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CENTER FOR DRUG EVALUATION AND RESEARCH

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PHARMACY COMPOUNDING

ADVISORY COMMITTEE

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P R O C E E D I N G S

8:32 AM

DR. JUHL: If I could have you take your seats so we can get started, I would like to begin day 2 of the Pharmacy Advisory Compounding Advisory Committee meeting.

We will begin as always by a reading of the waivers. Kimberly Topper, our Executive Secretary, will do the honors.

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

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

A copy of these waiver statements may be obtained from the agency's Freedom of Information Office, Room 1283 in 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 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 firms or products they may wish to comment upon.

Thank you.

DR. JUHL: Thank you. Even though we did this yesterday, I would like to go around the room and have each of the Committee members hold the microphone close to their mouths and introduce themselves, starting with Carmen.

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

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

DR. SELLERS: Sarah Sellers, infusion pharmacist, Network Pharmacy, Gainesville, Florida.

MR. RUSHO: William Rusho, University of Utah.

MS. MC CLAIN: Anna McClain, consumer representative.

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

MR. TRISSEL: Lawrence Trissel, University of Texas, M.D. Anderson Cancer Center.

DR. JUHL: I am Randy Juhl, University of Pittsburgh School of Pharmacy.

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

MS. RIFFEE: I am Judy Riffie, the College of Nursing, University of Florida.

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

DR. RODRIGUEZ: Bill Rodriguez, Children's Hospital, National Medical Center, Washington, DC.

MR. LIEBMAN: David Liebman, compounding pharmacist, IACP, Baltimore, Maryland.

CAPT. TONELLI: Bob Tonelli, Office of Compliance, Center for Drug Evaluation and Research.

MS. OGRAM: Lana Ogram, Office of Compliance, Center for Drug Evaluation and Research.

MS. AXELRAD: Jane Axelrad, Center for Drug Evaluation Research.

DR. JUHL: Yesterday we made it through three of the four categories for the bulks list, and before we begin today on Category IV, I would like to ask if anyone had a bad dream during the night and had second thoughts or other thoughts they would like to provide for us on yesterday's deliberations.

Carmen Catizone has apparently had a printer in his room and put together some of his thoughts, and I would like him to discuss those with us, and if there are others,

please join in as well.

Carmen?

MR. CATIZONE: Thank you, Randy. I just wanted to summarize for the Committee's consideration some thoughts I had about yesterday's meeting, and all of you, I think received a copy of the document.

Perhaps I could just walk through it and then just open it for discussion. The concerns I had are one that the FDA has proposed to us some criteria for nominating bulk drug substances for inclusion or exclusion on the list, and I am not sure if the Committee ever gave back a clear answer to the FDA about the acceptance of the criteria or the applicability of that criteria in the Committee's decisions or recommendations to the FDA.

If you look back on some of the decisions or recommendations that we may make it seems that we varied in the interpretation or application of the criteria proposed by the FDA without much clear direction or without any replicability for future decisions that the Committee may have to make.

In that regard I would propose in terms of the recommendations on Page 2 that we accept the criteria which the FDA has proposed and that we, also, reach some agreement on the substances that were presented yesterday and may be presented in the future so that the drug products listed in

Group I because they have met all three criteria proposed by the FDA, that those would be included or recommended to be included on the list of bulk drug substances which would mean that mild(?) silver protein then which was something that we had excluded would now go back into the included list.

With regard to Group II, I think the Committee should use its expertise to evaluate whether or not the product should be included in the absence of use data, and I think the Committee was able to provide information or documentation that all of those products should be included within the list of products that the FDA would maintain on the list.

In regard to Group III I think we need to pay serious attention to the toxicity concerns raised by the FDA and the data in the literature and in that regard I think the Committee's expertise should be used to gage whether or not there is a serious medical need for this product, whether or not patients have accessibility to other alternative therapies and whether or not there is a documented benefit-to-risk ratio for patients who will utilize these products and in that regard I think only three of those products will meet those criteria and would exclude from that consideration DNCB and the hydrazine.

In regard to Group IV based upon the information

presented, I think all of those products should be excluded from the recommendation of the Committee for inclusion on the list of bulk substances.

MR. LIEBMAN: Carmen, I think you have done a terrific job. I am not sure that, maybe I misunderstood, I am not sure that we agreed that DNCB would be one of those which -- that didn't quite fit in, that it was in the same category as hydrazine. Maybe I misunderstood it.

MR. CATIZONE: David, I was confused, too, and that is why it helped me to put together my thoughts. I would defer to the Committee if something else was decided, but that was my recollection.

DR. JUHL: Does anyone else have a similar or different recollection?

MR. TRISSEL: I recall it being withdrawn from the nomination list.

MR. LIEBMAN: Did I misremember?

MR. TRISSEL: It was withdrawn. We had information on it, and we did consider it although not as, well, I guess I asked the question, in the absence of a nominator do we still consider, and the agency wanted to hear our views if we had any on the DNCB as I recall.

MR. LIEBMAN: Elizabeth, do you all use it?

DR. MC BURNEY: Yes, in our discussion yesterday we use it topically as a topical agent. We do not use it

systemically at all, and I think that was where the discussion was yesterday that it is being used by physicians for treatment of recalcitrant warts that have not responded to other therapies.

MR. LIEBMAN: Because that was my understanding that I have physicians who use it topically.

I am sorry, is it withdrawn or is it not withdrawn? I didn't understand that it was withdrawn. Do I misunderstand? Has it been withdrawn?

DR. JUHL: Jane, how do you want to handle this as a formality.

MS. AXELRAD: I think that as a formality it was formally withdrawn, but I think that it was then put back on the table by one of the Advisory Committee members who indicated that it is being used, and since we have evaluated it, I think that we will consider it to have been nominated, albeit informally through the Committee process here, and I think that we should get a recommendation from the Committee on it.

DR. JUHL: As I recall from my impression of yesterday's discussion the Committee accepted the relatively widespread use of this in dermatology, not common but apparently used by several dermatologists. I think, Bill, you had mentioned that it is used in your institution as well, and I think it is one that should be on the list, and

we need to seek further information as published in the Federal Register.

MR. CATIZONE: Dr. Juhl, a point to that consideration is the sponsor of the nomination withdrew the nomination because they realized they could obtain and use this product to treat patients through another more acceptable means, a means that has already been approved by the agency.

DR. JUHL: That was a special case.

MR. CATIZONE: But if that product is available through that why would not other institutions have the ability to use that product?

DR. JUHL: The nominator, well, I won't speak for you, but that was in a project that included an IND, and not everybody has that IND.

MS. AXELRAD: I think really partly for efficiency if we were to say today that we wouldn't consider it to be nominated since the nominator withdrew it, tomorrow we would get a letter saying, "We nominated it." So, I think that we may as well consider it to be on the table and evaluate it.

DR. JUHL: It makes it no less easy to consider because it is a, this is a scary piece of work in terms of a drug and its toxicity, and the agency has withdrawn things that have been toxic even though people wanted it before.

So, I think we have that range of options, but I

would like to hear from the Committee if we want to revisit this.

MR. TRISSEL: Are we going to revisit DNCB at this time?

DR. JUHL: That is what I am asking.

MR. TRISSEL: I wonder if I could ask the individuals, the dermatologists and the compounding pharmacists who actually work with this what kind of precautions they take compounding of a very potent agent?

MR. LIEBMAN: In terms of our practice, one, we do it in the hood. We have our people wear a mask, and they wear gloves. They are very careful, and no one works near them when they are using it. We put it in glass, and we have only dispensed it back to the physician at the university. We have never given it to a patient, unlike Bill, and physicians know the caution that must be utilized when using this or applying it for their patients. So, that is the only way we have done it.

DR. SELLERS: This falls under OSHA regulations, does it not?

MR. LIEBMAN: I don't know, to be honest with you.

DR. SELLERS: It does because the material is not in a final dosage form.

DR. ALLEN: I believe though that OSHA makes allowances for pharmacies that use small quantities, and

they are exempt. That is one of the areas that basically is an exemption from OSHA because to require pharmacies to meet all of OSHA's requirements for the wide variety of chemicals they have would be basically unreasonable. It is a question that has come up quite often, but there is an exemption for small quantities like in pharmacies.

MR. LIEBMAN: Sarah, the physician will give me a gram of it and say, "David, make it for me in the following dilutions." So, I don't have a whole lot to start with, and whatever is left over goes back to the physician's office.

CAPT. TONELLI: I just would like to point out that none of these would be excluded from the investigational new drug procedures, and we can always entertain an IND for any of these products. So, just by excluding them does not mean they cannot be used at all. The IND procedures are still available which is what M.D. Anderson happens to be doing with them.

MS. LA FOLLETTE: I would concur. If an IND is already in process I don't think this Committee should be addressing this drug. It should be removed. We, also, talked yesterday, and we are not discussing this that because of the danger of the drug and the toxicity that it should be monographed, and it should have auxiliary labeling because we were talking about different practices here.

We were talking about one, it being dispensed to a

physician and in Bill's case it is being dispensed by a pharmacist and going home with a patient, and I don't think proper packaging is being used or auxiliary labeling possibly.

MR. TRISSEL: Just as a point of clarification, our IND is not for DNCB. It is for a vaccine in which the DNCB is used as a diagnostic agent. So, we don't specifically have an IND for DNCB. It is under the overall umbrella aegis of that vaccine IND.

DR. ALLEN: Also, there would be no reason to develop a monograph for it in the USP if it is not an item that is being used. So, to develop a monograph for it --

MS. LA FOLLETTE: This was the recommendation yesterday when I brought up the point about using labeling or some warning. Dr. Juhl made that recommendation. I wrote it down.

DR. ALLEN: Oh, if it becomes, yes, if it is on the list then it could be monographed, yes.

MR. TRISSEL: I would, also, just point out that at our institution this is regarded as a very toxic substance, a very dangerous substance to work with, and we take precautions the same as we do with other carcinogenic materials, although I have to say that this one has not, at least as I could find, was not specifically carcinogenic, but it is mutagenic, and it causes sister chromatid

exchange, and it shouldn't be excluded as a proven non-carcinogen at this point, but more importantly it is an extremely potent skin sensitizer. Its efficacy in this regard is hard to deny, and we have great concerns for our workers when we make this material.

So, we do it in biological safety cabinets, fully gowned, gloved, masked, face shields and in an isolation room, and we are still concerned.

MS. SELLERS: In light of that, it sounds great, but there may be places where that is not happening, and you know, there is a wide variety of environments where it may be used in the absence of regulations and my concern would be for actually the safety of the pharmacists or technicians who may be exposed to it.

MR. LIEBMAN: Could we ask the suppliers of this drug to, when they supply it to give a full listing of or give a warning sheet that is very clear and says that you are dealing with some serious stuff here; so, these are the precautions we strongly recommend that you take when dealing with this drug?

MR. RUSHO: David, that is already available. Material safety data sheets have that material on them.

MR. LIEBMAN: Okay, I am trying to respond to Sarah's suggestion, Sarah's concern, I am sorry.

MR. RUSHO: And I think that the points are well

taken here. It is a very, very toxic substance, and when we prepare it we do the gloves and mask, too. We don't use a hood because we don't want it blowing back in our face, but the contact time to the air, we try to limit that, and we try to limit the number of people around there. It sounds like Larry has got a much better deal, and from what I am hearing we would actually be better off making this in a chemical fume hood rather than a laminar flow hood.

MR. TRISSEL: Well, a horizontal laminar flow hood, certainly a biological safety cabinet is a vertical flow that exhausts up so that the air is being pulled in.

MR. RUSHO: Right, but you, also, have an open substance there, and most of those are vented into the room.

MR. TRISSEL: There is more than one type of these cabinets. Some of them are vented to the outside.

MS. LA FOLLETTE: But I think you are pointing out the disparity in how this drug is being prepared and not many places have biological safety cabinets.

I think it is too dangerous. I really do, and once you approve this and put it on the list you don't have the control of how it is going to be handled or prepared, and all you have to have is one mishap. I think it is too dangerous, and I think we have to take the responsibility here.

MS. SELLERS: Also, speaking to the MSDS, I don't

believe, and you can correct me on this, but I don't believe that a pharmacy is required to have the MSDSs available for their employees, and in the absence of any OSHA regulations where is the protection for the employee?

DR. ALLEN: According to the USP chapter on good compounding practices, you know which is not required, but you know highly recommended the MSDSs are a part of the documentation that is suggested.

MR. TRISSEL: And having just gone through JCHO they were very interested in whether we had MSDSs on all the stuff.

MS. SELLERS: Right, but you may not be a pharmacy that is covered under the Joint Commission.

MS. OGRAM: I think it is important to re-emphasize the point that Bob and Carmen brought up and that is that there is a process in place within the center for emergency and individual INDs, and so if you decide to recommend against putting this on the list, there is a process by which institutions or individuals can still get this drug.

DR. JUHL: Other comments?

MS. RIFFEE: Dr. Juhl, I would just like to review the five substances in this group that we finished with yesterday and make sure that we really all know what our final opinions were.

DR. JUHL: Okay, let us deal with this one first then.

Other comments on DNCB?

I guess I would like to try to get a sense of the Committee on where we stand with this and we are not going to take votes initially, but I think in this situation I would like to know how many would like to proceed with this and how many wouldn't.

So, if there is further discussion, let us do that, and then I will ask for a show of hands.

DR. MC BURNEY: I am hearing from the pharmacists and the people who prepare the compound on the Committee that that is where the greatest concern is, is actually the compounding of the solutions that we are using, and I really cannot address that directly because I depend on my pharmacist for preparing it or the physicians do.

