 patients, and what calculations we could make based on existing information suggested that the numbers might be much lower than that.

Clearly, in a cost-sharing program of this kind, the fewer patients you have, the most expensive that it will become for each individual. The point that it becomes a positive feedback, where less and less people enroll. So, that was the major -- the major issue was that it was very difficult to know what the costs would be and how they could be planned for.

DR. JUHL: If I could go back to the minutes of the last meeting, you weren't the person who appeared the last time, but the committee felt intimidated by the presentation from your company.

Let me read from the minutes. "With this in mind" -- this was Dr. Cohen reading -- "Acorda has informed CDER that if fampridine is not placed on the list on allowable substances for compounding, Acorda would be willing to

sponsor long-term expanded access, clinical study of our formulation."

Later on he continues, "If the compound fampridine is allowed, we will be unable to offer such a program." At least in my recommendation, that weighed heavily on what I decided to recommend to the agency. Now, the agency obviously has the last word in this, but it appears to me to be rather irresponsible for your company to come in with such a strong position, be so cocksure of what it is that you are going to do, tell the committee you had better not put this drug on the list for pharmacists to use, because otherwise we won't do the program, and now a year later you are not doing the program.

Why is that?

DR. BLIGHT: I think that statement was factually correct, that if, in fact, compounding were to continue, there would be very little pressure on us to put forward an expanded access program at this time in the development process.

I am sure we are very sorry if that came across as being at attempted intimidation. That was simply a statement, I think at its base of the situation as it stood from our point of view, and it was very clear that that was only our point of view and that clearly, there are other issues to be considered. So, I would apologize for such an

impression, and I am sure Dr. Cohen would also if he were here.

DR. JUHL: Dr. Allen.

DR. ALLEN: I guess a couple of comments. One, I believe the vote of the committee was very dependent upon the input from the manufacturer and the understanding that they would follow through, so I think I would like to request that that be revisited at some point in time.

As far as having patients available for your clinical studies, in many clinical studies, you know, the drug products are provided free of charge to the participants in the studies, whereas, in the current distribution system for compounding, the patients have to pay for the product, so there is an incentive for them to be a part of a clinical study.

So, I am not sure that it would adversely affect the number of participants in the studies, you know, provided you had your principals involved. So, I guess I would like to request that we at some point revisit this bulk drug substance.

DR. JUHL: Larry.

MR. TRISSEL: I would like to second that. We certainly discussed the extent of the potential patient load for your company, and 10- and 20,000 patients was discussed, and the company assured us that they could meet that with no

problem.

There were some of us who thought that was probably not going to happen, and apparently that was true. I think it is incumbent on us now to revisit this issue based on the reality of the situation the way it is now, because the committee's consideration was based on fault information provided by Acorda.

DR. BLIGHT: I think that, in fact, if the numbers could be assured to be between 10- and 20,000, it would be possible to calculate sufficiently well to produce such a study, but if, in fact, the numbers fall significantly below 10,000, then, it becomes much more difficult to distribute the costs of such a study, and that is the major concern, not that it would be too big, but that it would be not big enough.

DR. JUHL: Are you more interested in patients with MS or spinal cord injuries?

DR. BLIGHT: Well, as a company, we were founded primarily to develop therapies for spinal cord injury, but because of our interest in demyelination in spinal cord injury, we have broadened that to include MS.

So, we are now equally interested in both conditions, although our roots are in the spinal cord injury side of this.

DR. SELLERS: I would just like to comment that

supply was not one of the criteria that we were supposed to base our decision on, and we would have to reestablish new criteria for listing drugs on the list.

DR. JUHL: Other comments?

[No response.]

DR. BLIGHT: Thank you.

DR. JUHL: Thank you.

I believe given the situation that has occurred, at anytime anyone can repropose that a drug be reconsidered for the bulks list, and as disappointed as I am at the company not being able to fulfill the promises that were made to us with some degree of emphasis, neither have we seen the development of information about people who were on this drug, who have been severely and adversely affected by it either, so I think we also need to call upon the community who would propose that the drug be reconsidered to provide information to the agency that could be examined by the committee in order to reexamine the issue, if that meets with the committee's approval and if I make a bit of sense to you.

DR. ALLEN: Just one comment along those lines, it is my understanding that as soon as the bulks list becomes official, the compounding can no longer be done on anything that does not meet the FDAMA requirements, USP,NF, et cetera, et cetera.

So, if this continues on the list to not be included and the bulks list is published sometime in the next few months, and it may be longer than that, and it may be longer than that before we meeting again, that means there may be an interim period of time where this product could not be compounded.

Could we ask that this product be put on hold until we review it? Do you see what I mean?

DR. JUHL: I understand. Does the agency have a response to that?

MS. AXELRAD: Well, I think that there is two ways to go here. We don't have any additional technical information to present on this. I am not sure what information you would be seeking to have someone who wants it reconsidered that they would propose.

I am not sure you are looking for technical information about the safety of the product. I gather you are looking for how many people are actually taking it and what effect would it have if it was not made available to them.

DR. JUHL: I guess what I am suggesting is that on the MOU, for example, compounding pharmacists generated 6,000 responses to the agency on your request for comment. Compounding pharmacists at this point haven't generated that kind of information and comments on this drug.

If those patients are out there, I would really like to know about it. That was really the concern of the committee, are there patients believe, and their physicians believe, that they are being helped by this, that will no longer have it available to them.

A year ago we had some concern. We were told some numbers. The agency was quite clear in its decision about the drug. That has not seemed to raise alarm amongst patients, pharmacists, or physicians regarding the drug. I guess that is the kind of information that I thought should we make one more last plea for.

MR. TRISSEL: But also we were expecting to have a program in place, so no one should have been particularly concerned. The drug would be available through Acorda, but that didn't happen, and now we are going to have a potential where the drug is in some sort of limbo state that makes it unavailable for patients, and that is different than what we had been led to believe last time.

MS. AXELRAD: I would like to say we did that in the proposed rule where we were not going to put 4-AP on the list. We received a number of comments, somewhere in the neighborhood of 200. Somebody can correct me, but my recollection is it is somewhere in the neighborhood of 200 comments on 4-AP from MS patients, families and friends of MS patients, physicians, and other individuals in favor of

including the substance on the book drugs list, but the majority of these were letter and E-mail testimonials about the benefits of 4-AP, and they really did not provide any scientific data that contradicted the information that we have. I mean they are just anecdotal statements of how it may have worked in individual cases, which is a far cry from scientific data that shows that the drug is, in fact, effective, which is why we believe that it ought to be studies in adequate and well-controlled trials, because there is a large placebo effect and unless you do those kinds of trials, you really don't know.

Also, it needs to be studied in numbers of patients before you can get a true safety profile. We already know that there are some concerns about this. We have somebody here from the division who is probably better able to address this if you wanted more detail.

But I guess what I am saying is we did get a lot of comments on this. We didn't get any scientific evidence that would suggest a change.

DR. JUHL: Well, I think it is kind of ridiculous to expect that you are going to get scientific evidence when we know there isn't any. The committee is concerned there is patients who are receiving the drug, they and their physicians believe that they are receiving benefit. They are going to be put in a situation of not having it, or they

and their pharmacists are going to be breakers of the law.

We were looking for a way around that. The company promised us a way around that, and now we don't have that anymore. So, it is the concern for those 200 patients who sent in their testimonials, and that is all we have at this point.

MS. AXELRAD: What I am suggesting is that rather than having us put it on hold, if the committee would like to revote now. I don't perceive that by putting it on hold we would be getting any additional scientific evidence for the committee to consider that would justify us waiting until the fall.

What I would suggest is the committee could revote.

DR. JUHL: We are talking right past each other. We are not looking for scientific evidence. Again, what we are looking for is some estimation of the number of patients who are going to be inconvenienced and possibly adversely affected by having the drug removed from their access.

MS. AXELRAD: I have no way of getting that number.

DR. JUHL: I understand that, but that's the issue that I have for me anyway. If other members of the committee would like to jump in -- Garnet?

DR. PECK: Since last year -- and I am not

prepared to present scientific data -- I have a concern over stability. We have been approached about this compound, and there is a feeling of interest about the stability of the material. Consequently -- well, first of all, there may have been information presented a year ago and I do not remember it from the chemical standpoint, so I would question the compound from that standpoint.

DR. JUHL: Yes, there was information that was presented on the difficulty in providing a suitable formulation.

DR. PECK: Well, that is the reason for the controlled release system, it supposedly stabilizes it, but basically, it is my understanding that there is a stability problem, and it should be addressed. So, I have a concern even though there have been patients taking the drug.

DR. SELLERS: At our last meeting, we were instructed not to use supply as a basis for deciding whether or not we should list these drugs. In addition, we also discussed the availability of these drugs under emergency INDs. I think we need to remember that in this discussion.

DR. JUHL: Other comments?

MS. AXELRAD: Dr. Juhl, what I was going to suggest is that we can just assume, you know, that there is at least a large number of patients that are taking this drug. It may be in neighborhood of, you know, anywhere over

1,000 patients are on it, and the committee, without sort of stipulation, might want to take another vote based on the evidence that they heard, and determine whether given that it may not be available to those patients if it is not put on the list, you know, whether they want to change their position having heard the statements about the toxicity of the drug and our position about the need to study it under an IND.

DR. JUHL: Maybe if I could ask Dr. Blight, what is your status of your controlled clinical trials and the need for enrollment in, and the availability, of the trials to patients in distant geographies from where we are studying.

DR. BLIGHT: As I mentioned, we are in Phase II with both indications. We have just begun a 90-patient study in spinal cord injury, just completed a 24-patient study in MS that was addressing issues of dosage, and our plan is to complete Phase II's in both indications by the beginning of next year. It is obviously not clear what the outcome will be, but in the best case, we would move into Phase III's in the first half of next year and proceed from there.

Obviously, this is not a predictable course for any drug development, but it is in our interest, of course, to do this as rapidly as we can, and our current time line

calls for completion of Phase III's again within the course of a year, but we obviously cannot guarantee any stage of the development program, but we are pushing ahead with it.

DR. JUHL: Thank you.

Loyd.

DR. ALLEN: Related to the stability that Garnet brought up, I don't see any difficulty in determining the stability of solid or oral dosage form as capsules and a beyond use date, for example, could be published in the literature, whether it is 15 days, 30 days, 45 days, 60 days.

We are certainly not looking for a two-year expiration date, but something that would be appropriate guarantee the purity and the stability of the product for a reasonable amount of time. That should not be too difficult to come up with.

DR. JUHL: But we don't have that data.

DR. ALLEN: Not yet. I think it could be generated in a matter of a few months, though, pretty quickly.

DR. McBURNEY: I am a little reluctant today to reconsider the issue and vote on it because the data was presented over a year ago, and I did not come prepared to this meeting and have reviewed the data, so I would have some reluctance at that today.

I would be glad to review it this evening if that material was given to me, but that would be my concern as an informed committee member.

MR. TRISSEL: Far be it from me to declare stability not to be an important issue, and make a career out of this, but these are two very significant health problems that have no effective treatments, and to me, stability, while the love of my life, may not be the most important issue on a short-term, few weeks basis from compounding.

To me, the treatment of someone with a spinal cord injury or MS, where there is nothing else effective, may be something to consider.

MS. LaFOLLETTE: I just wanted to reemphasize that all these drugs can be available by an emergency IND. It is not like we are eliminating patients from getting the drug.

DR. ALLEN: The emergency IND or the compassionate IND is a topic that I would like to discuss at some point at this meeting, to try to get more information. As I understand it, it is a little bit more complex than just filling out a single sheet of paper and submitting it.

So I think it would help us as committee members to understand the situation a little better if we could have a discussion of it and, you know, possibly look at some alternatives.

DR. FEENEY: If I could address that. I am Dr. Feeney from the Division of Neuropharm Drug Products.

The emergency IND regulations would allow us, on an individual patient basis, to supply the drug, but I would anticipate that whatever number of patients are on the drug already, be it 1,000, be it 200, be it 10,000, would eventually have to be supplied with drug, and to my knowledge, right now Acorda is the only company in a position to do that.

So, I don't know that financially, this puts them in any different position than they would be if they opened up a large open label treatment protocol.

MS. AXELRAD: Dr. Feeney, could we grant emergency or compassionate use INDs if the pharmacist who was compounding the drug indicated the formulation and how they were preparing it? In other words, if the supply was coming from a compounding pharmacist as opposed to from Acorda, could we do that?

DR. FEENEY: I guess we would be able to do that. That would be kind of a monumental task for our chemists to review the individual data. It might be worth talking to our chemists about that.

To give you an example of how the emergency IND works, for diaminopyridine, Jacobus has been -- if the patient needs diaminopyridine for Eaton-Lambert, they

currently get an emergency IND through their treating physician with an LOA to Jacobus' chemistry.

MS. AXELRAD: That is a letter of authorization.

DR. FEENEY: And then Jacobus supplies the drug free of charge. I don't know if Acorda would be willing to do that.

DR. JUHL: I am assuming that they wouldn't. That was kind of the situation that we had hoped would be established, and the real question is can a patient who is receiving a non-Acorda compounded product from a pharmacy avail themselves to the IND process on a one-time emergency basis, and if your contention is that they would need a chemist review, similar to the chemist reviews that the agency is accustomed to seeing, all that obviously isn't something that a compounding pharmacist would be able to provide.

DR. FEENEY: Sure, and beyond that, it does create a certain roadblock in terms of paperwork for the patient and their physician. So, you know it is not going to be easy for them.

DR. JUHL: So, we have an answer about the IND.

MS. AXELRAD: I wouldn't rule it out. I mean I think there are a lot of obstacles, I think, you know, we would have to explore among ourselves exactly what the paperwork would be. We do emergency -- there are different

kinds of INDs we are talking about here, but we would have to see what would be involved in terms of chemistry.

It certainly isn't the kind of chemistry seen in New Drug Application. The chemistry submission for an IND is pretty basic. We would have to discuss how basic it would be and what kind of paperwork would be involved for all the parties, whether the pharmacist, the physician, and the patient, and then whether we would have the resources to deal with something of that size, you know, where we are going to get 1,000 or these.

We could look into that.

DR. JUHL: Let's defer further discussion on this, and if it is possible to get some clarification sometime during the day on that topic.

MS. AXELRAD: We might be able to do that, but we are going to be here, so it might be hard for us to get in contact with all the people that we need to, to get back to you.

DR. JUHL: Let's give it a try and then reconsider this later on, if that is okay. You don't mind procrastinating? Okay. Thank you.

Let us now move to the drugs withdrawn or removed for reasons of safety or efficacy.

Captain Scott.

Withdrawn or Removed List of Drug Products

CPT SCOTT: Good morning. I will be talking with you about several proposed additions to the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness.

First, I would like to briefly review what has been done up to this point with the withdrawn or removed drug product list and then I will present the five drug products that we are proposing to add to the list.

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As you know, one of the conditions of Section 503A of the Act is that the licensed pharmacist or licensed physician may not "compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products 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 not effective."

In October 1998, we presented to this committee 60 drug products, represented by 60 ingredient names, as potential candidates for the Withdrawn or Removed Drug Products list.

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We published a proposed rule on October 8, 1998, which was 63 FR 54082, for this first list containing the 60 drug products. The primary focus of the list was drug products that have been withdrawn or removed from the market

for reasons of safety.

Because of a comment received to the proposed rule, the agency decided to postpone final action on parenteral drug products containing neomycin sulfate because of the pendency of various administrative actions concerning that drug. That brought us to 59 drug products.

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The final rule, published on March 8, 1999, and it was in 64 FR 10944, and it contained 59 drug products that may not be used for pharmacy compounding under the exemptions in Section 503A of the Act.

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I would now like to briefly discuss five additional drug products that we are proposing to include on the Withdrawn or Removed Drug Products list.

The first two drug products are aminopyrine and astemizole. On January 4, 2000, in 65 FR 256, we published a proposed rule to include these two drug products on the Withdrawn or Removed list.

The other three drug products, cisapride, grepafloxacin, and troglitazone, were identified after we had prepared the proposed rule. They will appear in a future proposed rule proposing to add them to this list.

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Aminopyrine, which is chemically related to

dipyrone, a drug product already on the list, was inadvertently overlooked during our first review and is now being proposed for addition to the list, and we are proposing to add it to the list, so that no drug products may be compounded using aminopyrine.

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Drug products containing aminopyrine were used as an analgesic and an antipyretic. Aminopyrine caused agranulocytosis, some cases of which were fatal. In 1964, we declared drug products containing aminopyrine to be new drugs.

We invited New Drug Applications, NDAs, for these drug products, but only for use as an antipyretic in serious situations where other safer drugs could not be used. We received no NDAs for the drug products containing aminopyrine, and so those unapproved drug products were removed from the market by their manufacturers, and that was 42 FR 53954, October 4th of 1977.

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The second drug product appearing in the January proposed rule is astemizole, and we are also proposing that no drug products may be compounded using astemizole.