As I stated yesterday, I do not use this particular compound, and many of the points that were brought up such as it being mutagenic by Ames test although it is not carcinogenic and the other comments that have been made about it have, also, been listed for other compounds that we have gone through here, and I am wondering if we are not being consistent in what we are doing, and it is almost who can speak the most convincingly for each drug as to how we are making this decision rather than being uniform in our

decision making.

MS. LA FOLLETTE: Prior to taking a vote could Lana elaborate for the Committee more on the process of having an exception to an IND, you know, how an individual could proceed with that so that everybody is more aware?

MS. OGRAM: I am not an expert in this process, but we do have someone from one of the divisions here who could elaborate on that.

MS. AZELRAD: I can speak about it a little bit. Basically I guess I am not entirely sure in the case of where it is being used as a treatment for warts that it is realistic to expect an individual physician to obtain an IND to use a substance. It is a different situation that Dr. Trissel has where it is being used as part of a protocol for an IND for another drug, but basically the process for obtaining an IND is you submit a submission that is called a request for an investigational new drug exemption, and it includes chemistry and toxicology data, and it is submitted to the review division, and the division reviews it.

We have 30 days to review it, and if we don't object it can go into effect. It has chemistry and toxicology data and how the substance would be used basically.

DR. JUHL: And, also, how the dosage form would be produced is part of that process.

MS. AXELRAD: Right.

MS. OGRAM: In emergency situations, too, it can be done over the phone, and paperwork can follow.

MR. TRISSEL: All of that is true, and we have individual investigators who do file their own INDs, but the intent of that is for research, and this is not research. This is treatment. That is a different issue, and I am not sure the IND process is to be used for treatment on a routine basis without a research objective.

MS. OGRAM: There are individual patient and emergency INDs. The data that is obtained is helpful in some instances, but it is not necessarily for research. It is used in a compassionate sense to help individual patients get access to the drugs that their doctors feel they need.

MR. TRISSEL: Would that include non-life-threatening, non-emergent situations like warts?

MS. OGRAM: I cannot answer that, not being in the division that handles those. It is a good question.

MR. LIEBMAN: Bill, you are using it in your hospital. If you did not have it as part of your armamentarium would it cause any great hardships?

MR. RUSHO: I cannot answer that. I don't know. I would have go back and talk to the dermatologists. I don't have a strong feeling on this because I don't know exactly what the dermatologists' feeling is, if they can use an

alternative agent. I would have to have more time and bring it back to the next meeting.

MR. LIEBMAN: I can talk to my derms, and if you could talk to your people and find out if it is a serious drug and if they feel that given the concern we have about its safety that they could use something else or if they couldn't have access to this it would cause any great hardship, if my people feel that it just, you know, at Hopkins and at the university that it just is not a big to do, and if you all would get the same sense of it, maybe it is not worth the fight. It might be worth letting is just sort of go.

DR. MC BURNEY: If I may speak, I think that to kind of put it in a clinical perspective here that this drug would only be used to treat warts after they have failed with multiple other modalities, such as surgery, cryosurgery using liquid nitrogen, such as use of topical acids, such as salicylic acid and perhaps, also, even surgical removal by laser therapy, and at that point then we would have the back against the wall and would use it. I don't know if this is appropriate or not, but one of the reasons that the American Academy of Dermatologists proposed squaric(?) acid, and that was actually to replace the use of DNCB which is, also, a topical sensitizer and it has not been shown to be mutagenic and is not carcinogenic, and so that that was one of the

reasons that was on the list that we will discuss at a future time which could be used as a replacement for the DNCCB and has a, in my opinion a better safety record than the DNCCB.

If that information could be kept in mind as we go forward on that, I would be willing to remove this or exclude it from the bulk list.

DR. JUHL: Other comments?

Let me try to phrase the question, and I can do it in the negative or the positive, but I am sensing that the group has serious concerns about the safety for this drug. So, let me phrase it in that way, that we have, and this will be a yes or no question.

We have serious concerns about the safety of this drug, would hesitate recommending it for inclusion on the bulk list but anxiously await additional information that could be forthcoming from others that may use this about which we are not aware.

I think process in reviewing this drug has suffered in that it was nominated in a very narrow sense, M.D. Anderson for one particular situation, and I think there may be broader use that we just weren't aware of because it wasn't included in the nomination, that we do need some additional information about it, but I will revert to the phraseology that I used. Yes or no, I have serious

concerns about the safety of this agent and would be hesitant at this point to recommend its inclusion on the bulk list.

Are we clear on the question?

Those who would agree with that statement, please raise the hand, either right or left?

DR. MC BURNEY: A point of information. Does that mean we are going to have a follow-up discussion on this, say in February when we meet?

DR. JUHL: I think there will be additional, there will be opportunity for information to be developed from all interested parties as a result of the Federal Register announcement that will go out, and I think at that point preliminary review by the agency to see what comes in and either discussion or report back to the Committee depending on what is found would be appropriate.

Other clarifications?

All in favor, please raise your hands?

(There was a show of hands.)

DR. JUHL: Those that are opposed?

(No response.)

DR. JUHL: Any abstentions?

(No response.)

DR. JUHL: I see that all voting favored the wording, and I think that will be our recommendation to you

on that agent.

Now, when last we left, Carmen was in the middle of discussing. Did we get to the end or are there other questions that you would like to raise with us?

MR. CATIZONE: I think that is it. I, also, would recommend that the hydrazine be excluded from the list in our recommendations to the FDA based upon the toxicity data and the inability of that product to meet the three criteria as outlined by the FDA.

I would support the aminopyridine(?) and the metronidazole being included in our recommendations for the list of bulk substances.

DR. JUHL: I think my recollection of our judgment yesterday was that we wanted to defer on hydrazine and have a review of that at a longer session, but we can revisit that today. Are you suggesting, Carmen, that we make a decision on that now or --

MR. CATIZONE: As one of the Committee members pointed out yesterday, we have some double-blind studies that indicated that this product has either a placebo effect or a deleterious effect on patients. It is a toxic product and so the use data comes back negative.

I don't see if we get, how the additional information is going to sway the Committee's decision. If the criteria used to make decisions are based upon a

critical need and based upon the lack of harm to patients, I feel there is sufficient data to make a decision on the hydrazine product.

DR. JUHL: Other comments on the topic?

DR. ALLEN: On the hydrazine due to the fact that we have got five to ten thousand terminal patients on it, I would feel more comfortable getting more information before we make a final decision, and, also, a consideration is if it is at some point excluded from the list that some time period be allowed for the physicians and the patients to do alternate therapy.

MR. TRISSEL: I would, also, certainly as one who raised the issue with the double-blind studies, I have some serious concerns about this product, but I, also, recognize perhaps as much as anyone based on where I work that there are significant end-of-life issues as well, and there are undoubtedly individual biological variations that we need to, also, take into account. Not everyone behaves the same with the same product.

So, I would be willing to consider this at a later time with more information.

DR. JUHL: I guess my preference would be to continue with the recommendation that we arrived at yesterday, I think for a number of reasons, some of them having to do with science and others having to do with

process. I think this is a controversial topic, and I think the Committee not contacting and making use of experts in the field would find itself open to criticism for that, and I think that is my view that I think we should, with all the provisos that have been raised about the problems with the drug, I would prefer that we consider that at another time in a more expanded session.

MS. LA FOLLETTE: May I remind you that is one of the reasons I asked the FDA to review the process? There other means to have a drug available to patients, especially in this case where you have 10,000 patients taking this drug as was relayed yesterday, and you already have clinical studies, double-blind studies that show a concern.

So, the facts are in, and there are other mechanisms for patients to receive this drug. I see it pretty cut and dried here.

DR. JUHL: I don't share your black and white view of that.

MR. CATIZONE: Randy, if I can ask a clarification of an issue that I am trying to understand, also, if a physician goes to a conference and learns that in another country because it may not be legal here in the US or it may not be acceptable that she is able to take a new product and through compounding provide a new treatment for patients who haven't been able to obtain relief from approved products or

products with the USP monograph, and that physician then writes a prescription and a pharmacist is asked to compound that prescription, how will that be handled by the agency and how will the pharmacist respond to new products that aren't included on the list that we may recommend to the FDA?

DR. JUHL: My judgment is that if a physician writes for a drug that is not on the list or on the withdrawn list --

MR. CATIZONE: No, no, just isn't on the list.

DR. JUHL: That just isn't on the list, then the pharmacist is not able to compound that prescription.

CAPT. TONELLI: It would fall outside of the exemptions provided by this part of the bill?

DR. JUHL: That is correct.

CAPT. TONELLI: It would become subject to all of the new drug provisions and so forth that have been previously in place.

MR. CATIZONE: How do you get a new drug on the list once we have made a recommendation on the products that have been nominated today and perhaps at the next session?

CAPT. TONELLI: This list is evolving. We will take recommendations or new nominations for this list at any time, and we will bring them to the next session of this Committee after we have done our review of it.

So, in the meantime I don't know that we would take an enforcement action against somebody like that. I couldn't say. If everything else was okay, I would assume that we would not.

MR. CATIZONE: So, before the pharmacist could dispense or compound that prescription, the physician or pharmacist has to nominate the drug for inclusion on the list?

CAPT. TONELLI: We would hope that would happen and preferably even if it is a new drug we would hope there would be an IND.

DR. JUHL: I feel a need to state explicitly that this is not a route that should be used for developing new drugs. There is a process for doing that, and compounding is for things that we have a relatively large amount of information about. A new product coming out, this is not a way to subvert the new drug application process.

MR. CATIZONE: But I don't think the statutory intent, also, was to restrict innovative practices and innovative therapies, and this may have a chilling effect in that regard.

DR. JUHL: I guess it depends on the definition of innovative.

MR. TRISSEL: Randy, there are some examples of products that have come out of pharmacy compounding and gone

into mainstream manufacturing, and the discovery in initial development was done by pharmacy compounding, sterile talc for pleural effusions being a good example.

DR. JUHL: But there is the new drug application process that eventually comes into play, and an IND is very often the start of that process.

MS. OGRAM: Could I add to that and read from the conference report?

DR. JUHL: Yes.

MS. OGRAM: This section is not intended to subvert the requirements that apply to investigational new drugs or to result in experimentation without appropriate human subject protection, including proper informed consent. That was addressed.

DR. JUHL: Other questions?

DR. RODRIGUEZ: I would like to address the criteria.

DR. JUHL: Have we finished with hydrazine?

PARTICIPANT: I think it is still on the table.

DR. JUHL: Yes, that is my fault. Let us --

MS. AXELRAD: Finish with hydrazine, and I would ask if you could please clarify where you are on 4-aminopyridine(?) and 3,4-diaminopyridine because --

DR. JUHL: That would be next.

MS. AXELRAD: I wasn't sure on that either.

MR. RUSHO: I see some of the same inconsistencies that Elizabeth just mentioned. We just talked about DNCB and felt that that was too toxic, and we are dealing with hydrazine which is a strong reducing agent. It is very toxic itself, but we are considering that for inclusion. I am seeing some inconsistencies in how we are handling these different compounds.

DR. ALLEN: I think part of the problem is there is a little bit of a difference in an agent that is used for the treatment of warts versus an agent that is used in terminal stages of life where we now have five to ten thousand patients on something versus maybe I am not sure of the actual number on the DNCB but it is going to take a little bit more judgment, I think in a situation like this with the hydrazine.

MR. TRISSEL: There, also, seems to be an unspoken fourth criteria here which is a human compassionate criteria for use of products that perhaps didn't extend to warts.

MS. SELLERS: Do we need to add that as a criteria?

DR. JUHL: I think it is kind of implicit in the verbiage of the report that we have where it talks about the availability of other treatments when they exist have been considered. I don't remember the language, Bob.

CAPT. TONELLI: Generally we didn't consider it

unless there was a toxicity that, also, brought it to concern. We didn't look for alternative therapies unless we had a toxicity. In this case we did have a toxicity.

DR. MC BURNEY: If you look under the toxicity of this drug it reads just like DNCB. I mean it is almost word-for-word the same.

DR. JUHL: Let us move it off the table. We have the opportunity to include it on the list without further questions or exclude it without further questions or to ask for more information and review it in an expanded session.

MS. LA FOLLETTE: Could I ask a question? If this drug was provided on compassionate use through official channels through the FDA, is there a mechanism then in place for adverse drug events? That is one of my concerns with going the route of setting up drugs on this compounding list that there isn't an official process to report adverse drug events. So, I mean if you went the other route on a compassionate or emergency basis like a named patient type of situation is there a mechanism then for adverse events as opposed to not having a mechanism if we go on the compounding route?

DR. JUHL: I cannot answer that. Can anyone from the agency?

DR. OSTERBERG: Bob Osterberg, CDER. In the review division we occasionally get phone calls or we get

letters in from physicians for either single patient treatment or perhaps compassionate use.

After we grant these particular approvals, what we do ask the physician is to submit the results of that patient's therapy to us, but we can only ask for that. We cannot demand it, and so, our frequency of getting responses back is low, but nonetheless we do ask for it.

MS. LA FOLLETTE: And then is the information published so that a collection of a database could be established?

DR. OSTERBERG: Unfortunately, it is an IND. So, we don't comment on it.

DR. WOODCOCK: Yet sponsors under INDs are subject to the same reporting requirements, whether they are single physician sponsors or pharmaceutical companies. So, as far as adverse events, serious events are required to be reported and so forth. So, it is the same system that we have for other compounds that would be sponsored by a pharmaceutical manufacturer.

MS. LA FOLLETTE: So, there is a mechanism?

DR. WOODCOCK: Oh, yes. For effectiveness there is much less follow-up information available, but then those are single patient experiences or a small series of experiences.