Astemizole tablets were marketed under the proprietary name Hismanal and were indicated for the relief of symptoms associated with seasonal allergic rhinitis and

chronic idiopathic urticaria. We approved the NDA for astemizole tablets in December of 1988.

Within a few years of the approval, it was learned that low-level overdosages of astemizole were resulting in life-threatening heart arrhythmias. Patients with liver dysfunction or who were taking other drugs that interfered with the metabolism of astemizole were also found to be at risk of serious cardiac adverse events while taking this drug.

The manufacturer of astemizole tablets, the only astemizole drug product on the market, removed the product from the market on June 18, 1999. A notice was published in the Federal Register on August 23, 1999, 64 FR 45973, announcing FDA's determination that astemizole tablets were withdrawn from the market for safety reasons.

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As I mentioned before, the following three drug products that I will present are not in the current proposed role. This is because the proposed rule was prepared prior to the removal from the market for safety reasons.

The first one is cisapride, and we are proposing that all products may not be compounded using cisapride.

Cisapride tablets and suspension are marketed under the proprietary name Propulsid and are indicated for severe nighttime heartburn experienced by adults with

gastroesophageal reflux disease not adequately responding to other therapies.

We approved the tablets on July 29, 1993, and the suspension on September 15, 1995. As of December 31, 1999, use of cisapride had been associated with 341 reports of heart rhythm abnormalities, including 80 reports of deaths.

Most of these adverse events occurred in patients who were taking other medications or suffering from underlying conditions known to increase the risk of cardiac arrhythmia associated with cisapride.

Because of the risk of serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, QT prolongation, and death associated with use of cisapride in certain patients, the manufacturer of cisapride, in consultation with the FDA, has decided to discontinue marketing both cisapride tablets and suspension as of July 14, 2000, and make them available only through an investigational limited access program.

Because cisapride will only be available through treatment protocols under this limited access program, institutional review board approval, completion of a Form 1572, and signed informed consent will be required.

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The next drug is grepafloxacin, and again all products containing grepafloxacin we are proposing should

not be compounded.

Grepafloxacin tablets were marketed under the proprietary name Raxar. Grepafloxacin is a fluoroquinolone antibiotic indicated for the treatment of infections caused by strains of bacteria susceptible to the drug, such as community acquired pneumonia, chronic bronchitis, and various sexually transmitted diseases.

We approved grepafloxacin tablets on November 11, 1997, and Glaxo Wellcome, who marketed grepafloxacin under a licensing agreement with Otsuka, voluntarily removed all licensed formulations of grepafloxacin from the market on October 27, 1999, as a result of emerging safety concerns.

Glaxo Wellcome conducted an extensive review of the safety of grepafloxacin and determined that due to an effect of the drug on cardiac repolarization, manifested as QT interval prolongation on the electrocardiogram, some patients may be at risk of a very rare but serious ventricular arrhythmia known as torsades disease pointes.

Although torsades disease pointes had been reported very rarely in patients taking grepafloxacin, it was considered by the company that the therapeutic benefit of treatment with grepafloxacin may be outweighed by the potential risk to patient safety, especially given the availability of alternative treatments.

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The last drug we will be discussing is troglitazone. Again, all products containing troglitazone are proposed not to be compounded.

Troglitazone tablets were marketed under the proprietary name Rezulin. Troglitazone was indicated for the treatment of type 2 diabetes mellitus. We approved the tablets on January 29, 1997.

Severe liver toxicity has been known to occur with troglitazone since 1997, and the drug has been linked to reports of confirmed liver failures and deaths.

On March 21, 2000, the manufacturer removed troglitazone tablets from the market due to a recent review of safety data that had showed that troglitazone tablets were more toxic to the liver than two similar drugs in its class.

FDA felt that compared to similar alternative diabetes drugs, the continued use of troglitazone tablets posed an unacceptable risk to patients.

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In summary, we are proposing to update the Withdrawn or Removed Drug Product list to add the five drug products discussed above. We invite the Pharmacy Compounding Advisory Committee to discuss these five proposed drug products.

Specifically, we are seeking advice on whether

additional drug products should be added to the list and whether the drug products now being proposed should go on the list.

Thank you.

DR. JUHL: Thank you, Captain Scott.

Are there comments or questions from the committee?

DR. ALLEN: So, the current discussion will be primarily on all five or just the top two that action would be taken on at this meeting? I am not clear.

DR. JUHL: I think the agency would be interested in hearing comments on any of the five. I think in all instances, these are drugs that have a clear record, they have been withdrawn from the market, and in all instances, there are alternatives with the possible exception of cisapride, for which there is a limited use program that is in force.

Do I assume by the lack of comments that there is general agreement with the proposal?

MR. WELDER: I would just like to comment on the cisapride. How tough will it be to get cisapride on special needs?

CPT SCOTT: I have invited Dr. Talarico, the division director from Gastrointestinal and Anticoagulation Drug Products to speak on any questions you may have about

that.

DR. TALARICO: There are three limited-access protocols available for cisapride. One is in the pediatric population for newborns with very severe reflux which manifests with apnea, bradycardia and other serious complications.

The second is in adults with gastroparesis with motility disorder. This is use of cisapride in off-label use because the drug was approved initially only for nocturnal heartburn. But the therapeutic value of the drug was perceived to me more in this additional indication than in the approved one.

And then the third protocol is for children with failure to thrive because of reflux that would be beyond the age of a few months of first group I mentioned.

There is a registration needed by the physician to enroll and they will have to provide evidence that they can comply with all the requirements, which are quite stringent, for these protocols.

The physicians will be screened, will be found to be suitable to handle these patients. There is a very extensive, very detailed informed consent for both the physician and the patients, any legal representative for the patient, and so forth.

The hospital IRB will have to be informed of these

programs going on. So I would say they are limited-access protocols to make sure that, first of all, the patients enrolled is the patient who really needs the drug and that the drug is used in the safest possible way.

These are the two aims of this program.

DR. JUHL: So, it would be safe at least in the pediatric population to assume that the distribution would in all likelihood be limited to specialists in children's hospitals and other specialty tertiary care?

DR. TALARICO: Yes, neonatal intensive care unit mostly. Some of them might continue the drug outside the step-down units, but primarily in intensive care unit.

DR. JUHL: And for the adult populations?

DR. TALARICO: Adult population will be mostly gastroenterologist specialty, board-certified gastroenterologists with knowledge of the disease, so that truly the patient selection is very, very stringent, very appropriate, and that the drug is given appropriately.

The drug is influenced a lot in terms of safety by concomitant factors like additional drugs that are metabolized by the same pathways and by concomitant underlying condition. It just so happened that many drugs that interfere with the safety of cisapride are common drugs, like antibiotics, for example, and many underlying conditions are not grave diseases, are diseases that are

frequently found in patient population and older people.

That is the reason why this drug is unsafe, because many factors continue to be a problem.

MR. WELDER: My concern, we have used cisapride, and in pediatrics, my concern would be to get some of those for those kids that need it, and from the comments made, it was most of the patients that have problems had many other problems and also were taking other meds, and the kids that we have used it for, that would not be a criteria, because they weren't on other meds that I know of.

DR. TALARICO: Yes, that limits quite a bit. Of all the physicians or centers that have applied, the requirements are so stringent that some have not pursued it, and some have not found it to be suitable, so there is a big selection in the process of all will be allowed to use cisapride.

DR. JUHL: And this is in a patient-by-patient selection.

DR. TALARICO: Yes, patient-by-patient selection.

DR. JUHL: And also I think it would be fair to say that the scrutiny of the physician prescribing is quite heavy, too.

DR. TALARICO: Oh, yes, indeed, yes.

DR. ALLEN: As I read the materials that were provided, Janssen is only going to make the product

available through mid-August 2000. What will occur after that point, will the patients' physicians not have it to use?

DR. TALARICO: I am sorry?

DR. ALLEN: On the materials that were provided to us, it states that Janssen will market the product until July 14, 2000, and the product will remain available through pharmacies until approximately mid-August 2000.

Does that mean that after --

DR. TALARICO: No, Janssen will cease distribution on July 14, but today, they will continue to make it, the formulation, or they might have enough that they anticipate a substantive period of time suitable for deciding how valuable this drug, or if a new drug, say, might come on the market.

DR. ALLEN: Well, it states here --

DR. JUHL: Limited access will continue. It's the in-pharmacy distribution --

DR. ALLEN: Well, this talks about the investigational limited access program.

DR. TALARICO: Right.

DR. JUHL: Oh, really.