Occasionally we have approved drugs based on the

collection of experience that has been gained over years in using it basically for some treatment application under an IND.

MR. CATIZONE: Randy, in regard to the hydrazine, I think our role as an Advisory Committee to the FDA focuses on some different issues. It is good for us to introduce issues as background, but I think we have to realize that the decisions or recommendations we make and the final decisions that the FDA make will have little or no effect on the regulations governing the practice of medicine and pharmacy in that even a drug product that has gone through the NDA process even though the FDA has approved it for certain indications, there is nothing prohibiting a physician for prescribing that product for an unapproved use or for prescribing that products for a dosage form that hasn't been approved by the FDA.

So, if we try to extrapolate some of our decisions here on behalf of the FDA into the practice sector we may be confusing or confounding our deliberations.

In that regard I think products that we are evaluating, we are evaluating based upon the toxicity and the historical use. The efficacious evaluation or data become important, but it is not one of the critical determinants, and in that regard any product that is not toxic and is being used out there should be approved to the

list.

Products that are toxic but demonstrate an important need for patients and whose use overrides the toxicity should be included in the list.

Products whose toxicity is so great and that the need is such that it doesn't override the toxicity, and if these medications are then available by some route for patients who direly need these medications should be excluded, and I think hydrazine falls within that third category. It is extremely toxic. Yes, there is a patient need, but patients can obtain this medication through other routes such as an IND and an IND may be a preferable route for this product so that it can be monitored and the safety of both the patients and the practitioner is assured.

DR. JUHL: I think the dilemma arises between your Category II and Category III and whether or not the need overrides the toxicity, and that is the judgment we are dealing with here, and there are valid positions on both sides.

MR. LIEBMAN: Dr. Juhl, from a practical standpoint are we going to be having hundreds of physicians writing to the FDA asking for permission to use this product? Is that reasonable to expect?

MR. CATIZONE: Even if that occurred, David, I think that is outside of the scope of this Committee. We are

looking at the safety and use of a product to make a recommendation. If the FDA gets flooded with requests, I think that is a different committee or a different section of the FDA to respond to.

MR. LIEBMAN: But if you are saying that we should not include it because there is a mechanism whereby physicians can write, again, coming back to the point that Loyd Allen makes you have got 10,000 patients out there, plus or minus a few who are currently on the product, are on the compound or on the medication. What happens to them?

MR. CATIZONE: Let me ask sort of the leading question then, and what is the purpose of this Committee? I guarantee that I could come up with a number of patients utilizing any one of the medications in all four of the groups, and if I use as criteria the fact that there are patients utilizing this medication, then I would recommend that the Committee approve all the products and that any future products that are nominated, also, be approved.

I think we have to make some distinguishing criteria here, and the criteria are is this a safe product and if it is not a safe product is there an overriding need for this product in the medical and pharmacy community, and if there is not an overriding need, then those patients and physicians have to use alternative methods to obtain that product where those toxicity issues can be addressed and

monitored.

Otherwise we might as well approve every drug on the list and every future drug because I am sure the sponsors or nominators of those products can demonstrate to us that there are patients utilizing those medications.

MR. LIEBMAN: Refresh my memory. Did the double-blind study show that the drug was ineffective, less than effective or that it was dangerous?

MR. CATIZONE: The double-blind studies, there were two. Focusing on the survival curves of the treated group versus the placebo group one study showed there was no difference. The other showed that the treated group had a substantially shorter survival than the placebo group. That is the worrisome one.

MR. LIEBMAN: The inference being that those who took the medicine died faster?

MR. CATIZONE: Died earlier.

MR. LIEBMAN: As a result of?

MR. CATIZONE: Presumably as a result of the hydrazine.

DR. JUHL: Are you ready for the question?

The question will be the three options we have to deal with this drug, one, to recommend its inclusion on the list; two, to recommend that it not be on the list and three, to seek additional information in an expanded

session.

Are we all clear?

All those who would go with option one which is to recommend inclusion on the list today, please raise your hands?

(No response.)

DR. JUHL: I see no hands.

All those who would recommend today that we recommend that it not be included on the list, please raise your hands?

(There was a show of hands.)

DR. JUHL: Do I count six? Please keep your hands up. We have five.

Those that would prefer the third option of an expanded session, please, raise your hands?

(There was a show of hands.)

DR. JUHL: Six. We have a mandate of six to five favoring an expanded session, and I believe we will proceed in that fashion then from the Committee's perspective, and the agency will view that as a recommendation from us.

Let us now move to the aminopyridines.

DR. RODRIGUEZ: I had a question earlier about the criteria and the question that I have is as follows: I understand that you did not put the effectiveness there because you may not have it for all, but if you have

information telling you that something is better than water, are we going to ignore that? Because if we don't need that we might as well not have it except for where it makes a difference for toxicity, but you know I find it very difficult to vote positively on some things where I have the information and I should ignore it because it is not in the criteria, and I had a question. I don't know if anybody else has the same feeling, but I am having that feeling sitting here..

MS. SELLERS: I am having that same feeling. We discussed this yesterday, if there is negative information about efficacy. I don't believe that we, well, I don't feel like I can ignore that in evaluating the compounds when there are effective treatments out there for indications.

DR. JUHL: I think that is the difficulty that we all have. Safety and it is not toxicity that we are examining, it is safety and inherent in safety is the question of compared to what.

DR. RODRIGUEZ: So, essentially what I am wondering is could there be a corollary here if the information is available to us why not use it? In other words, we have to remember that what is provided for us is provided in an unbiased fashion from multiple sources and we have the option of either accepting it and saying that this is good, but it doesn't mean anything or saying, "This study

looks like it was conducted appropriately, and we have that information," and that is my concern.

DR. JUHL: I think that is the judgment that we haven't been able to make in the fashion that we are normally accustomed to in our evaluation of the study, reviewing raw data and making those judgments, and that clearly is outside of what was intended, and I think that is why the question is like being a little big pregnant or using a little bit of the data. It is easier and I think more appropriate to only consider safety, but as I have said, it is impossible to ignore, especially when we have negative safety, negative efficacy data for a drug that treats a very serious condition to not consider the entire multitude of information available to us.

DR. RODRIGUEZ: I certainly would find it very difficult to say that I will make statements without taking that into consideration because it is illogical in my mind. So, it is going to affect it. Even if we say that we won't do it, it is still going to impact there.

DR. JUHL: I think if that is the view of the Committee, then that is our answer. That is why the Committee is here to give our opinions and recommendations on drugs that are nominated for the list.

MR. TRISSEL: Randy, am I hearing that you are saying that if efficacy data is available it should be

considered, but if the efficacy data is not available that is not in and of itself a reason to remove it from the list; is that what you are saying, Dr. Rodriguez?

DR. RODRIGUEZ: That is what I am saying. In other words, if it is available we should be able to use it or say if it is coming from unreliable sources, I mean you know where some of the better studies are done and at least medically I know where some of the better studies are done, and I can weigh that information.

Now, that information is probably a little bit better than to hear that it has been used for 20 years, and nothing has ever happened which is what we are doing at this moment.

So, in my hands, it is a degree higher than the testimonial information that it has been used without any problems.

DR. JUHL: Other comments from the Committee?

MR. CATIZONE: I think if the product is non-toxic and the efficacy data indicate that it is not creating an adverse reaction, and this is saying that it may not be as effective as water but it is not doing any harm to patients, and some patients are benefitting I don't see any problem in including the product rather than excluding the product.

DR. JUHL: You don't think we have difficulty on that end of the scale. It is the other end of the scale

that causes us the difficulty.

Gina, did you want to make a comment? Please identify yourself for the record?

DR. FORD: Gina Ford with the International Academy of Compounding Pharmacists. The data that you had is because that is what is available. There may be efficacy out there in 300 patients, but it has not been studied due to reasons that no one has initiated that study in the sense that you are looking at the research today.

I just want to make that comment, that the reason you have it is because somebody put forth the dollars to make that efficacy study and that is not always practical in these substances that you are looking at.

DR. RODRIGUEZ: I don't think we are penalizing because of the lack of information. In other words, if it isn't there, it isn't there. So, I wouldn't hold it against the -- but if it is out there, and we have it in our hands, that is when I would say, "Gee, you know, this is one step above, and we have that information. How could we ignore it in making a decision?"

DR. FORD: If that is the case, then we as the nominator need to be allowed to give you that kind of information whether it be anecdotal survey, patient, pharmacist, we need some means to be able to get that kind of information to you.

DR. PECK: The thing that we are faced with is no compilation of information regardless of the size of the population, and we are asked to make a decision not knowing some degree of effectiveness regardless of how it is determined. So, you know, it is hard to work with nothing.

DR. FORD: Sure, and that is what I just want to clarify at this point is that in these submissions that was not considered. We supplied the information based on what was asked of us, and if there was peer reviewed medical literature that is what we supplied.

DR. JUHL: I think we are straying away from the question on the table. It is if we have peer-reviewed information available to us, what do we do with it in this case, and Dr. Woodcock wanted to jump in.

DR. WOODCOCK: I believe that nominators were encouraged to give whatever information was available, and I guess perhaps that was confusing or whatever, but whatever information was available, I mean the history of use, for example, the information you have given I think has been quite useful in establishing the fact that these products have been used historically for example.

So, it isn't that a nominator -- we welcome for future nominations a complete package that has as much information as possible, both on the extent of use and whatever reports there are of usefulness as well as toxicity

of the product.

DR. JUHL: Do I hear a sense of the Committee that we will consider all information that is available to us or not?

PARTICIPANT: If relevant.

DR. JUHL: And do we need to make a criterion or recommend a criterion based on that or is it simple enough to say that we are happy to look at anything that will be provided?

MS. SELLERS: If the criteria is used by the FDA in the initial evaluation of the drugs that may come to the Committee in the future I think it needs to be a formal criteria.

DR. JUHL: Eventually we will have the same criteria because we are looking at the same thing, and our recommendation to them should be based on what the criteria are, but that is the question and do we want to recommend some degree of formality to it or is the statement that is there which Jane is going to read to us now sufficient?

MR. CATIZONE: Dr. Juhl, I would suggest that based upon the proposal by the FDA to use the three criteria they have given to us yesterday as well as the Senate and statutory direction that efficacy data is important but should not be one of the primary considerations or the single determinant of whether or not a product is approved.

So, I don't think we should add to those criteria and ignore our statutory directions.

If we have the information I think we should look at it, but it should be looked at in the context of the three criteria which the FDA proposed yesterday.

DR. JUHL: We don't have statutory direction on the criteria. We have statutory direction on the information that will be used.

MR. CATIZONE: I think the direction was that it should not follow the same approval or be held to the same standards as a new drug application which looks at safety and efficacy, and the Committee report was clear that we look at history of use and safety. So I think there is some direction there, and that is why the FDA came up with the criteria they did, those three components.

DR. JUHL: The question is though is consideration of information that is available the same as the NDA process of determining efficacy, and I think there are degrees of that. I look at that as an analogue scale, not a digital scale.

MR. TRISSEL: Also, I am not sure we are obliged to ignore the information from a peer-reviewed source just because we are on this Committee.

DR. WOODCOCK: The new drug approval process requires substantial evidence of effectiveness which is a

quite different standard. Ordinarily it is considered evidence from at least two adequate and well-controlled clinical trials that are backed up by the primary data from those studies although not in all cases.

So, that is quite a different kind of standard than you are proposing in looking at the reports in the literature of effectiveness or whatever.

MR. LIEBMAN: It would seem to me that if a group or individual were submitting a drug for consideration it would behoove them to give us as much information and some of that information may well be letters from physicians who are using it saying that it is important to my patients or letters from patients who say that before I used it I was such and such, and I am using it and I feel better.

At least we will have the information. We can well decide if we think that information is important or relevant or is a determining factor, but I think the more information we have the better our decision making would be.

MS. AXELRAD: At the moment there isn't anything. We had talked though among ourselves about what we would say about negative efficacy data, and we may well include something like that in the Federal Register notice when we propose the criteria. I couldn't find it in here now. It may have been in an earlier draft and been removed, but we have talked about that among ourselves, and believe that where

there has been actual controlled trials that have shown negative efficacy that it ought to be taken into account.

DR. ALLEN: I agree with Carmen basically that we need to look at the original legislative intent. We can consider this, but I think it should be done in a more informal way, you know, as supportive information rather than in a more declarative way.

MS. OGRAM: The original legislative intent gave us some criteria to go on but gave us the option to include additional criteria and I think that that is one of the things that came to the Committee yesterday as to whether or not we should add or change the criteria that were presented to you by the agency. I don't know whether it would be appropriate to revisit that at this point.

DR. JUHL: It seems to me, and correct me if I am wrong, but I think the legislation included sources of information but really didn't speak to criteria as directly, and the interpretation of historical use, peer-reviewed medical journals and other sources of information were included in the legislation and then we need to translate that into criteria and safety and safety and historical use were the criteria that the agency came up. Am I remembering that correctly?

MS. AXELRAD: The statute says, "The Secretary shall include in the regulation the criteria for substances

which shall include historical use, reports in peer-reviewed medical literature or other criteria the Secretary may identify," and what we have done in our draft Federal Register notice is include the historical use data and, also, the other two criteria, chemical characterization and safety, and of course, articles in peer-reviewed literature would be used to support safety criterion, as well as the historical use criterion.

DR. JUHL: So, we are directed to use peer-reviewed literature.

I guess the question is how do we use it. Do we just look at the safety part of the study and ignore the efficacy part of the study? I don't think that is reasonable to assume that we would do that and it would be rather Neanderthal to do.

MR. TRISSEL: Given that Carmen's three criteria seem to fit based on our ability to include peer-reviewed information. It would fit with this thing.