DR. TALARICO: The limited access program is just initiated, and will continue we don't know until when, but the distribution, the marketing of the drug will stop as of

tomorrow.

DR. ALLEN: Maybe they have two different things in this one paragraph, and it was a little bit confusing, I guess.

So, in essence, this means that physicians that will prescribe this will either need to be board certified or eligible for board certification in specific areas, et cetera.

DR. TALARICO: Yes. There will be many patients who may indeed need the drug, and they may have some contraindication, some very severe contraindication, and that is typical of patients that is still at this point difficult to determine.

I am not sure whether there will be a compassionate use additional distribution. We haven't looked into that yet, whether the responsibility will be strictly between patient and the physician.

DR. ALLEN: I guess my concern would be a lot of the individual patient's physicians that don't live close to major medical centers, you know, to try to be involved in a study like this, it's the death knell, you know, for that patient, they will not go through the necessary processes, and with the hundreds of thousands of patients that have been on cisapride successfully, you know, I would hope that those patients could continue, the specific pediatric

patients would have access to the drug until something new came along.

DR. TALARICO: The newborn population, it is straightforward, because they will have to be in neonatal intensive care unit. The adult patient with gastroparesis represents probably the biggest population where there might be limited access to research center, sophisticated hospitals, et cetera, but then it will be on the physician responsibility to document that the diagnosis has been done appropriately.

In other words, even a known specialist can communicate with some specialists, they can have consultations and make sure that the diagnosis has been made accurately.

DR. JUHL: Other questions or comments?

[No response.]

DR. JUHL: Then, if I could reassert, I am assuming that lack of comments means agreement by the committee that these drugs that have been withdrawn for reasons of safety, we would recommend that they be added to the list, that they not be available for pharmacy compounding.

DR. ALLEN: Would that be the top two that have been requested, that have already been withdrawn, thinking the other three have not been withdrawn yet?

MS. AXELRAD: They may never be withdrawn. I mean most drugs, and many of the drugs that we considered before, are never formally withdrawn. They don't have to necessarily withdraw the application. As long as they are withdrawn from the market for reasons of safety, we believe that they ought to go on the list.

DR. JUHL: And I again was taking the group as a group of five. If anyone wants to consider them individually, I would be happy to do that, too.

DR. ALLEN: Could we consider them individually?

DR. JUHL: We can indeed.

First taking aminopyrine. May I assume concurrence with aminopyrine?

The shaking of heads, are we willing to do that? The shaking of heads doesn't show up in the transcript is my reason for -- we haven't been asked for a vote, but --

MS. AXELRAD: You should take a vote. We should have asked you to take a vote.

DR. JUHL: You want to? Okay.

MS. AXELRAD: Why don't you just vote on each one, and then we will have a clear record.

DR. JUHL: Let's do it formally then.

Those who are eligible to vote that concur with aminopyrine being put on the Withdrawn for Reasons of Safety and therefore not available for pharmacy compounding list,

please signify by raising your hand.

[Show of hands.]

DR. JUHL: Opposed?

[No response.]

DR. JUHL: None were opposed. It was unanimous.

Astemizole. Comments?

[No response.

DR. JUHL: Same question. Those who would recommend that it be placed on the withdrawn list, and not available for pharmacy compounding, please raise your hands.

[Show of hands.]

DR. JUHL: Opposed?

[No response.]

DR. JUHL: Again, it's unanimous.

Cisapride. Additional comments?

MR. RUSHO: In our hospital, the withdrawal of cisapride has not made any impact at all. Physicians have been able to go to proton pump inhibitors and other things, and the loss of cisapride has not been significant.

DR. JUHL: Other comments?

[No response.]

DR. JUHL: If not, the same question. Those who would recommend that cisapride be placed on the withdrawn and therefore not available for pharmacy compounding list, please signify by raising your hand.

[Show of hands.]

DR. JUHL: Opposed?

[One hand raised.]

DR. JUHL: One opposed. And how many voting? Nine in favor of the recommendation, 1 opposed -- excuse me -- 8 in favor, 1 opposed.

Grepafloxacin. Comments?

[No response.]

DR. JUHL: All those who would recommend to the agency that grepafloxacin be placed on the withdrawn list and therefore not available for pharmacy compounding, please signify by raising your hand.

[Show of hands.]

DR. JUHL: Opposed?

[No response.]

DR. JUHL: It's unanimous.

Troglitazone. Comments? Discussion?

[No response.]

DR. JUHL: All those who would recommend that troglitazone be placed on the withdrawn and therefore not available for pharmacy compounding list, please signify by raising your hand.

[Show of hands.]

DR. JUHL: Any opposed?

[No response.]

DR. JUHL: None opposed. It also is unanimous.

Additional comments on the Withdrawn for Safety list?

[No response.]

DR. JUHL: If not, we are five minutes early. We will take a 15-minute break and reconvene at 10:10.

[Recess.]

DR. JUHL: We will reconvene. Our next topic is the Demonstrably Difficult to Compound. Section 127 of FDAMA instructed the agency to prepare a list of drug products that had demonstrable difficulties in compounding.

This is the first introduction that we, as a committee, have had to the white paper on this topic, and to get us started is Dr. Kathleen Anderson.

Demonstrably Difficult to Compound

Introduction: Factors and Approach

DR. ANDERSON: Good morning.

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I will be providing an overview of the approach FDA is proposing to use in developing the Difficult to Compound list. This afternoon, our CDER experts will present the scientific rationales based on our preliminary findings for including certain products on this list. They will also be available to answer any technical questions.

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Section 503A(b)(3)(a) of the Federal Food, Drug, and Cosmetic Act states that "a drug product may be compounded under Subsection (a) only if such drug product is not identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product."

To do this we convened an internal agency work group and worked with experts from CDER. It was decided that the best approach to develop this list would be to identify criteria or factors that we could use to evaluate products for inclusion on the list.

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In developing these factors, we considered attributes that could affect a product's safety and efficacy, namely a product's potency, purity, and quality. We then identified factors that we could use to help us evaluate the effect of compounding on a product's potency, purity, and quality.

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The first factor is the drug delivery system. Is a sophisticated drug delivery system required to ensure dosing accuracy and/or reproducibility?

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Another factor was drug formulation and

consistency. Is the sophisticated formulation of the drug product required to ensure dosing accuracy and/or reproducibility?

Because of the sophisticated formulation, is product-to-product uniformity of the drug product often difficult to achieve?

Is the safety or efficacy of the product a concern if there is product-to-product variability?

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The third factor is bioavailability. Is it difficult to achieve and maintain a uniformly bioavailable dosage form?

Is the safety or efficacy of the product a concern if the bioavailability varies?

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Complexity of Compounding. Is the compounding of the drug product complex?

Are there multiple, complicated or interrelated steps?

Is there a significant potential for error in one or more of the steps that could affect drug safety or effectiveness?

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Facilities and Equipment. Are sophisticated facilities and/or equipment required to ensure proper

compounding of the drug product?

Is there a significant potential for error in the use of the facilities or equipment that could affect the drug safety or effectiveness?

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Training. Is specialized, highly technical training essential to ensure proper compounding of the drug product?

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Testing and Quality Assurance. Is sophisticated, difficult to perform testing of the compounded drug product required to ensure potency, purity, performance characteristics, or other important characteristics prior to dispensing?

Is there a significant potential for harm if the product is compounded without proper quality assurance procedures and end-product testing?

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We propose to evaluate products in light of each of these factors in developing the list of Difficult to Compound Drugs. Each factor would be balanced on a case-by-case basis in deciding whether a product would be an appropriate candidate for inclusion in the list.

We seek input from this committee on any additional factors that should be used in evaluating

products for the list. We specifically request comment on whether to consider as a factor the difficulty or importance of achieving stability for a drug product on this list.

We would like the advice of the committee on the use of these factors. Are they appropriate?

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After we developed the factors, we then began a preliminary evaluation for inclusion on the list, focusing on products with evidence in the literature and potential to affect the public health.

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In this preliminary evaluation, we found that some products with similar characteristics raise similar concerns for pharmacy compounding. For example, all drug products contain uncertain dosage forms, such as metered dose inhalers, if compounded, could present the same difficulties in assuring the safety or effectiveness of that product.

We have also tentatively determined that the compounding of all dry powder inhalers and transdermal drug delivery systems are difficult to compound. Therefore, we are tentatively proposing to include both specific drug products and categories of drug products grouped by relevant factors, such as metered dose inhalers, on the list of Difficult to Compound Drugs.

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We also found in this preliminary evaluation that some products could raise concern for pharmacy compounding if minimum standards are not met. For example, we recognize that the compounding of sterile products is a complicated issue.

As described in our concept paper, the preparation of sterile products is unavoidably complex. We believe that the concerns associated with the compounding of sterile products may be alleviated by the use of minimum standards.

We evaluated a variety of existing guidelines for pharmacy-prepared sterile products and have tentatively concluded that USP Chapter 1206 describes comprehensive controls that, if followed, would ensure the quality of sterile drug products.

Therefore, we are tentatively proposing to include drug products that are demonstrably difficult to compound unless certain minimum standards are met, and we are tentatively proposing that sterile drug products, compounded under procedures other than those described in USP Chapter 1206, would be considered demonstrably difficult to compound.

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Our concept paper describes in detail our preliminary findings. We seek input from this committee on our proposed approach and whether it is appropriate to

include the following products on the Difficult to Compound list: metered dose inhalers, dry powder inhalers, transdermal delivery systems, and sterile products compounded under procedures other than those described in Chapter 1206 of the USP.

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This afternoon our CDER experts will be presenting the scientific rationales for tentatively including each of these products on the Difficult to Compound list. Dr. Brian Rogers from the Office of New Drug Chemistry will discuss metered dose inhalers and dry powder inhalers.

Dr. Vinod Shah and Dr. Amit Mitra, from the Office of Pharmaceutical Sciences, will discuss transdermal drug delivery systems. Dr. Peter Cooney, also from the Office of New Drug Chemistry, will discuss sterile drug products.

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We view this process as an ongoing project and intend to continually identify and evaluate additional products, as well as categories of drug products for inclusion on this list.

We seek input from this committee for products for evaluation as candidates for the list.

Thank you.

Committee Discussion

DR. JUHL: I would like now to have the committee

engage in a discussion of the criteria that have been presented by Dr. Anderson, and your view of the suitability of those criteria in making determinations of both the products and product categories that are before us at this meeting and may come before us at other meetings.

Who would like to start? Larry.

MR. TRISSEL: First, I would like to say that I do think that a good effort has been made to put together some valid points for consideration here, so anything I have to say that is not positive should be taken in that light.

I have a couple of concerns with regard to the criteria, not many. The complexity of compounding issue may be one of interpretation. It is hard to envision something more complex than a multi-component parenteral nutrition admixture, but it must be compounded, there is no way to deliver this in any other way. So, that issue should be viewed in the light of having to delivery complex mixtures when there is no alternative.

The other thing that you had specifically asked for was about stability, something that is, as I pointed out, near and dear to my heart. The stability issue clearly is one related, not to categories, but to specific molecules.

I would note that the agency has approved over the years any number of commercial drugs for sale that have

really remarkably short stabilities. The one that comes to mind right now is a melphalan injection with a 60-minute stability from time of compounding. We don't like that by any stretch of the imagination, but we do work within that to deliver this drug to patients.

It is hard to envision trying to give something with a lower stability than 60 minutes, but we did have one, an investigational drug that had 30 minutes, and even at 30 minutes it was 15 percent decomposition. That was imidazole carboxamide some years ago.

Fortunately, for those stability purists, this is not a drug that had much therapeutic value, but melphalan does, and is approved for sale in this country with a 60-minute stability. I am not sure how you would use stability in light of that other than to make professional recommendations of use within some time frame.

I think I will stop there because you are just asking at this point about the criteria.

DR. JUHL: Loyd.

DR. ALLEN: I have a couple of things. Incidently, this is a very good presentation as far as the components of it.

On drug delivery system, is a sophisticated delivery system required, I think probably the intent was to include a delivery system, active drug product component

together, however, the way it currently reads is any sophisticated drug deliver system, for example, I.V. ambulatory pumps are very complex, programmable systems that pharmacists have to work with, intrathecal pumps are very sophisticated. We could even look at iontophoresis and phonophoresis as being sophisticated delivery systems even though they are not necessarily a part of a system that I think may have been envisioned by the metered dose inhalers and the DPIs, the dry power inhalers.

So, I think the terminology of sophisticated drug delivery systems needs to be considered and narrowed down.

Like Larry, sophisticated formulation, you have got TPNs, you know, that are very sophisticated, so again the use of that term might be one that needs to be modified.

A little concern related to bioavailability, and I think the intent here was reasonable bioavailability, but Larry brought up an example of a very short stability item, and I will bring up an example of a very low bioavailability, FDA-approved product fosamax with a bioavailability of less than 1 percent.

If you look at some of the variances in bioavailability, you know, you are looking at 30, 40 percent variation among the products, you know, at least it is listed in the PDR.

So, I am not sure exactly how that will be

applied, if it is measurable, because with compounded products, we don't generally measure bioavailability. I understand what the concept and the intent was, but it does need to be looked at.

As far as testing and quality assurance, I guess we will get into this more in detail tomorrow on sterile products. There are some tests which, for example, sterility, which may take seven days, and so if you got a product that the patient and the physician is waiting on, in fact, may only be stable for 24 hours, then, we can't wait for a stability, but I guess we will take that up tomorrow.

So, that would be all at this point.

DR. JUHL: Other general comments?

MR. RUSHO: Just a couple comments. First of all, those of us in the hospital are already under JCAHO regulations. We have ASHP regulations, and ABP is already in here, and now we have FDA regulations.

All of these have a slightly different twist, you know, and it would be nice if they were consistent. For example, certification of laminar flow hoods. One agency will say once a year, other agencies will say twice a year.

The other general comment or a question on this one is who is going to enforce this.

DR. JUHL: I think that does bring a good question, although I think JCAHO, the ASHP isn't

regulations, it is suggestions and guidelines. What we are talking about here, though, is going to be having the effect of law on pharmacists.

MR. RUSHO: Well, ASHP does if you have a residency, which we do.

DR. JUHL: And the question of enforcement, I guess it falls back to the State Board of Pharmacy to enforce, and they would be responsive, not only to their regular inspections, but to complaints that are filed, as we have now.

Larry.

MR. TRISSEL: We are just now beginning the process of preparing for our next JCAHO inspection, and one of the criteria that we are looking at, that they have set out for us, is compliance with the FDA rules on compounded formulations, so JCAHO may be doing some enforcement on this, as well.

DR. JUHL: You are going to have to be quite a sage to comply with those before they are written.

MR. TRISSEL: Well, I did point that out, but do the best you can.

DR. JUHL: Other general comments?

MR. TRISSEL: I am sorry, one more. Loyd brought up about bioavailability, and I had forgotten to mention the real problematic ones are the ones that are erratic, not

that are low. We can deal with it when they are consistent, it is when they are erratic that is a problem, but even then, we have an example of an commercial product with extremely high variability that was approved by the agency in THC capsules.

Clearly, an inhaled dosage form might be a more consistent delivery system, but for other reasons, this drug, this more erratically bioavailable product has been approved, and we have lived with that.

DR. JUHL: Fortunately, no one suggested that be added to the bulks list as yet, so -- although I wouldn't rule it out.

I have a couple of general comments. One, I would like to echo Larry's statement that I can tell there has been a lot of work that has gone into this document, and some of the things that you probably fought back and forth on with yourselves.

These things are difficult to understand when you don't have examples, and it is much easier in that context, and it is also, as has been pointed out, difficult to deal with when we are not talking about drugs -- I don't mean drug products -- I mean a drug compound.

There is much variability in a lot of things that don't really have a significant effect on safety and efficacy, and with some drugs it has a tremendous impact, so

that has a difference, too.

We will see when we talk about the general categories a difference in the way that they are dealt with. In the case of sterile products, what the white paper suggests is that sterile products should not be done unless certain guidelines are followed. With the other categories of products, the recommendation is that they shouldn't be done, period.

Now, it is much easier to deal with the former than the latter, but the profession has developed guidelines that allows the agency to feel comfortable in making that kind of a recommendation with sterile products, whereas, guidelines and standards haven't been developed for the compounding of inhaled dosage forms for transdermals, and so on. So, I think that difference will become apparent as we go through the discussions.

I found that Nos. 2 through 4 are kind of hard to differentiate, again examples of specific drugs will make it easier, and as also has been pointed out, the definition of sophisticated and specialized and complex is kind of in the eye of the beholder, but it is inherent to each of the definitions.

For example, are sophisticated facilities of equipment required? Well, someone who is a compounding pharmacist would say yes, but I have those sophisticated

facilities and equipment. They would be sophisticated probably by virtue of their cost.

Is technical training essential? Well, being in that business, a pharmacy degree is a technical and highly specialized training. So, I think we will have a set of guidelines that could be applied in most any direction. There is great flexibility in that, but there also is not much predictability in that without having gone through, I guess, and developed what amounts to case law in the treatment of various examples.