DR. JUHL: David Horowitz?

DR. HOROWITZ: I just want to go back to the literature again. The statute does not direct us to use any criteria. Let me read it again. The Secretary shall include in the regulation the criteria used for such substances which shall include historical use, reports in peer-reviewed medical literature or other criteria the

Secretary may identify.

So, what I interpret that to mean is that there is a couple of suggestions here but the Secretary is left with full discretion. Now, FDA has taken these recommendations quite seriously and focused on historical use and looked at the peer-reviewed medical literature. There is nothing in here that would preclude the agency from looking at data on safety and effectiveness but I think it is the agency's view that the statute does not envision the agency using the substantial evidence standard which is the standard that would traditionally be applied for NDAs.

Clearly we wouldn't have enough information to do that. However, that does not preclude us from looking at and factoring in as formal criteria the information that we do have about safety and effectiveness.

DR. JUHL: Is everybody comfortable with that?

If I could try to summarize this, then, the Committee would recommend that the agency have available to it all information that can be provided about the particular compound for inclusion or exclusion on the list which would include information about its effectiveness, but this would be considered in the totality of all information available and not as a sole primary single criteria.

Are we happy?

Can we move to the aminopyridines?

When last we visited these drugs my impression and please correct me if I am impressed in the wrong way was that were going to ask for additional information on these drugs from the clinicians who make most use of them, and consider that in an expanded session at another meeting.

We have the option to revisit that, but that is my remembrance of our discussion yesterday, and the floor is open for this subject.

MR. TRISSEL: That is, also, my recollection. I would support that.

DR. JUHL: I see heads nodding affirmatively and we will consider that to be the disposition of that topic.

Are there other topics from yesterday that we need to revisit?

If not, then let us move to today.

DR. ALLEN: Could I bring up one thing? The item Carmen distributed under tentative recommendations from the Advisory Committee I am a little confused on items numbered one and two, exclude versus approve. It looks like those might be reversed in a cut and paste on the computer, maybe.

MR. CATIZONE: Those were just my notes. I wouldn't take them as official, but No. 1 referred to Dr. Rodriguez's concern with the mild silver protein and I wasn't sure if that was excluded, and No. 2, the approved, I thought that was the DNCB. So, that was just a reflection

of my recollection of the discussion and where we were, but that has been clarified today.

DR. JUHL: Are there other things, Carmen, that you wish to revisit from your notes?

MR. CATIZONE: No.

DR. JUHL: Let us then call on Captain Tonelli to present Group IV.

CAPT. TONELLI: I am glad we completed Group III yesterday. The Group IV nominated substances. Nominated drug substances that are not being proposed for inclusion on the bulk drugs list. FDA is proposing that the following nominated drug substances not be included in the list of bulk drug substances that may be used in compounding under the exemptions provided in Section 503(a) of the FD&C Act. After carefully considering the relevant evaluation criteria, FDA does not believe that general compounding with any of these substances is appropriate.

The agency points out, however, that exclusion of these substances from the bulk drugs list would not automatically exclude their legal use in medical or pharmacy practice. These substances still may be available through an investigational new drug exemption.

The Group IV bulk drugs, betahistine dihydrochloride. Betahistine dihydrochloride is chemically well characterized. It has been used to treat symptoms of

vertigo in patients with Meniere's disease and was formerly marketed as Cirq(?) tablets.

In 1970, however, FDA withdrew the approval of the NDA for Cirq tablets because they were found to lack substantial evidence of effectiveness. In a separate rule making FDA intends to propose this substance for inclusion on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective. For these reasons FDA is not proposing to include betahistine dihydrochloride on the list of bulk drug substances or compounds.

Cantharadine, a substance obtained from Chinese blister beetle among other beetle species has been used topically in the treatment of warts and molluscum contagiosum. Cantharadine is well characterized chemically. It is, however, an extremely toxic substance. Not only is cantharadine destructive to eyes, skin and mucous membranes, it can be fatal if inhaled, swallowed or absorbed through the skin.

As little as 10 milligrams of cantharadine has been reported to cause death. Topical application of cantharadine has produced acute lymphangitis and persistent lymphangitis. Ingestion of cantharadine can produce burning of the mouth, nausea, dysphagia, hematemesis, hematuria, dysuria, erosion and hemorrhage of the upper GI tract, renal

dysfunction and failure due to acute tubular necrosis and destruction of glomeruli.

Low-grade disseminated intravascular coagulation, also, has been reported in patients with acute cantharadine poisoning.

For these reasons, FDA believes that the hazards associated with the use of cantharadine outweigh any benefits to be derived from its medicinal use. This is especially true given the availability of safer alternative drugs for the indications that cantharadine is being used.

Cyclandelate which is well characterized chemically is a vasodilator that has been used in the treatment of cerebral vascular and peripheral vascular disorders as well as diabetic retinopathy.

It was formerly marketed in cyclospasmol(?) capsules and tablets which were removed from the market for lack of effectiveness in 1966. In a separate rule making FDA intends to propose this substance for inclusion on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective.

For these reasons FDA is not proposing to include cyclandelate on the list of bulk drug substances acceptable for compounding.

Sulfadimethoxine is a chemically well-characterized antibacterial agent that was formerly marketed

in Madrosidin(?) capsules. Madrosidin capsules were removed from the market in 1966, for safety reasons after being associated with Stevens-Johnson syndrome.

In a separate rule making FDA intends to propose this substance for inclusion on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective. For these reasons FDA is not proposing to include sulfadimethoxine on the list of bulk drugs acceptable for compounding, and that concludes those in Group IV.

PARTICIPANT: Pentylenetetrazole?

CAPT. TONELLI: Oh, did I skip one? Sorry.

Pentylenetetrazole which is chemically well characterized has been used to enhance the mental and physical activity of elderly patients to treat schizophrenia and in the diagnosis of epilepsy. It was formerly marketed in numerous drug products, all of which were removed from the market for lack of effectiveness.

In a separate rule making FDA intends to propose this substance for inclusion on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective. Sorry.

At this time the two substances that we did not consider, if anybody had comments we would like to entertain them on the two substances that came in in the letter that

were not considered by FDA, the dicencytrone(?) and squaric acid dibutyl ester. We would love to hear comments for them, too.

Thank you.

DR. JUHL: Let me begin the discussion by talking about the withdrawn for safety and efficacy list. That is something we will need to talk about this afternoon or later this morning when we get to it, but we, also, need to consider that here.

If you recall yesterday during our discussion of the Act the question was asked whether or not in the legislative history that somewhere we couldn't find was there a judgment that was supposed to be addressed in the safety and efficacy list, and there didn't seem to be much or didn't seem to be any evidence that this was other than a list that was reasonably cut and dried, and I would like the Committee to discuss that now. The statute says that any drug that is withdrawn for safety or efficacy cannot be used for pharmacy compounding.

Is there an interpretation to that other than something on the list can't be used for pharmacy compounding?

MR. LIEBMAN: In terms of efficacy while it may not have been efficacious for the reason it was commercially produced it may well have great value when compounded and

used in, quote, off-label uses for other kinds of conditions. So, I am not at all with saying that if it is dangerous, if it is toxic maybe we ought to look at it very seriously and consider exclusion, but efficacy in and of itself I think is too broad a brush to just slap on and say that that is a good reason to exclude.

DR. JUHL: What I am trying to resolve is the language that Congress gave us and what we are supposed to do with that, and that is the language they gave us. I guess I am looking for other interpretations, and if you have one I would like the Committee's --

DR. ALLEN: I think what David is referring to is a good point. If you look at the removal of a drug for lack of effectiveness it is due to the original labeling, I believe, the original intent of use and with the off-label use and alternative uses that wasn't really addressed in the original INDs, etc., quite possibly, and as we all know there is a lot of off-label use going on, not that there is going to be a bunch of them or anything like that, but there are some that might be of benefit. So, my interpretation is that the safety and effectiveness relates back to the original labeling of the product and does not necessarily address the off-label uses because obviously those weren't addressed originally anyway.

DR. RODRIGUEZ: So, could we request that when we

have an information such as withdrawn because of lack of effectiveness that gets spelled out? For example, betahistine dihydrochloride may have been used for quote, unquote, allergies, and it was found to be ineffective, and that is why it was withdrawn, while talking here of Meniere's and vertigo and other things which was part of the original reason for betahistine dihydrochloride and we don't have that information available to us. So, maybe up front withdrawn because one, two, three.

MR. CATIZONE: Dr. Juhl, how much discretion do we have in this area because if the products have been withdrawn for either safety or efficacy, aren't they already on the list that the FDA maintains?

DR. JUHL: The FDA was directed to make a new list specifically for pharmacy compounding, and it included drugs that have been withdrawn for safety and efficacy.

MR. CATIZONE: So, any of the products that have been listed here that were withdrawn in the past may not necessarily be included on the list?

MR. LIEBMAN: May be included for compounding if I understand you correctly. It was withdrawn for efficacy for its original purpose, Dr. Menendez said. It may well be added back into the list because it has utilization for off-label uses.

MR. CATIZONE: That was my question whether or not

removing it in the past would predicate that it now be included on the list of withdrawn products or there was an opportunity for this Committee to decide what products should or should not be included on the new list of withdrawn products.

DR. JUHL: The question is how loosely do we want to play with the congressional language, and I appreciate the argument that you make about being withdrawn for one indication, and it may be useful for something else. The countervailing argument that I am sure was part of the discussion is that if something else arises there is a process for development of new drugs, and that is the process that should be taken.

So, those are the two issues, and neither one of them found their way into the legislative history or into the language.

MR. CATIZONE: But I think we still haven't resolved the consistency issue, and that is how we are going to use the efficacy data. If a product has been removed from the market simply because it wasn't effective, and we have approved other products or delayed consideration of those products because there was no toxicity shown, and I think three of the five products on this list have no toxicity but were removed for efficacy reasons should be included in our recommendations on the list. If, however,

we say that if they have been withdrawn for efficacy then we shouldn't include them on the list, then we need to go back, and there are two products where we have questions about their efficacy that should not be included on our recommendations for the FDA.

MS. AXELRAD: I have to clarify this, and some of this will become clearer when we get into the other list, but basically the other products were not withdrawn from the market for lack of efficacy, the products that we have discussed previously. In fact, they had never been approved. They never had an approval at all.

So, the issue of whether they were effective or not was never actually addressed by the agency although there are studies in the literature for one of those that suggests that it may not be effective.

What we have here though in these cases are drugs where there were approvals before the agency of some form and where the agency has actually addressed the efficacy for something and identified that they were found to be not effective for that particular use, and there is documentation of that which we will be supplying later.

Now, in the list that we have published so far we have only addressed those products that have been withdrawn and removed from the market because they have been found to be unsafe. We haven't yet addressed substances or the

products that have been withdrawn or removed from the market for efficacy reasons, and so in a way the discussion of these substances is sort of getting into what we intend to get into in a future meeting when we discuss substances that have been removed for efficacy reasons.

DR. JUHL: So, one way to handle these which have been nominated for the bulks list and that is why they are here now is to defer discussion on those until we get into the list that is going to be made of drugs that have been withdrawn for reasons of efficacy.

MS. AXELRAD: Yes.

DR. JUHL: We have to consider those general criteria then in response to something that is --

MS. AXELRAD: Right. Now, one of the drugs on here is actually on the other list as having been withdrawn for safety.

DR. JUHL: Safety I think we are all comfortable with.

DR. RODRIGUEZ: One point that comes to me is an antibiotic I proposed to the FDA for quote, unquote, strep throat but yet it is effective against soft tissue infections, but the only indication that you get is the strep throat in a sense. So, physicians like myself may be using it for soft tissue infections along with the strep throat. It is not effective against strep throat. It is

only effective against staph, for example. You take it out of the market or deny it. It is still effective against staph, and that is why this is a very pertinent point about the unapproved uses of the unapproved or subsequently disapproved products.

MS. AXELRAD: I think that we will have to address the question when we get to the list of products that have been withdrawn for reasons of efficacy of what to do about a product that has been found to be ineffective for some use, presumably the use that is on the label but for which there may be data that may or may not have ever been evaluated by the agency with regard to some other use.

The agency hasn't addressed that question yet because we haven't taken up the universe of products that fall under that. The statute says that we have to put on the list, we are required to put on the list drug products that have been withdrawn or removed from the market because they have been found to be unsafe or ineffective. The statute doesn't address ineffective for what, and so we will have to address that question in developing the list. We haven't done that yet. So, it might be advisable to defer discussion of these that have been withdrawn for efficacy reasons until we get to that issue with the other list.

DR. JUHL: I am sure the subject will come up again for other compounds that are going to be on that list.

MR. TRISSEL: I would certainly encourage the agency to include the indication for which the product was found to be ineffective on the list.

MR. LIEBMAN: I did that. Those that I presented, those indications I presented that it was being used for are the indications that it was prescribed.

MR. TRISSEL: I meant on the broader list that you are working on.

MS. AXELRAD: But I guess what Bob just said is that these were included on the list of things that we didn't want to include because in fact the agency addressed whether they were effective for the uses that are listed in the Federal Register notice and determined that they were not effective for those specific uses.

MR. TRISSEL: So, do I understand that if there is a nominator of one of those substances for some use other than the ones that were found to be ineffective they could be considered by this Committee?

MS. AXELRAD: That is going to raise a very tricky legal issue because theoretically if it has been withdrawn from approval for a particular use then there is no approved new drug application out there. The question would be whether they could use the active ingredient for some other use which would depend on whether there is a USP monograph or whether it is on our bulks list.

MR. TRISSEL: That is what I mean, whether it could be considered under the general rules we are using for the other bulks for a different indication than had been previously found to be ineffective.