One final comment. The testing and quality assurance, most every compounded product would have a shortcoming in this area almost by definition. There is very little in the way of testing and quality assurance on the product, as the FDA understands, it for other products that occurs with compounded products.

Are there other general comments that this group would like to make? We are going to have to live with these guidelines for some difficult discussions, so now is the time to speak up if there are specific changes or suggestions you could make to the agency.

MR. RUSHO: Tomorrow, aren't we going to discuss the sterile product guidelines specifically?

DR. JUHL: We will.

MR. RUSHO: Okay. I will reserve comments until

then.

DR. JUHL: Okay.

DR. ALLEN: I have one question. According to the FDAMA '97, there are two professions that can be involved in compounding. One would be pharmacists, the other would be the physicians. So, am I correct in understanding that physicians would also fall under everything that we discuss in the next two days?

DR. JUHL: My hope and my assumption is that is true.

MS. AXELRAD: Yes.

DR. JUHL: I see a nodding concurrence from the agency.

MR. TRISSEL: That is a point I was going to raise tomorrow, but since it comes up now, I am aware of at least one large chain of oncology centers that uses nurses to do all of their compounding, so are you telling me that they don't have to comply with these rules because they are nurses?

I think that would be a poor precedent to set. If I was the president of a company using pharmacists and could get out of doing anything for quality assurance by hiring nurses, I might be inclined to do so. I am not sure that is the right thing to do.

MS. AXELRAD: We are going to be addressing the

issue of who can compound in our general regulations, but we also know that pharmacy technicians also do a lot of the compounding under the direction and supervision of a pharmacist, and so we will be addressing how it would work in terms of nurses or others that would be compounding under the supervision of a physician. That is something we will handle in our general compounding regulations.

DR. JUHL: And will there be a relatively specific definition of, "under the supervision"?

MS. AXELRAD: Well, we hope there will be enough of a definition to allow for what is actually happening out there, as long as there is somebody who is qualified, who is responsible for actually happens.

Also, it will probably be, in part, it will be a matter of state law. You know, different states allow different people to do different types of activities. So, we will have to have a definition that is broad enough to encompass differences between the states in terms of what they allow.

It will be put out for comment, and there will be an opportunity for comment on it, so if we draw it too narrowly in the first instance, and we get comments on it, we can adjust it.

DR. JUHL: Do you have an idea of when that might be available?

MS. AXELRAD: We are hoping by the end of this year.

DR. JUHL: Okay. Garnet.

DR. PECK: So, that would handle, then, No. 6, which involves training of individuals to do this particular compounding, and it is recognized that highly technical, it could also -- the words "well trained," and I am assuming that that will take care of that.

DR. JUHL: I think we are talking about two different things here. In one instance, she is talking about the general regulations for who may compound, and here we are talking about drugs that fall under the Difficult to Compound rubric, and training is one of the components we are considering.

DR. PECK: What I heard had to do with who will direct the compounding and the like, and that does have an element of training to it.

DR. JUHL: It certainly does, but it is not No. 6.

DR. PECK: I realize it's not No. 6, but it also is covering training.

MS. AXELRAD: Well, I think we are going to cover in the definitions, the general discussion of who is allowed to compound and the relationship between their people and people that they supervise. I don't think we have any particular plans at the moment to put out any detailed

criteria, and certainly not in the regulations, on what kind of training would be appropriate.

I think that the use of this factor here is designed to say for certain kinds of things, there are some very specialized training that the pharmacists or physicians or nurses, or whoever might be doing it, might not be likely to have, and if there is a dosage form or a type of drug or a particular drug for which that kind of training that is not the norm in pharmacy compounding as required, then, that would be one thing that we would consider in determining whether that particular drug or category of drug should go on the list of products that are difficult to compound.

DR. JUHL: Other comments? I think in our questions to be answered - Do you agree that the following are the appropriate factors to use in evaluating drug products or categories of drug products to determine if they should be included on the difficult to compound list? If not, what additional factors would you suggest we use in the evaluation? Do you think that the difficulty or importance of achieving stability should be considered as a factor?

There are several questions there. Let me take the first one and have a formal discussion and conclusion on it.

Do we agree that the following are appropriate factors to be used in evaluating the products as to whether

or not they should be on the difficult to compound list?

Is there further discussion on that before calling the question?

I think it is one of your handouts, Pharmacy Compounding Advisory Committee questions, and the factors to which I refer are those which were made in Dr. Anderson's presentation and in the white paper in your preliminary information.

Is everyone ready?

Do we agree? All those that agree, would you please signify by raising your hand?

Do you agree that the following are the appropriate factors to use in evaluating drug products or categories of drug products to determine if they should be included on the difficult to compound list?

MR. TRISSEL: All of them in this category?

DR. JUHL: Or we can take them individually depending upon the wishes of the committee. I am calling all right now.

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

[Show of hands.]

DR. JUHL: Opposed?

[No response.]

DR. JUHL: It's unanimous.

Are there additional or different factors that we would suggest that would be used in the evaluation? This is multiple choice.

MR. TRISSEL: I think, not additional, but different in the sense of providing some explanation for some of the more nebulous terminology would be very helpful. What is sophisticated? Give some examples. What is complex? Is it more complex than the TPN, and in what way, that sort of thing, would be very helpful for guidance for everyone on what you are thinking.

DR. JUHL: Yes, my assumption is that our recommendation to the agency would be taken in the context of our previous discussion and suggestions.

Sarah.

DR. SELLERS: At our first meeting, we described compounded drugs as representing maybe 1 or 2 percent of the total amount of drugs that are dispensed, but for certain drug products, the amount that are compounded from bulk active substances may be a lot higher, and the sheer volume of the amounts of certain drug products that may be compounded from bulk active materials may suggest that we need to consider that because if we are compounding much more amounts, we are going to increase risk.

I am thinking specifically of nebulized medications and potentially intrathecal type of medications.

DR. JUHL: There is in the criteria neither a mention of risk of the product nor of benefit. As has been suggested, TPN, the only we can do that is to compound, so it would seem that some consideration of risk and benefit would need to be considered, as well.

Other additional factors that you would like to see the agency consider and for us to use in considering?

MS. LaFOLLETTE: I believe stability, even though we have mentioned it, that the compatibility and interaction with the packaging component and with the formulation definitely needs to be discussed.

DR. JUHL: That is the next question.

MS. LaFOLLETTE: Okay.

DR. JUHL: Good. Moving on to that - Do you think that the difficulty or importance of achieving stability should be considered as a factor?

Other comments on that?

MR. TRISSEL: I am not sure how you can do that other than on a case-by-case basis, and as I have said, other than pointing out what the demonstrated stability criteria are, particularly -- we do have guidance from the USP on this for compounded products by category, and I suppose the idea is if you want to exceed those maxima that are in the USP, you need some documentation of that, but we do have criteria already established for this, that we are

supposed to be following for all compounded formulations.

So, I am not sure what the agency is proposing with regard to stability, something different than the USP has already said?

MS. AXELRAD: Well, we are not proposing it. We were asking the committee, it was something that came up in our discussions. In fact, it could be taken into account in the second factor on drug formulation and consistency. You know, we decided it didn't deserve a special mention at least at this time, but we really did have a lot of debate about it, so we wanted to hear what the committee had to say with regard to that.

DR. JUHL: Loyd.

DR. ALLEN: Yes, it is addressed in Chapter 795, pharmacy compounding practices in detail, and there will probably be more additional work done on that in the future, but basically, there is a general guideline, but those can be modified by any published valid data, you know, that has been published in the literature or whatever documentation the pharmacist might have.

DR. ANDERSON: I think the intention, I think it was more if there are specific products, that maybe there would be a problem with stability, that maybe we should be considering for certain things. There may be things out there that maybe it would be a factor that we should

consider.

DR. JUHL: Do you have some examples that would be helpful?

DR. ANDERSON: I think Dr. Trissel had mentioned one earlier, but we haven't looked at any of those, we haven't considered this yet, it is just something that the work we have had, have debated about, and I think we needed more guidance on it, and that is why we brought it to the committee.

DR. JUHL: Well, it is certainly a factor that any pharmacist would take into consideration when making anything, but the question is I guess would we use it in our considerations of difficult to compound, and I think the answer is yes.

DR. ANDERSON: Some drugs maybe, there is the polymorphic, which could relate back to the formulation. It may fit better under the formulation.

MS. LaFOLLETTE: My concern was more with the type of delivery systems that we are talking about today, the metered dose inhalers and transdermals. You could be having interaction with material components, and that isn't going to be obvious to everyone, and it may not be in the literature if a unique formulation is being used, it hasn't been demonstrated before, and these things do occur, I can attest to that by experience.

DR. JUHL: Garnet.

DR. PECK: This is a general statement about stability, but we are going to be talking about specific types of delivery system, and there you can cite specific examples, metered dose inhalers, for example, and the stability of the particulates that are inside a system that has particulates or insolubles, so you can cite those as specifics, and that is nice, and also you can cite it specifically in sterile products.

So, as a general category, maybe you cannot come up with examples. It is just something that we all live with, and that is stability. I guess that was the reason for asking the question.

MS. AXELRAD: In some cases, I think, establishing stability and making sure that it is there in a particular product is more difficult than in other places, and those are the cases where we would focus in terms of whether somebody ought to be compounding them when they don't have a regular stability program or some way of making sure that the product is stable when it is made and stays stable for its use.

Again, I think that fits fine under Factor 2, under Drug Formulation and Consistency, and could be incorporated in those cases where, for example, in metered dose inhalers, there is that type of an issue.

DR. JUHL: Other comments on stability? Any last comments on the criteria before we move forward?

[No response.]

DR. JUHL: Hearing none, then, let's proceed to a discussion of metered dose inhalers and dry powder inhalers. Dr. Brian Rogers.

MS. AXELRAD: Dr. Juhl, it might be helpful to actually have a vote, so that we have in the record a vote on the stability issue, like does the committee want to or does not want to include as a factor, stability specifically.

DR. JUHL: Let me propose that we not have a specific factor on stability, but include that in the various places of the existing criteria where it would normally be considered, such as drug formulation and consistency, Category No. 2.

MR. TRISSEL: Possibly 1, too.

DR. JUHL: Possibly 1, drug delivery system. Other possibilities?

Let me make that as a proposal and then is there further discussion before we vote on that?

[No response.]

DR. JUHL: Seeing none, let's call the question then. The recommendation to the agency that they not have a specific stability criteria, but include that in the other

criteria where it is appropriate.

Those that would favor that recommendation, please raise your hands.

[Show of hands.]

DR. JUHL: Opposed?

[No response.]

DR. JUHL: I see that as unanimous.

MR. WELDER: On the basic question that we took a vote on a while ago, I have a little bit of concern. Are we going to discuss each one of these categories individually at some time, because we took a general vote on approving from the drug delivery systems all the way to the testing and quality assurance, because there are a lot of questions in between there on a lot of these things like who defines whether a compound is complex or not, how do we determine that, are we going to discuss that in this meeting?

DR. JUHL: We can discuss that further if you would like.

MR. WELDER: Does no one else have a question on who defines these things? When I have a pharmacy that does compounding, who determines whether the drug product is complex?

DR. JUHL: I think the use of these guidelines is to determine whether or not products or categories of products get placed on the Difficult to Compound list. So,

that judgment would need to be made by the agency and by this committee. Individual pharmacies wouldn't need to make the judgments because we are making the judgment on the categories.

MR. WELDER: So, these individual items won't be up for discussion at this meeting then.

DR. JUHL: They can be.

MR. WELDER: The vote that we took approves all these things, and I kind of had a half a hand up because there are so many questions.

DR. JUHL: Let's go ahead. I want you to have the opportunity to make suggestions for clarification changes or anything that would you feel more comfortable.

MR. WELDER: One of my questions would be what is a sophisticated facility and/or equipment required to ensure proper compounding of the drug product. I can speak for my pharmacy in that we have everything that we need for a particular product. We don't do compounding -- we don't do all compounds, but what we do compound, we have the proper equipment and facility.

My question is, are the rules going to be developed for everyone, and does every compounding pharmacy have -- will they be required to have every piece of equipment if it fits in a category by the FDA? The category itself bothers me a little bit, in categories of drugs.

MS. AXELRAD: I think that others have pointed out the issue of sophistication of the facility being not as clear and asked for examples of that. I think that when we got through the particular categories that we are going to talk about today, you will see some examples of where we think sophisticated equipment or facilities are necessary.

Certainly not all pharmacies would be required to have it, but I think for certain categories of products where you have to have very specialized equipment that is not likely to be something that your average pharmacy would have, but more likely something that a manufacturer would have, then, those are the types of things that we think should go on the list as difficult to compound.

DR. JUHL: This is where we get into the problem of the two approaches that are being taken, one for sterile products, there is sophisticated equipment, there is sophisticated training, there is sophisticated this, that, and the other thing, but if you have them, you can do them.

With the metered dose inhalers, even if you have the equipment, we are saying you can't do it. I think that is the issue that raises its head on this.

DR. ANDERSON: We are trying to use these to help us evaluate the products. We are not trying to say that every pharmacy has to have these, but again, you said it depends on the approach, but it is something for us to use

to look at these different drugs to say are they difficult or not.

DR. JUHL: Larry.

MR. TRISSEL: I hadn't actually thought of what Tony was saying. Are you thinking like State Boards require every pharmacy to have a sink and a balance, and those are mandatory, and you are concerned that somebody will make every single piece of compounding equipment mandatory in every single pharmacy, something like that, because I didn't read it that way.

I thought if you were going to compound a particular product, you needed suitable facilities and equipment for that product. That is the way I understood it. If that is not the intention, we should know that now.

DR. ANDERSON: Yes, right.

MR. WELDER: Well, that was my intent of the question, because every serious compounding pharmacist would have those things available, and the definition of what is complex still bothers me, a little better categories of drugs that would be put in difficult to compound.

For instance, in Item 4, Complexity of Compounding, is the compounding of the drug product complex, are there multiple, complicated or interrelates steps? Well, sure there is a lot of things that we compound that have many steps, they are multiple, and they could be

complicated, but who defines -- I mean they are easy steps, you take them one at a time, it is like reading a recipe in a lot of case -- so who defines, are these drugs going to be on a list because there are multiple steps? I am concerned about that.

DR. ANDERSON: I don't think that it is one, everything is going to be a case-by-case basis, and I don't think that one single factor would make a product on the list. There are things that we are trying to use to evaluate the products, to consider, to look at these products, and look at each product.

MR. TRISSEL: Tony, I don't read these as pass/fail kinds of things. They are just topics for consideration. Is that what the agency intends?

DR. ANDERSON: Right.

MR. TRISSEL: These are just things that normal people would consider.

DR. ANDERSON: Right, and we just need input whether we are going in the right direction, whether these are the things that we should be looking at, when we are looking at different drug products.

MR. WELDER: Okay.

DR. ANDERSON: I don't think any single factor would be overriding or any one would be dispositive. It's an overall thing to help us how would we approach this list,

how are we going to make this list.

MR. WELDER: Okay. I was just a little bit uncomfortable with the vote and including all of these things without any questions being asked, and so they are not just blanket okay on it. Okay.

DR. JUHL: If anyone wants, after we go through these categories of drug products, to go back and look at the criteria and say, well, you know, after our discussion, this one didn't seem to work or we need to add one more, so I will reserve our opportunity to do that at the end of our discussions if we want to. I want everybody to feel comfortable with this when we get done with it, because it is going to be used along down the line.

Sarah.

DR. SELLERS: Do we cover under these points, the route of delivery?

MS. AXELRAD: You mean the route of administration?

DR. SELLERS: I am thinking risk of applying a drug directly to the lungs that may be contaminated certainly is a concern, likely injecting pyrogens into the intrathecal space is a big concern. It appears to me that the route of delivery may be a consideration when you are compounding.

DR. ANDERSON: It could fall under several, but I

don't think there is a specific one, but it is something that we could look at.

DR. JUHL: I think that would actually be important in the overall risk to benefit considerations.

Any other comments.

[No response.]

DR. JUHL: Let me move on then to the metered dose inhalers and dry powder inhalers, Dr. Brian Rogers.

Metered Dose Inhalers and Dry Powder Inhalers

DR. ROGERS: Good morning.

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I am going to be talking about the difficulties associated with compounding metered dose inhalers and dry powder inhalers. I will summarize the characteristics of these drug products, which not only have potentially complex and environmentally sensitive formulations, but are required to be contained in complex drug delivery devices.

These devices require tight controls with difficult-to-perform tests to assure reproducible and accurate drug delivery to the patient. In these two drug products, reproducibility of the drug delivery to the patient means both accurate delivery of both the mass of the active expelled from the device, but accurate and reproducible deposition at the correct site in the lungs, and this is controlled by control of the particle size

distribution.