MS. AXELRAD: With a historical use basis.

MR. TRISSEL: With a historical use basis.

MS. AXELRAD: Right, but I think we will have to have some interesting legal discussions about this because the one deals with drug products; the other deals with active ingredients. We aren't limiting the uses, for example, when we putting an active ingredient on the bulks list. We aren't limiting it to particular uses or we haven't proposed to limit it for particular uses and so we hadn't really discussed whether the withdrawn list would, also, say that it had been only withdrawn for a particular use. It gets very tricky how those lists are going to interact, and we have to figure that out.

DR. JUHL: Let me try to narrow this down. Let us take those drugs on this Group IV that have been withdrawn for reasons for safety and I believe those are --

PARTICIPANT: There is only one. It is just sulfadimethoxine.

DR. JUHL: And PETN was not a safety issue? Okay.

DR. RODRIGUEZ: How about cantharadine?

DR. JUHL: That is not a withdrawn one. Then we

will look at the toxic one.

Is there any discussion on sulfadimethoxine and from the Academy --

DR. FORD: Just from International Academy of Compounding Pharmacists, we will withdraw that nomination after looking into its widespread use in this country. It is not based on human use at this point.

DR. JUHL: Any further discussion?

I have a sense then that the Committee would concur with the agency's categorization of this compound.

We then have two that are on the list because they were withdrawn for efficacy. My proposal is that we, I am sorry, three, betahistine, cyclandelate and PETN, and my proposal is that we defer judgment on these until the criteria have been developed and discussed for drugs to be put on the list that have been withdrawn for reasons of efficacy. Does that make sense to everyone?

CAPT. TONELLI: I would just like to make one comment. If the nominators would then have another indication for which they wish us to consider that drug we would appreciate any information they would have on that be sent to us.

DR. FORD: We will make that clear.

DR. JUHN: Other comments on that category of drug?

Okay, we will defer consideration from the Committee's perspective until the second list comes up which I suspect will be at the next meeting.

We then have cantharadine to consider which is a drug that is on the list that has never been approved, doesn't have a USP monograph, and the agency is suggesting that it not be included in pharmacy compounding because of its toxicity.

I call upon the nominator, the Academy to present any information you have for us on that?

DR. FORD: Gina Ford of the International Academy of Compounding Pharmacy. In regard to cantharadine and its use in pharmacy compounding, cantharadine has been used since the days of Hippocrates for wart removal. We estimate that in this country there is less than 1 kilogram sold annually.

Cantharadine did actually appear in NF10 and in the 1955 US Dispensatory. In the NF10 the product that the monograph was actually written on was Cantharades(?) but it was standardized on 0.6 percent of cantharadine content.

The reason for our inclusion of cantharadine on this list is because when the manufacturer of products, Cantharone(?) Cantharone plus Verex(?) Varisol(?) and Vercant(?) were taken off the market, not for reasons of safety, physicians then turned to compounding pharmacies to

still be able to use this medication for wart treatment.

In discussing with physicians they prefer this product because of the cleanness that it exhibits when used in wart removal. It is used primarily in a physician's office. It would be supplied to the office for use there. The physician would make the application. That is what we have got.

DR. JUHL: For clarification is there a commercial product that is available that is on the market?

DR. FORD: Not at this particular time.

DR. MC BURNEY: Who would have known that warts would have been such a hot topic?

(Laughter.)

DR. MC BURNEY: But I venture to say if we took a poll here everybody has probably had at least one in their lifetime. So, it is quite a common skin disease. Cantharadine is a very ancient drug that has been used by dermatologists for years, and it is still used primarily by the more senior members of our specialty, and I am rapidly approaching that, I might add.

It has been pointed out by Bob that it is the juice of a blister beetle and when it is applied to the skin within a few hours it causes a very huge blister on the skin, and if it is properly applied you can get a controlled reaction in the skin with removal of the wart.

It is an extremely potent drug in that if too much is put on as has already been indicated you can get a lymphangitis or red streaks up the arms with development of painful red lymph nodes. It has been used more recently particularly in treating patients with immunosuppressed disease, HIV patients that develop these large numbers of widespread warts or molluscum contagiosum which is a viral disease, also, that they are prone to get, and it gives us an agent that requires a one-time application that can be done in the office that is generally not extremely painful, and that is the basis of its usage.

DR. JUHL: Could I ask you, Bob, how did the agency differentiate this and DNCB which is, also, a very potent nasty old drug; why did this end up on IV and the other one on III in your mind?

CAPT. TONELLI: Actually I believe because of the talk, the LD50 on this one was so low that we thought that giving this to a patient to take home at all would be beyond any use that we could imagine. It was the LD50 and just the high toxicity level at such a high dose differed it from the DNCB which is a sensitizer, but it had a different LD50.

MR. TRISSEL: DNCB was in the hundreds of milligrams per kilo.

CAPT. TONELLI: It wasn't even close to the LD50 for this one.

DR. JUHL: Comments or questions about cantharadine?

MS. LA FOLLETTE: I would like to hear about how it is actually prepared as far as the safety of the compound as a bulk drug substance, since it is so toxic from those that are using it.

DR. MC BURNEY: I have no idea. I really couldn't comment on that. I get it from the pharmacist, and so, I cannot comment on the compounding of it.

DR. FORD: For sure the compounding of this particular product is done with the utmost safety for the personnel making it, double gloves, mask, gown, full skin protection. I don't believe there is a requirement as far as that being made in a biological safety hood. Those facilities that have it available, I am sure would take advantage of that.

I would just like to take a moment to let you know that the Academy did submit it, but, also, the submission did, also, come from the American Academy of Dermatologists.

MR. TRISSEL: Those kinds of precautions are the kind we take routinely with cancer drugs, for obvious reasons, and it is not unusual for pharmacists to have those available at least in the institutional or home care setting. I think it is probably a little less so in the retail setting.

DR. MC BURNEY: Also, in regard to the question about whether it is given to patients to take home, I am not aware of anyone who would give that to be taken home by a patient.

MR. LIEBMAN: If it is a single use application there would be no reason to give it to the patient.

DR. MC BURNEY: They don't come back afterwards.

(Laughter.)

PARTICIPANT: Was that a positive comment?

DR. MC BURNEY: Oh, I am speaking of the warts.

DR. RODRIGUEZ: What alternative do you have then for the treatment of these warts? In other words, it sounds like it is very effective but very toxic, and the question is do you have any alternatives if this were to disappear?

DR. MC BURNEY: Yes, Dr. Rodriguez, and of course, the list is, as I always tell my patients the more treatments there are for a disease the less effective any of them is, and warts certainly falls into that category. Usually we will try cryosurgery with liquid nitrogen, laser therapy with either the CO2 laser, the pulsed dial laser. We will use topical acid applications and in Louisiana we, also, use tretoirs(?) which are healers, anything that will help the warts go away.

Unfortunately though we do have patients as I have stated that are immunosuppressed that we have a real

problem, and none of these therapies work consistently, and this gives us another option to offer to patients that have a very extensive disease.

DR. RODRIGUEZ: In your experience this sounds almost like a last resort, what is your experience in eradicating, I mean since we don't have any other information?

DR. MC BURNEY: I think you have to divide it into separate groups, those patients that are what I would call immunocompetent that have very large warts and they appear not to develop a cellular immunity against the human papilloma virus itself and in those patients they do quite well. We get an acceptable cure rate of approximately I would say 70 percent in those patients.

However, in immunosuppressed patients we are very successful in eradicating the individual lesion, but they frequently have recurrent disease.

MR. TRISSEL: Can you speak to the clinical consequences of not having this particular agent available for those patients who have failed all other therapies?

DR. MC BURNEY: That is a very difficult question for me to answer because it is only after you have frozen a wart 10 or 15 times or you have tried to perform surgery on them and you have got patients that are significantly ill that we look for other options to treat these, and although

it is interesting that sometimes in our very seriously ill patients it seems to be the more banal things that they concentrate on, they may be perhaps dying from their HIV disease, but they are more concerned about the clinical appearance of their face with multiple warts over it, and that is where their attention is directed, and if we did not have this we would continue with the other things that we have available, I think. I don't know if I have answered your question.

MR. TRISSEL: I was thinking if the other things have been shown to be ineffective, you are just not getting those out, how do the patients, what do they do? What is their clinical course? What is their mental outlook with massive warts? This is a very negative thing.

DR. MC BURNEY: It is very depressive to patients, certainly, and it is very disturbing to the patients and the physician treating them, certainly, and if untreated and unattended to they continue to enlarge, become disfiguring and can, also, interfere with functions depending on the sites or the location of these viral infections.

DR. JUHL: Other comments from the Committee?
Carmen and then Garnet.

MR. CATIZONE: I think we are back to the question of whether or not we are going to include every drug that has been nominated simply because we can demonstrate that

there is some patient use and need for that product. We have a highly toxic substance here. We have a limited patient use. We have alternative therapies that are available, and we can assure that the patients would have access to this treatment through other methods that ensure more course monitoring and safety considerations.

I would recommend or vote for consideration of excluding this product from the list rather than including and to look at the criteria again that we are using in making decisions about whether or not products should be included or excluded.

DR. PECK: For the sake of going back in history I think of my days in pharmacy school when we did actually look at crude drugs, and I had in my hands these particular beetles, and we had to learn how to recognize them. To treat warts, this was it back in those days. We didn't have before us, however, the toxicity data that was summarized here which I think is significant.

I have heard over the 2 days other treatments for warts, and I wonder whether this should remain in the armamentarium for wart therapy. If we are using safety as a criteria for these particular drugs this one has not a very good history as far as safety is concerned. So, I am really not in favor of changing the decision, placing this in this particular category.

MR. LIEBMAN: I share your concern about the safety. I think the point that you missed was Dr. McBurney said that there are other modalities all of which have failed. So, while there is access to other choices, they are unacceptable choices. They are ineffective choices, and if you don't give them at least a try at this thing with the appreciation of an understanding of it is a dangerous drug; the pharmacist who prepares it needs to be extremely careful, and the physician who is applying it is going to be extremely careful, and the patient understands the potential of danger, but you heard her say, "The warts don't go away. They have already tried surgery 15 times. They are going to end up with warts. While they may focus in on the banal kinds of things, they have got these huge warts all over their bodies. It is disfiguring," and I deal with patients. I don't know how you say, "No," to these kinds of people. I mean I know it is dangerous, and I know it is scary, but the alternative is saying, "You are going to have to be disfigured, and you are going to have to be a monster physically because we are concerned that while you are dying of cancer or while you are dying of AIDS, okay, you are going to be a monster until you die because we are afraid you may have a toxic reaction." I have trouble with that, I am sorry.

MR. CATIZONE: I agree with you and I don't think

anyone's intent here on the Committee is to deny patients treatment and good quality of life. I think the issue is whether or not a medication is safe for use, and this Committee in its recommendations to the FDA has to draw a line and say that these products are safe, and these products are not safe. By not including a product on the list does not exclude the availability of that medication to patients who truly need that therapy.

There is the IND route. There are other routes that the physician and patients can travel to obtain that medication. I know that may be difficult or may be more time consuming than simply approving the product, but if we don't determine a criteria for differentiating between safe and unsafe products that should be included on the list, then my recommendation is to include every drug that is nominated on the list today and in the future and save the Committee and the FDA some time and research.

MR. LIEBMAN: Can we ask the two physicians on the Committee how many times they have needed a drug, couldn't find it and therefore submitted an IND so they could have access to a drug?

MS. LA FOLLETTE: They can, also, make a phone call to the FDA and get this.

MR. LIEBMAN: How often have they done that?

MS. LA FOLLETTE: Maybe they weren't aware of it.

I mean that is why I wanted this brought out to the Committee. There are mechanisms, and people should understand that.

MS. SELLERS: I have potential concerns for off-label uses of this drug. In our book there are many herbalist uses that are cited, and that is where my concerns fall. If this is a generally available substance will it be used for these types of treatments, and I think that is where we have a major concern for toxicity.

MR. TRISSEL: Also, the toxicity concerns can be of two kinds. There are toxicities from inappropriate use, poisonings, ingestions, industrial exposures and those things are all very severe. You have to look at the toxicity with the actual indicated use here, and this is not an innocuous comment when used as it is supposed to be used. It has some significant toxicities associated with it. That is a different issue than massive overdoses.

DR. JUHL: Do you have any knowledge of why this was removed from the NF10?

DR. ALLEN: No, I would defer to, Joe. Do you have any idea?

PARTICIPANT: Probably just the extent of use.

DR. ALLEN: The low extent of use, yes.

DR. JUHL: For the record, Mr. Valentino from USP said that the drug was removed from the NF probably from low

use.

Dr. McBurney?

DR. MC BURNEY: Could I ask Bob why it was removed or withdrawn by the FDA from the market? There had been several proprietary preparations of this in the past, and I think a mention was made of that in your presentation.

CAPT. TONELLI: I believe the OTC review is what actually -- it was an OTC product that was on the market, and they took it off the market because it was deemed it should only be used at least under an IND at that particular time.

DR. MC BURNEY: So, it was an OTC product?

CAPT. TONELLI: At that particular time.

DR. MC BURNEY: Thank you.

DR. JUHL: Are there other pieces of information you desire before we make a decision?

MR. TRISSEL: Could I ask for a clarification on the quote in our briefing book here? It says, "It has been recommended that," quoting now, "owing to the high toxicity of cantharadine it is recommended that preparations containing it should not be used medicinally." Who made that quote? It is not attributed.