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Metered dose inhalers are a pressurized system containing a liquified gas, the propellant. The propellant suspends the micronized drug substance and provides energy to both propel and disperse the drug substance in metered doses.

Generally, surfactants are used to stabilize the suspension formulation. Co-solvents may be present to aid in formulating. MDIs may dispense from a few micrograms to milligrams of a drug substance per actuation, and the volume of formulation delivered by the valve in an MDI is typically 25 to 100 microliters.

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Once the specified quantity of formulation is expelled from the valve, the liquified gas vaporizes, both propelling and dispersing the suspended or dissolved drug substance along with any non-volatile excipients.

The dispersed drug substance in a discrete actuation contains a range of particle sizes characterized by the size distribution. Also, the distribution of the drug substance mass per minimum dose is characterized by dose content uniformity.

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Dry powder inhalers contain a micronized drug

substance with or without a carrier, with lactose being the most commonly used carrier.

Energy for dispersion of particles is supplied by either patient inspiration, compressed gas, or some form of motor-driven device. Current designs in include pre-metered and device-metered DPIs.

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This slide shows the various designs of DPIs currently available. The devices may have its formulation dispersed by the patient's energy of inhalation or by some form of internal power source, as I just described.

These two types may be further subdivided by whether a device has an internal metering process or has the dose pre-metered as in a blister or a capsule. The pre-metered type of DPI can either have the dose removed directly from its container or the dose can be transferred to a holding cavity for later inhalation.

The device-metered DPI generally has the dose transferred to a holding chamber.

The pre-metered type of device may contain either single or multiple doses, and the device-metered DPI is exclusively multiple dose in character.

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In addition to dose measurement and particle size issues, further complex and subtle interactions may occur

between the drug substance carriers and components of the container closure system.

These may include gravitational, fluid dynamic, and other interactive forces, such as electrostatic, Van der Waals, and capillary forces. Together, these forces are responsible for the differences in fluidization behaviors exhibits by different powders within an inhaler.

It is critical to have a precisely reproducible formulation to obtain device-to-device and batch-to-batch reproducibility.

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General Concepts. The aerodynamic particle size of the inhaled particles containing the drug substance affects the point of deposition in the airways. Normally, the smaller the particles, the greater the penetration into the lungs.

Patients need to inhale drug substance particles generally particles generally less than 5 micrometers in diameter to be effective in treating diseases of the airways. The range of effective particle sizes is narrow with larger particles only contributing to systemic exposure and contribute no clinical benefit.

Unlike other conventional drug products, these are highly dependent on the particle size distribution for their safety and effectiveness. Concepts of classical

bioequivalence and bioavailability are usually not applicable.

Bioavailability is difficult to determine since the dose is too small for blood analysis. Its concentration ends up being in the parts per billion range in general. Bioequivalence studies are hindered by having 85 to 90 percent of the dose absorbed through the GI tract instead of the biological target.

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Dosing and performance and thus safety and efficacy are directly dependent on design reproducibility and performance characteristics of the container and closure system. The most important dosing and performance characteristics are particle size distribution and dose content uniformity.

Both the metering valve and any canister lining must be compatible with the formulation. A canister lining should be proven to not have pinholes. Pinholes or porosity in the lining will allow corrosion of the canister metal by reaction of the underlying metal with components of the formulation.

There is also a definite potential for absorption of the drug into plastic components. Absorption may also cause swelling of elastomers. Extraction of plastic and elastomeric component by the formulation may result in

leaching of carcinogens or compounds that patients are sensitive to.

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Here are a couple of versions of actuators. This first example is an actuator designed to be used with an integral spacer. The second drawing here shows the same actuator with the first part of the spacer shown, and the spacer extends in this direction for a little distance.

The other example of an actuator on the right is a standard actuator, such as used in standard MDIs. Above the actuator is a canister with a valve stem shown here and the ferrule here, and this is the canister proper.

The canister fits within the actuator down in here with the valve stem seeding in this insert here, and that forms a seal, and when the canister is actuated by pushing down with finger pressure on the top, the valve stem is compressed and the plume is expelled from the valve stem down into this area here and out through the orifice in this direction, so that the plume is expelled approximately 90 degrees from the angle of the valve stem.

In this device, the canister sits at a slight angle and again the plume exits more or less perpendicularly to the valve stem.

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Here is a diagram of a typical MDI valve in a

relaxed or a pre-actuation configuration. As you can see, the valve is very complex with many of the components interacting with and depending on one another. Any changes to a valve will likely cause changes in the performance characteristics. The parts of the valve are labeled there, and I won't go into them.

In the rest position, as shown here, the metering chamber is full, that is this area here, and in contact with the bulk formulation, which fills this outside area here, the canister inserting in this area and basically forming this kind of shape here, and a good portion of the canister not occupied by the valve is formulation.

Once the canister is depressed to actuate the device, the stem is pushed upward by the finger pressure and as soon as this happens, the metering chamber is closed off from the bulk formulation in the canister, and then a little further pressure and distance moved of the valve stem allows this little hole here to actually come into the metering chamber, and then the metering chamber becomes exposed to the atmosphere and the pressurized contents of the metering chamber is expelled through the valve stem under great pressure.

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The function of the actuator is to generate aerosol particles, direct the dose, influence the velocity

of the aerosol, control the amount of medication delivered, and the particle size distribution available to the patient.

The valve precisely measures the formulation volume and provides a leak-proof seal to prevent changes in the formulation concentration.

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Here is a diagram of a typical dry powder inhaler. The one shown here is only average in complexity relative to others, and this DPI is considered a pre-metered multi-dose unit. It has the formulation inserted into individual blisters on a strip coiled around a wheel here in the bottom of the device, as it is shown here.

When the dose is desired, the patient causes a ratcheting of the device, so that a new blister is moved into position here, and just prior to the moving into the position, the backing strip off of these blisters is removed by this wheel, and the formulation is exposed to the air intake that the patient will pull air through.

Once the dose is removed by inspiration, the used portion of the blister, the used half of the blister will be coiled on this wheel.

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In conclusion, the MDI and DPI drug delivery systems are sophisticated and complex. Precise formulating is crucial to drug dosing accuracy and reproducibility from

the standpoint of both dose uniformity and particle size distribution. Container enclosure components directly affect potency, purity, and quality of the drug product, hence, safety and efficacy of the product.

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In the interest of time, I have chosen to focus on the complexity of compounding MDIs, however, the issues are equally applicable to DPIs with some obvious exceptions which pertain to liquid formulations, and I think those will be obvious to you.

The formulation in an MDI is a mixture of micronized or solubilized drug substance in a matrix of oily excipient material, propellant, and possibly a co-solvent.

The composition and physical chemical properties of each component is crucial to performance. Also, the composition has a direct effect on the extent of agglomeration and suspension stability.

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Important drug substance properties which must be controlled during compounding include the particle size distribution, particle morphology, solvates and hydrates, clathrates, morphic forms, the amorphic character, the solubility profile, the moisture content and/or residual solvent content, microbial quality, pH profile, and specific rotation.

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Important aspects of the formulation liquid phase include propellant identity, the presence of a co-solvent, surfactant identity, concentration, and quality. Relative proportion of the volatile components influence the internal canister pressure.

Important physical/chemical properties of the formulation include polarity, surface tension, and density. These all affect the suspension characteristics of the two-phase formulation.

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Factors adversely affecting the formulation's physical stability include preferential interaction of the suspended drug substance with container components, settling and creaming resulting from differential densities between the liquid phase of the formulation and the drug substance.

The above factors result in a less homogeneous suspension and thus greater inconsistency in the dose delivery and particle size distribution.

These inconsistencies are seen in the beginning to end of canister variability, canister-to-canister variability, and batch-to-batch variability.

Properties of the liquid phase need to be carefully optimized and controlled to minimize the above problems.

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The individual formulation components require very careful control of impurities and degradation products. Minor changes in concentration or dose of an excipient can be result in large changes in toxicological properties.

Very careful control of impurities and degradation products in all formulation components is required to prevent possible bronchospasm in lungs of sensitive individuals.

As a result of the Montreal protocol, CFC propellants are becoming very difficult to obtain an acceptable purity. Tight controls on purity are needed to be implemented to assure drug product quality.

As a result, the composition of the formulation and complexity of this dosage form make it very difficult to formulate outside of a dedicated manufacturing environment. Minimizing product-to-product variability, that is, obtaining the best possible dosing accuracy is necessary for obtaining safety and efficacy.

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Compounding of MDIs and DPIs require multiple, complicated and interrelated steps. In each of these, there is a significant potential for error. The formulation must be carefully handled, mixed, dispensed, and so on.

The container and closure system design and