DR. OSTERBERG: Bob Osterberg, CDER. Unfortunately there was no name mentioned with that quote. It was contained in an article, but I put it in because it was one

of several including one that said, and I will quote this from Dr. Narens in Current Therapy 1976, who said that cantharadine is a potent vesicant and should only be applied by a physician. It is not to be dispensed to the patient, and that is the only reference I have for that statement, but the other one, as I said, had no author attributed to it, and I am going to look into it further to see if I can come up with an author.

DR. MC BURNEY: I know Dr. Art Narens. He is the former Chairman at the University of Indiana, and a well-respected dermatologist, and I certainly concur. I in no way mean to minimize the strength of this drug as I have tried to indicate in my presentation, and I feel very strongly it should be administered by a physician if it is approved.

DR. JUHL: I think for purposes of the discussion it should, also, be noted as I think it was earlier that this compound was submitted by the American Academy of Dermatology but contained no information other than a one-sentence description, and perhaps that organization could be communicated with after the meeting and ask that they provide additional information to the docket.

MS. AXELRAD: I believe they have already indicated that they will be submitting additional information to support the nomination.

DR. RODRIGUEZ: Could I raise a question here?

Since the population that seems to be needing it the most are the immunocompromised or patients with HIV one of the questions is whether through the AIDS research trials or whatever or an office such as that we can get some information on how useful that it is, quote, unquote, to them or would they support the use within that venue which would then essentially be like an IND type evaluation and that might be another thing that since it is for those patients that I hear the plea that there is nothing more that can be done.

DR. JUHL: Okay, let us make a recommendation here. My sense is that the Committee is hesitant to remove this from the category that it is in but would, also, note that the information we have may not be complete.

MR. TRISSEL: May I ask a point of clarification? If the Committee elects to vote to leave this in the category it is in, and then an additional nominator or an existing nominator brings forth additional information, can the Committee reconsider its recommendation?

DR. JUHL: I think the Committee can ask to do anything it wants. Whether we get to it or not is another - I think that is a reasonable route to take, but the additional information will go to the agency in response to the Federal Register request and the agency evaluates that as due course in deciding for themselves whether or not to

continue to leave this in and may choose, and if it is controversial you can bet they will bring it back to us. If it is easy, they will do it themselves.

DR. ALLEN: I was just going to mention that if something is not included on the list at this point in time and is not still in the pending status, then as I understand it it would not be able to be used during that interim period. This may be one since if we are expecting additional information that we may want to put in the same category as aminopyridine, get the additional information and make the decision in February.

DR. JUHL: My assumption is that the enforcement flexibility would apply to these, too. Would Jane clarify that?

MS. AXELRAD: Yes, I think as we indicated yesterday that we are going to be putting out something that indicates what our enforcement posture is going to be and for things for which we believe that we need to get additional information and do further evaluation for something that we think is controversial and that we will be getting information during the comment period on the rule, we will address that, and I don't think that we have any intention of taking these things away from people before we have thoroughly evaluated the information.

DR. JUHL: Other points of clarification that need

to be addressed?

Let me restate the premise and see who agrees and disagrees. At this point the Committee, and this is a yes/no and not a command from me, the Committee would recommend that the drug stay in the category that it has been placed in but would, also, note that the information available to us may be incomplete, and we would like the nominators to provide additional information on this particular agent.

MR. CATIZONE: Dr. Juhl, as a clarification if it is included in this group that means then that it won't be included on the BDS list; is that correct?

If we vote to keep it in Group IV, the recommendation of the FDA is not to include it on the BDS list?

DR. JUHL: That is true but pending receipt of comment.

MS. SELLERS: So, is this a two-part question?

DR. JUHL: Yes, and the second part is how would you like to parse it?

MR. TRISSEL: There is a third alternative and that is the one that we have done with the aminopyridine which is to recognize that we don't have adequate specialist information from the specialty community that uses this and to hold that in abeyance until we find that out.

MR. LIEBMAN: If we accept the third option which means put it into category with the other two drugs, we haven't lost anything. It is easy enough to get additional information and then either add it in or put it back onto the kill list or the exclude list.

CAPT. TONELLI: We may get additional information on its use, but I don't think it is going to change its toxicity at all.

DR. JUHL: No, but on the other hand, handling toxic drugs, that is what pharmacists and physicians do, as well, and if there is a valid need, that needs to be considered as well.

CAPT. TONELLI: The other thing I would just point out is that the IND process is still there, and this is going into general compounding if it goes on the list, general compounding.

DR. JUHL: Let me try to restate the options, and let me do it the same way we did the previous drug.

One is to recommend its inclusion as a category IV which would mean not available for pharmacy compounding. Two, we can decide that it should be available for pharmacy compounding, and three, we can go our procrastination route of evaluating the additional information when it is made available to us by the nominators.

Is everybody happy with those choices?

Let me do No. 1 then. Dr. McBurney?

DR. MC BURNEY: I just don't mean to beat a dying horse here, but I really am seeing now as we discuss this issue almost a teasing out of there being some drugs that we recognize are definitely toxic, and I don't think anyone sitting at this table would deny that with this particular drug in question, and which I am not comfortable with putting it out there for bulk compounding, but I am feeling a reluctance to ban it completely, and those are my choices as I have understood it, and they continue to put forth that we can put forth individual INDs, and it just doesn't happen out there. It just doesn't happen, particularly in non-academic settings, and I am just wishing that there was another place to put these, and I guess maybe there is not.

DR. JUHL: Presently there doesn't exist; it is either on the list or it is off the list. There is the possibility that we talked about yesterday, but we could recommend most anything. Whether or not we can do it is another issue, but we could recommend that a drug be included on the list with restrictions.

DR. MC BURNEY: Can we do that?

DR. JUHL: We can recommend it if we think that is appropriate, and we should.

DR. MC BURNEY: I know this isn't a parliamentary procedure, but I would like to put that suggestion on the

table, particularly for a drug such as this one and some of the other ones with very rigid restrictions on it. I would be comfortable with it being available through compounding if that is an option.

MS. AXELRAD: I think that you can recommend it, and we will certainly take the recommendation into account and explore our legal options and what we can and cannot do.

DR. MC BURNEY: For instance, Larry just made a very good point, a suggestion, and that was that this could only be used and given to a physician and be applied by a physician.

DR. JUHL: That was the restriction I was alluding to.

DR. MC BURNEY: You were getting ready to make that, and I could then be more comfortable because the toxicity studies I don't think I want to ignore or can ignore.

DR. JUHL: Do we then have a fourth option, and I guess let me ask the question what is the Committee willing to consider today? As Captain Tonelli pointed out the toxicity information that we receive down the road isn't going to be any different, and I think we do have evidence of use in a relatively broad community.

So, do we want to move on it today or do you want to wait for more information? Give me a clue as to how to

proceed or when to proceed, and then we will make the choices based on that.

MR. CATIZONE: Dr. Juhl, I think you have presented four options, and I would prefer voting on those options to see which way the Committee wanted to go.

DR. JUHL: The options aren't necessarily exclusive of each other, and that is my problem.

MR. TRISSEL: Start with the deferral and see if there is any sense that that is the appropriate one because that is distinct from the others. The others all require action.

DR. JUHL: Let us do that then.

Those that would like to defer consideration until additional information comes in?

(There was a show of hands.)

MS. SELLERS: What additional information are we looking for? Information from the HIV population or --

MR. TRISSEL: The dermatology group that was the nominator but hadn't gotten their information together.

DR. JUHL: Those that would like to defer, please raise your hands?

(There was a show of hands.)

DR. JUHL: Let me lay this out so that we are all clear on what the choices will be. First, we will ask the question whether or not we want to decide today or whether

we want to decide later. If we want to decide today, then we have the option of on the list, off the list and on the list with restrictions.

So, those who would like to decide today please raise your hands?

(There was a show of hands.)

DR. JUHL: Those who would like to defer, please raise your hands?

(There was a show of hands.)

DR. JUHL: We have eight to three to decide today.

We will then go to the possible options for recommendations from the Committee on cantharadine, and the options will be to be included on the bulks list, to be excluded from the bulks list or to be included on the bulks list with the restriction that the drug may only be dispensed through a physician for in-office, to a prescriber for in-office use.

Clear?

Let me see if I can remember the order I did that in.

First, those who would like to recommend that it be included on the list without restrictions, please raise your hands?

I see zero.

Those who would like to recommend that

cantharadine be excluded from the bulk compounding list, please raise your hands?

(There was a show of hands.)

DR. JUHL: One, two, three, four.

Those who would like to recommend that the drug be included on the bulk compounding list with the restriction that it may only be dispensed to a physician for in-office use, please raise your hands?

(There was a show of hands.)

DR. JUHL: We have seven voting for that option. So, that split vote will be our recommendation to the agency to consider.

Okay, I believe now we have concluded with the ones that are on the overhead.

Although there hasn't been sufficient time to review the entire group of drugs that have been submitted by the American Academy of Dermatology, the agency is interested in any comments that we may have, and I think those will probably come from Dr. McBurney on squaric acid dibutyl ester. I presume that you are speaking for yourself and not for the Academy?

DR. MC BURNEY: Exactly. This has been a most educational day and one-half for me thus far, and I can certainly speak to the clinical, but I have appreciated and respect the great concern for compounding this material and

the toxicity, and I really do not have the data on that to present to the Committee today, and so, respectfully I would like to suggest that we just delay this until our February meeting where we could have appropriate documentation on it so that all the questions can be answered.

I can speak to both of these compounds, both the squaric acid and the second compound, the diphenylcyclopropenone(?). Both of these are used in topical immunotherapy agents for two conditions, the first being the alopecia areata where they lose hair and the second being again, for treatment of recalcitrant warts.

I will say that they both in clinical trials have shown efficacy but not to my knowledge in double-blind controlled studies, and I really don't know if that information is out or not.

I can speak to squaric acid that studies have not shown it to be mutagenic on Ames testing and it is not considered a carcinogen. I cannot speak for the other compound though, and I would like us to withhold a full discussion of it until then.

DR. JUHL: Thank you. Are there other comments that people have on these agents?

Then I think our recommendation would follow Dr. McBurney's suggestion.

That concludes the consideration of the bulks list

for today, and I think if I could characterize just briefly both the agency and the Committee and the compounding community have been presented with a very large list of compounds to resolve in a very short period of time, and speaking only for myself I have occasionally been known to not get it right the first time, and would suggest that if we need to revisit things we will, if there is additional information that can be generated, and I think the Committee has shown their willingness to do that between last night and this morning.

However, at some point we do need to get on with life and make decisions and move on. The list needs to be finalized so that people are clear on their options to pursue both from the patient's perspective and from a professional's perspective.

I believe it would be prudent now if we take a 10-minute break. When we come back we will ask that the presentation of the withdrawn for safety list be considered.

(Brief recess.)

DR. JUHL: Okay, we will reconvene. I would ask the Committee to put down their red book and pick up the green book and go on to Volume 3 of our materials. We will now move to the list of drugs that have been withdrawn for reasons of safety or efficacy.

This is a separate list that was included in the

legislation. The Secretary was directed to publish this list, and this list would have drugs that were withdrawn for both reasons of safety and efficacy and would not be available for general pharmacy compounding.

This morning we will start by hearing a presentation on the drugs that have been removed for reasons of safety, and the drugs that have been removed for reasons of efficacy as we discussed earlier will be considered at a later time.

Making the presentation is George Scott, Regulatory Operations Officer in the Office of Compliance.

Captain Scott, if you would?

CAPT. SCOTT: Thank you. Good morning, ladies and gentlemen. My name is George Scott. I work in the Office of Compliance in the Center for Drug Evaluation and Research.

I will be talking with you a few moments about the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness.

In my presentation I will review how the list was put together, what is in the list and some special conditions or qualifications developed for several of the products on the list. These special conditions or qualifications may allow the compounding of certain drug products based upon whether the safety problems with the

withdrawn or removed drug product relate to the ingredient itself or only to a specific formulation of the ingredient or whether there may be an improved drug product on the market containing the same ingredient as the withdrawn or removed drug product.

I will go into more detail about this later in the presentation.

I would like now to move on to the specifics of the list. Section 127 of FDAMA which adds Section 503(a) to the federal Food, Drug and Cosmetic Act describes the conditions under which compounded drugs qualify for exemptions from certain adulteration, misbranding and new drug provisions of the act.

One of the conditions is that the licensed pharmacist or licensed physician does 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.

Before we get into how the list was produced and what is in it there are several basic precepts regarding the development of this list that are important to mention. The primary focus of the list in this first proposed rule is drug products that have been withdrawn or removed from the

market for safety.

FDA intends that future rule-making procedures will focus on drug products that were withdrawn for reasons of effectiveness and on additional drug products that will be proposed for inclusion on the list.

In our review of the drug products to consider for this list we did not re-examine or reconstruct the original process used to withdraw or remove the drug product from the market.

We gathered the data, reviewed it in terms of statutory requirements and developed a list based upon the mandate set forth by Congress.

As far as sources of information that we used, we searched and reviewed various sources of information in an effort to be as thorough as possible. The sources of information that were used to identify drug products withdrawn or removed from the market for reasons of safety were the following: We searched and reviewed Center for Drug Evaluation Research, CDER databases which assisted in identifying NDAs whose approvals were withdrawn for safety.

The CDER databases, also, assisted in providing NDA product-specific information and they assisted in providing standardized and established ingredient names.

We, also, reviewed the drug efficacy study implementation list which is the DESI list of products with

approvals withdrawn for safety. Several of the drugs that are on our list were withdrawn from the market as part of the DESI review.

For those of you not familiar with the DESI review I will explain it briefly. Formal requirements for the premarket approval of drug products began in 1938. At this time drugs were approved by the agency based only on safety.

In 1962, the Food, Drug and Cosmetic Act was amended to require that drugs, also, be shown to be effective before receiving approval.

The change in the law was retroactive. The law charged FDA with ensuring that all products currently on the market in 1962 were both safe and effective. Thus, the agency began re-evaluating all drugs previously approved based on safety between 1938 and 1962, to determine whether they were, also, effective.

During the agency's review if there was a safety concern, the drug was, also, re-evaluated for safety. These findings were published in Federal Register as DESI notices.

In addition, we, also, contacted CDER review divisions. Those are the offices in CDER that review, approve and sometimes recommend withdrawal of new drug applications, NDAs, and we asked them to review their records for any drug products removed from the market for safety reasons, including those drug products that are

currently appearing in a discontinued list of the orange book.

As far as other supporting documentation for ease of the presentation that I am giving to you this morning the drug products on the list have been divided into one of three groups depending upon the type of process used to withdraw or remove them from the market.

The first group consists of drug products whose approvals were withdrawn by final Federal Register notice. Additional information regarding the reasons for the withdrawal is available in the notice of opportunity of hearing, the NOOH or in the DESI notice which is published in the Federal Register.

The second group consists of drug products removed from the market by FDA through final rule making codification in the CFR, Code of Federal Regulations.

The third group of drug products was removed from the market either initiated by FDA action or by the manufacturer. The supporting documentation for this group of drug products may consist of various public announcement sources such as an HHS press release, FDA talk paper, Dear Doctor letter from the firm, a relevant journal article or other publicly available documents.

HHS press releases and FDA talk papers are documents typically prepared by the FDA Press Office which

is located in the Office of Public Affairs in FDA.

In reviewing the above-mentioned source documentations for Groups I through III, ingredients for each product were identified. In the case of multiple ingredient products the Federal Register notice or other source document identified the ingredient which was responsible for the safety concern.

The list consists of 60 ingredient names. This is a list of drug products that FDA is proposing must not be compounded. However, several of the ingredients on this list are proposed with conditions or qualifications that permit the use of drug products in certain strengths, dosage forms or routes of administration.

That is why some of you may recognize some of these ingredients as components of currently marketed approved drug products. I will get into greater detail about this in just a moment.

This is the first slide of Group I. Group I consists of 32 drugs, and it is so large we split it up into two slides of 16 drugs each. They are arranged alphabetically in columns. These are drugs whose approval was withdrawn by final Federal Register notice and you will, also, notice that those where we have recommended that special conditions may apply are denoted with an asterisk.

This is the second half of Group I. Group II is

the group that FDA directed the removal through final rule making in the CFR, and it consists of 12 drug products, also, denoted with an asterisk when a special condition applies.

Group III is those products removed from the market by the FDA or the manufacturer and other source documentation was available for those. There are 16 in this group, and some of these are denoted with an asterisk, also.

After the source documentation was reviewed a statement was prepared identifying the reason or reasons for the withdrawal or removal from the market of each drug product.

I would like, now to discuss briefly the development of the list and some of those special conditions or qualifications that we have proposed for some of the drug products.

The final list of drug products withdrawn or removed from the market for safety reasons was then prepared bringing together all the information that was gathered for each drug product.

Please keep in mind that this is a list of drug products that FDA is proposing must not be compounded because they present a serious risk to human health, either indirectly because a patient is being dispensed an ineffective drug product when an effective drug product may

be available or directly due to the toxicity of the drug product.

In fact, many of the drug products listed in the proposed rule have been associated with human fatalities. In many instances a drug product was withdrawn or removed from the market based upon safety problems associated with an ingredient in the drug product.

For example, the drug product withdrawn or removed for safety reasons may have been marketed as an oral tablet. However, the toxicity, safety problems or dangers appear to relate to all product formulations using that ingredient.

For example, the use of azaribine, formerly marketed as Triazure oral tablets was associated with very serious thromboembolic events. Since this was a severe systemic side effect, and we were aware of no other products on the market containing azaribine it was felt that the azaribine should not be used to compound any drug products.

Therefore, azaribine appeared in the proposed rule on the list as azaribine, all drug products containing azaribine. However, in several instances the drug product was withdrawn or removed from the market based on problems relating to only one dosage form or route of administration or strength of the product.

In such cases the listing for that drug product reflects that fact. For example, parenteral neomycin

sulfate was found to present toxicity problems when used to irrigate wounds and was found not to be acceptable for the treatment of urinary tract infections due to availability of newer, safer antibiotics.

Therefore we have proposed that neomycin appear on the proposed list as neomycin sulfate all parenteral drug products containing neomycin sulfate. So, that means that we are proposing that no compounding be done for parenteral dosage forms containing neomycin sulfate.

In a few cases there may still be an approved drug on the market that contains the same active ingredient as a withdrawn or removed drug product but in a different dosage formulation or route of administration.

In these instances compounding of the particular formulation, dosage form or route of administration is permitted, and the listing includes the appropriate qualification. For example, sulfathiazole, formerly marketed as Tresamide tablets and other brands of tablets and products was associated with renal complications, rash, fever, blood dyscrasia and liver damage.

However, since there are approved products containing sulfathiazole for vaginal use still on the market, sulfathiazole is proposed to appear on the list as sulfathiazole, all drug products containing sulfathiazole except those formulated for vaginal use.

Withdrawn and removed drug products are identified according to the established name of the active ingredient as it appears in our CDER database listed as a particular salt or ester of the active moiety.

For example, dexfenfluramine hydrochloride, all products containing dexfenfluramine hydrochloride. However, although this specific listing may be limited to a particular salt or ester other salts or esters of the active moiety will not qualify for compounding exemptions in Section 503 of the act unless among other requirements the particular salt or ester is the subject of a current United States Pharmacopeia or NF monograph, is a component of an FDA-approved drug or appears on the list of bulk drug substances that may be used for compounding.

The summary of available information for each drug was published in the proposed rule on October 8, 1998, in 63 FR 54082. Please note this notice will have a 45-day comment period.

Interested persons may on or before November 23, 1998, submit written comments regarding this proposal to Dockets Management Branch, Room 1061 which is located in this building. However, today and in the future we are seeking Advisory Committee comments on this listing.

The supporting documentation for each drug product may be found in Docket 98 N-0655 which is identified in the

heading of the proposed rule of the list. The supporting documentation is arranged in alphabetical order according to the established name of the active ingredient of the drug products.

At this time we invite the members of the Pharmacy Compounding Advisory Committee to review and comment on this list of drug products proposed by the FDA. Specifically we are seeking comment on whether additional drug products should be added to the list and whether products now on the list should remain on the list.

In addition, we are seeking comments on the economic impact of prohibiting compounding of the drugs on this proposed list.

Your comments and suggestions will be very helpful to us in issuing the most complete and accurate information to assist in protecting and promoting the health of the American public.

Thank you very much.

DR. JUHL: Thank you, Captain Scott. Let me propose a stepwise fashion to proceed. I think first I would like to hear the Committee's comments on the process that was followed, and if you have questions of Captain Scott or the agency on how they arrived at the conclusions that they arrived at.

Secondly, I would like then to proceed to the

agents, and I will ask the Committee members to give me any of the products that they want to consider. We will make ourselves a list and then go through them one by one if there are any.

Does that seem reasonable to the group as a way to proceed? Okay, and I will open the floor for discussion of the process by which the drugs withdrawn for safety reasons list was put together.

DR. ALLEN: I think they did a remarkable job considering that this hasn't been done in quite some time, if ever.

DR. JUHL: Yes, you are allowed to say good things, as well as to criticize. That is perfectly acceptable although highly unusual.

MR. TRISSEL: Obviously some of the items on here are in common use in other forms today. When you put this on a list, let us pick one like chlorhexidine which had a specific product withdrawn, do I assume that only that specific product cannot be compounded and any and all other products with that would be subject to a nominator and all that sort of thing? It is one specific prohibition.

CAPT. SCOTT: That is correct. My understanding is that that product was withdrawn as an tincture based upon how it was being administered, and apparently when it was being used as a preoperative preparation for patients it was

pooling below the patient and causing burns and fires in the operating room, as far as I understand it.

So, we are proposing based upon the Federal Register that was published explaining that situation the safety concerns related to it that it not be compounded for that particular type of use.

MR. TRISSEL: For the use or for that product? It was 1/2 percent chlorhexidine in some tincture formulation, presumably a lot of alcohol. What about an alternative formulation that eliminated the fire problem and whatever other problems there were.

PARTICIPANT: It is available commercially.

MR. TRISSEL: Yes, it is. It is very available commercially.

CAPT. SCOTT: Yes, we are just proposing that it not be compounded as a tincture formulated for the use as a patient preoperative skin preparation, and that would be, I believe in the 1/2 percent tincture.

DR. JUHL: Do we have, I cannot find in my notes a compilation of the special conditions for all the products that were listed. I don't think that appeared in the Federal Register, did it?

CAPT. SCOTT: Yes, it appears under the proposed codified section, I believe, at the end of the list. It gives the conditions proposed for each drug.

DR. ALLEN: Would it be correct to assume then that chlorhexidine could be compounded as a tincture for other uses, other than preop?

CAPT. SCOTT: I would say so based upon what we have put in the Federal Register.

MR. TRISSEL: And potassium chloride obviously widely used, it is one specific dosage form that is on the list, right?

CAPT. SCOTT: That is correct.

MR. LIEBMAN: And tetracycline, how can't you use it?

DR. ALLEN: I think you cannot use it in a concentration greater than 25 milligrams per ml for pediatric use; 225, yes, we have a monograph for that. That is being developed, but you cannot go over 25 for pediatric use.

DR. JUHL: If we could all refer to the Federal Register notice that was faxed to us titled List of Drug Products that Have Been Withdrawn or Removed from the Market for Reasons of Safety or Efficacy, and towards the end, and your page numbers may be different than mine there is a list of the drugs and their special conditions and the wording for that.

On mine it is the last two pages of that document. Other comments on the development of the list per

se, and then we will go to specific agents if there are additional questions?

Seeing none, I feel the need, also, to commend you for putting this list together. I am sure people got very dusty down in the basement looking at the old records, and it is a very useful thing for the agency to have for a number of reasons, but for this purpose as well, and there seems to be less area for wiggle and concern over this list than the bulks list for which we are, also, grateful.

Let me poll the group now and I don't want to discuss, I just want the names of products that you would like further information about, and then we will kind of take them in turn.

So, I will just write a list. Are there products, starting with David that you want us to discuss further or you want further information?

MR. LIEBMAN: Off the top of my head, no. I think they have done an excellent job.

DR. JUHL: Bill?

DR. RODRIGUEZ: Likewise.

DR. ALLEN: I believe the only thing possibly would be the adenosine phosphate. You might refer to that, but that is about all.

DR. JUHL: Okay, we will put that on the list.

Judy?

MS. RIFFEE: Nothing.

DR. JUHL: Garnet?

DR. PECK: Nothing else.

DR. JUHL: Larry?

MR. TRISSEL: I am still thumbing real fast.

DR. JUHL: Okay. Elizabeth?

DR. MC BURNEY: I would just like to clarify because I was going to put tetracycline on it, and I would like to ask George, we can have our pharmacist compound oral suspension of tetracycline; it just cannot be for pediatric patients, is that correct, in the dosage that is listed here?

CAPT. SCOTT: Right in the dosage of no more than 25 milligrams per milliliter.

DR. MC BURNEY: All right, then I have none to add to the list. Thank you.

DR. JUHL: Larry?

MR. TRISSEL: I, also, had a tag on adenosine phosphate because I could not find any specific notation of the safety issue in here regarding it.

DR. JUHL: Okay, we will put that on the list then.

Anna?

MS. MC CLAIN: Nothing to add.

DR. JUHL: Bill?

MR. RUSHO: Nothing to add.

DR. JUHL: Sarah?

MS. SELLERS: Nothing.

DR. JUHL: Joan? Carmen?

Adenosine phosphate, the floor is open for discussion on that topic. Larry has mentioned he would like to know about the specific safety issue and what was the other question, Loyd, was that yours?

DR. ALLEN: I believe it has some alternative uses now.

DR. JUHL: Okay, and the listing for this compound, adenosine phosphate as recorded in the Federal Register restricts all drug products containing adenosine phosphate.

CAPT. SCOTT: The information that we had indicated that the action was based on a lack of substantial evidence that adenosine alone or in combination with other ingredients generally recognized as safe and effective for any indication and I believe they were using it as a vasodilator and for anti-inflammatory properties that it may have been believed to have.

There was some work done within the division. We requested the reviewing division to respond to the safety of this drug, and it is very close to the adenosine which is approved except it is the salt, the adenosine phosphate, and

the adenosine by itself can cause cardiac dysrhythmias, sometimes fatal bronchospasms. It was just that this drug from my understanding it was injected and being injected intramuscularly I believe, and it has a very, very short half life, and it was not I think due to the lack of efficacy they could not find it was really getting into the body, into the system to really provide any type of relief for what they were trying to treat, and so I think by virtue of that it was one of those cases where because of the lack of effectiveness that they could find that there was a safety problem indirectly.

DR. JUHL: I understand this is a drug that was never approved via NDA.

CAPT. SCOTT: No.

DR. JUHL: It was a drug that was marketed as a non-approved?

CAPT. SCOTT: That is correct.

DR. JUHL: It was not grandfathered. It was simply not taken through the regulatory process at all?

CAPT. SCOTT: As far as I know there was never an approved NDA for adenosine phosphate. That is correct.

MR. TRISSEL: Did I understand you to say that adenosine itself was marketed as approved?

CAPT. SCOTT: Adenosine is, yes.

MR. TRISSEL: So, just the phosphate formulation -

CAPT. SCOTT: Adenosine salt has never been approved; that is correct.

DR. JUHL: I am not familiar. Adenosine itself is used how?

CAPT. SCOTT: Adenocard(?) which is used for supraventricular tachycardia, I believe.

DR. JUHL: That is via the parenteral route as well then?

CAPT. SCOTT: Yes, direct IV injection, and because it has such a short half life it has to be given, well, it is recommended in the labeling to be given IV because it works directly and with a very short period of time.

MS. SELLERS: Used mostly in the emergency setting, and it is a dangerous drug itself because of the AV no-bar(?) but my only question would be if it is used as an injectable, if you miss the muscle and get it into a vein systemically it could be --

CAPT. SCOTT: I think that was the concern that was raised from the medical officer that it does have severe side effects if not used properly, plus I think the only experience that we had was that it was being injected IM which because it only lasts in the body 10 to 15 seconds it is obviously not going to really work in the IM route, and

so it is basically like giving a placebo for some of the indications I believe that they were using were quite serious, and it was not having the effect. So, by having a lack of effectiveness it was indirectly a safety problem.

DR. JUHL: Loyd, you said that you had knowledge of it being used in something else?

DR. ALLEN: I don't have any direct knowledge. I would like to defer to some of the other pharmacists or physicians or someone in the audience that might have, but I have just heard that it has been used for some alternative -

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DR. JUHL: Parenterally?

DR. ALLEN: I believe parenterally.

DR. JUHL: Is anyone else able to add to the confusion here?

Would anyone like to speak for the drug being excluded from this list?

MR. TRISSEL: I haven't heard anything that would make me believe that it is any different than any other drug on this list. It doesn't seem to be the use in compounding that was identified by the sponsor, and it fits all the other criteria of this list. So, I wouldn't see any reason to make a special exception of it.

DR. JUHL: Seeing no other comments I would presume that would indicate the will of the Committee on

this particular product and are those who may have been leafing through during the discussion finding notes in your binder that would want you to consider, have us consider any other products on this list?

Seeing none of those, are there other things that the agency would like us to address?

MS. AXELRAD: I don't think we have any other issues right now.

DR. JUHL: Let me look at my watch. I think we will conclude early today which I hope doesn't disappoint anyone.

(Laughter.)

DR. JUHL: Before we do that though I am cognizant of the fact that we have an open public hearing that is scheduled for 1 o'clock. We, at this point have not had anyone who has registered with us expressing an interest to speak at the open public hearing, but I do want to give the opportunity for anyone who has come here hoping to speak to the Committee during the open public session to please identify themselves now, and we will do that at this time.

Seeing none, I am a bit uncomfortable with not having an open public session, but I, also, don't want needlessly to commit the Committee for another couple of hours.

Are we able to do that?

David?

MR. LIEBMAN: Do I remember correctly that there was a product on the market with glycerol, iodinated? Was it taken off? Was it put back on?

CAPT. ALLEN: It has been taken off, and then we have had some difficulty with that product and the USP trying to have the companies identify exactly what it is.

MR. LIEBMAN: What was the commercial product?

CAPT. ALLEN: Organid(?).

MR. LIEBMAN: It is not on the market; in fact it is off the market?

CAPT. ALLEN: It is off the market.

MR. LIEBMAN: Wasn't there a reformulation of it?

CAPT. ALLEN: Yes.

MR. LIEBMAN: With this ingredient?

CAPT. ALLEN: Yes.

MR. LIEBMAN: Thank you.

MS. AXELRAD: Dr. Juhl, before we adjourn or get finished talking about the list, we thought it might be useful if we could ask IACP or anyone else at the table who could comment on whether any of the products that we have on the list are presently being compounded because we need to do an economic analysis, and our preliminary thinking is that we didn't think that this list would have any significant economic impact, but we really would like to see

if there is any information that we could get into the record on whether the removal or the placement of any of these drugs on the list would have any kind of economic impact because some people are actually using them for something.

DR. JUHL: We would be happy to do that. Does anyone on the Committee have anything to give in response to that question?

MR. CATIZONE: Just support for that. I think if these products are not being used and if that is not reported then we are following the criteria we established earlier which was to weigh the toxicity against patient use and patient need. I think that would be an important factor to discuss or consider.

DR. JUHL: With this list I think we have not so much judgment allowed to us on the criteria. It is drugs withdrawn for safety and efficacy, and I think it is a different standard we go by.

MR. TRISSEL: But I think the question that was asked was was there any use of it that we are aware of that would have an economic impact. I, personally, have no knowledge of any of these being compounded.

DR. RODRIGUEZ: What is the function of this list of pharmacies for the glycerol products? Are these compounders or what?

CAPT. SCOTT: I believe that was the FDA directing that those manufacturers stop producing, manufacturing iodinated glycerol products.

MR. LIEBMAN: What these products cannot be used for is the specific identified notes in the Federal Register.

CAPT. SCOTT: Right.

MR. LIEBMAN: They can be used other ways but not this way?

CAPT. SCOTT: Correct.

MR. LIEBMAN: Thank you..

MR. TRISSEL: For those products that have that differentiation. Some are all because the molecule is a problem. Clearly some of these are used widely in medicine and are central, potassium chloride.

CAPT. SCOTT: Some of the conditions are inclusive, and some are exclusive. You just have to read it carefully because some of them say one thing or the other.

DR. JUHL: Gina, could I have you give us any information from the Academy on the economic impact of the drugs that are on the withdrawn for reasons of safety list?

DR. FORD: Sure, just in our initial evaluation of the substances we are satisfied with the list as well, as long as those inclusions or exclusions are applied.

We haven't had time to review everything as far as

what possibly might be used and would at some point want to submit that in the comment period.

DR. JUHL: Thank you.

Other loose ends you have for us?

MS. LA FOLLETTE: I have a topic I would like to discuss further. Now, that we have spent a day and one-half going over items or drugs to be included on the list I still don't feel comfortable with the fact that we have drugs that are not part of the normal process. I mean. I understand what the objective is here to identify those but I don't feel comfortable with the quality of just the C of A coming from suppliers that may or may not be established or have been inspected to discuss some of this recently, and I think there is concern among us about that.

I was wondering if we have identified these compounds, is there a way to identify suppliers that would be official suppliers or is that out of the jurisdiction?

DR. JUHL: Do you have specific suggestions within the legislative framework that was provided?

MS. LA FOLLETTE: We are identifying a need to supply drugs to patients that have a medical need, to make these things available. So, I appreciate that, but I am, also, aware that if you don't have a set standard, a chemical company can produce a C of A and as I had already alluded to before different synthetic processes used to

produce that chemical that could be residual solvents and things that aren't addressed on the C of A and you are actually exposing patients to other risks, and we are not controlling that at all.

DR. JUHL: I understand.

MS. LA FOLLETTE: They can be purchasing these compounds for all different sources, and I think it behooves us to talk about that. I mean it is one thing to make these things available that didn't go through the rigors of conventional what pharmaceutical companies go through, and I understand and I understand the purpose, but I don't think we are addressing how we are going to control that and the exposure you are putting patients through, and if the people here are proponents for or the people who are sponsors for these drugs or compounds, can we have like recommended suppliers, and then if another supplier wants to be on the list they could?

DR. ALLEN: I can maybe address that. USP is already starting to look at these products that are going ahead, depending upon the final outcome to establish monographs, and so those standards will be established hopefully fairly quickly on these, and then it is my understanding, also, that any supplier must be registered with the Food and Drug Administration to provide these items.

I think it would probably be inappropriate to actually name a company. I am not sure that we can do that, but as long as the standards are established by the USP and the provider, the manufacturer of the raw drug materials is registered with the FDA then I think that meets the requirements for most drug products.

MS. LA FOLLETTE: But Captain Tonelli said yesterday that there could be a supplier of an active ingredient that could be shipped out, and it isn't inspected. Those things can happen.

As a pharmaceutical company you have to register your drug substance suppliers. I mean you have to provide much more information than we are accepting that isn't. I mean you have to provide all your impurity profiles and how you produce it. If you don't the supplier has to provide a DMF, a drug master file. We are not looking at that. I understand that, but I just don't feel -- it is comforting to know that the USP is looking at it to monograph them. That is comforting, but we are approving things that right now I don't feel like -- we are sort of in a quasi area.

MR. LIEBMAN: In line with that is it possible to get a list of those chemical supply houses or suppliers that are registered -- Jane, you are shaking your head no -- that are listed with you all?

MS. OGRAM: We are looking into the possibility of

making a list of registered manufacturers available and that is what the statute says, that the manufacturer of the substance needs to be registered, not just the supplier.

DR. WOODCOCK: However, that won't be an endorsement by the agency. It won't necessarily mean that manufacturer has been inspected and found to be compliant with good manufacturing practices. There will simply be a list of people who have registered.

DR. JUHL: I think there is a limited amount that we can do. The regulatory route is a rather blunt instrument in this regard, and I think the USP setting standards is certainly useful, and I guess I would ask the Academy in terms of communication with your members do you make recommendations on source of supply and criteria for supply and the kinds of information that, what are the professional standards? I guess I am asking if there are any in this area.

DR. FORD: We don't endorse any particular supplier over the other. If someone perhaps is having difficulty locating we might help them in that search as to who might have it but as far as endorse a supplier or manufacturer, no, we do not.

DR. JUHL: The kinds of information that you had from a pharmacy compounder and knew in the business and somebody took me aside and said, "You ought to be ordering

things from people who can provide you with this list of information," is there some kind of a guidance that your organization either does or could provide?

DR. FORD: I think that we would simply defer to the legislation and say, "This is what is required that you have when you purchase this chemical."

DR. JUHL: That is what I am trying to get at. Is there something that goes above and beyond and addresses these other quality issues that have been raised that aren't part of the legislation?

DR. FORD: As far as a policy statement right now in the Academy no, there is not, but we would certainly address that.

DR. ALLEN: The general chapter does address that on source of supplies.

MR. LIEBMAN: Would it be reasonable to ask the Academy that if we could get a list of people who are registered with the FDA, would the Academy be willing to at least share it with their membership which is not an endorsement, but at least they have shared the information? So, at least you have got 1000, 2000, 3000, whatever members who at least have the list, and it becomes incumbent upon them then to, as with the generic drug house; you know, you need to look at them. You need to look at the percentage of recalls they have, and you need to see what you are dealing

with and then make the decision are you comfortable in buying from them, as an informational share only.

DR. FORD: As an informational sharing, yes, I think that we could provide that.

MS. AXELRAD: If we do develop such a list we will be making it available probably on the Internet. So, people will have access to it, and one of the difficulties in developing it is that once we develop it we would then have to maintain it and keep it updated which is almost a bigger chore than creating it in the first place and costs a lot of money, but anyway assuming that we were able to do that we would do that, and it would be up on the Internet, and we would try to keep the list reasonably current.

DR. JUHL: I think in developing that you may want to communicate with the profession and see exactly how useful that list might be. Sitting here it sounds like it might, but when you get down to it, it may not.

DR. PECK: There are certain chemical suppliers, research chemicals in particular who are now establishing a catalog of USP NF drug substances. I think they must have seen something coming, and they now have these noted and appropriately labeled as USP NF supplements. These are traditional research chemical groups.

DR. JUHL: While we are on questions that we have wondered about, let me ask this question, how many

compounding pharmacists have a copy of the USP, Loyd, and have access to the chapter on compounding?

MR. LIEBMAN: Everybody.

DR. JUHL: Everybody has the USP or everybody has the chapter?

MR. LIEBMAN: Everybody.

DR. JUHL: They don't know what year it is necessarily.

MR. LIEBMAN: State law usually requires that you have the most recent USP.

DR. JUHL: Not in all states any longer. They allow you to pick from a list of reference books. The USP may be one of them. My concern is that the several hundred dollars invested is a wonderful investment. You should all have a USP in the car, at home and at work. The chapter on compounding is now part of the legal landscape and it may be a good idea if you would, and I am speaking to the Academy, consult with USP and see if you cannot work a deal for if not a free-standing copy of the compounding chapter --

DR. ALLEN: That is available.

DR. JUHL: Is it?

DR. ALLEN: Yes, the two chapters on compounding of sterile products for home drug use and the general chapter on good compounding practices both the USP has put into a booklet that is available.

The USP has, also, if you look at the USP, the large 10 pound volume is primarily not only of use to practitioners but primarily it is oriented towards the industry and the USP is looking at the feasibility of having a second volume available for pharmacy practitioners that would pull out the appropriate materials.

Most pharmacists don't need access to the assay methods and all of this, but there is a lot of information they do need access to. So, they are looking at the feasibility of having a USP that would be of great usefulness to pharmacy practitioners. So, that is in the works right now.

DR. JUHL: I appreciate hearing that.

Other loose ends?

Hearing no other loose ends, let me thank the Committee for their diligence. It has been a pleasure to get to know and work with all of you, and I look forward to struggling with you again on future items. I mean that in the best of sense. We struggle together, not with each other.

I would, also, like to make note of the agency's effort to prepare this information for us. We always ask for more information, and we are never satisfied with what we get, but I don't want to ignore the fact that it took a lot of work to put it together, and you gave us what is

available as well. So, I appreciate that, and I would, also, like to thank those who have participated, to the Academy for your support and we will convene again sometimes in February perhaps, if we can settle on a date.

We are adjourned.

MR. LIEBMAN: I would like to thank the Chair before we leave. I think that Dr. Juhl did a tremendous job. I think we weren't sure what we were going to do and how we were going to do it, and I thought he handled it well.

DR. JUHL: Thank you. I will not follow my usual rules by allowing equal time for opposing views.

(Laughter.)

DR. JUHL: We are adjourned.

(Thereupon, at 11:50 a.m., the meeting was adjourned.)