**FOOD AND DRUG ADMINISTRATION**

**Center for Drug Evaluation and Research**

# Pharmacy Compounding Advisory Committee

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P R O C E E D I N G S [8:30 a.m.]

**Agenda Item: Call to Order/General Introductory Remarks**

DR. JUHL: Good morning. Welcome to the second meeting of the Pharmacy Compounding Advisory Committee. We have a full couple of days worth of work to do. I think we will -- we have started on time and we will make every effort to end on time as well.

Our first order of business, if we could go around the table and have everyone introduce themselves and their position. We have members of the committee. We have FDA staff as well. And to remind you that you need to be relatively close to the microphone and speak to it and our transcriptionist will wave her hands if we are not doing a good job of speaking into the microphone.

So, let me start -- Dave, if you would begin for us, please.

DR. LIEBMAN: Good morning. I am David Liebman. I am a compounding community pharmacist.

MS. RIFFEE: Good morning. I am Judy Riffee. I am on faculty at the College of Nursing, University of Florida.

MS. LA FOLLETTE: I am Joan LaFollette. I work with Bristol-Myers Squibb in Princeton, New Jersey.

DR. SELLERS: Sarah Sellers, now from North

Carolina, currently studying for the boards.

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

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

DR. JUHL: Rose-Ellen is a new member of the committee. Welcome.

MR. RUSHO: William Rusho, University of Utah.

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

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

DR. MC BURNEY: Elizabeth McBurney, dermatologist in private practice and on the clinical faculty at LSU Medical School in New Orleans.

DR. PECK: Garnet Peck, professor of industrial pharmacy, Purdue University.

DR. RODRIGUEZ: Bill Rodriguez, Children's Hospital and George Washington University.

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

MS. AXELRAD: Jane Axelrad. I am the associate director for Policy in the Center For Drug Evaluation and Research and one of the co-chairs of the Pharmacy Compounding Steering Committee that was created by FDA to

address the FDA Modernization Act implementation.

I am going to introduce Lana, who isn't here yet, but my co-chair, Lana Ogram, who is the director of the Division of Prescription Drug, Compliance and Surveillance in the Office of Compliance in the Center for Drugs, will be joining us, I hope, shortly.

DR. DeLAP: Bob DeLap, FDA Office of Drug Evaluation 5. Our office includes the dermatology area.

DR. OKUN: I am Marty Okun. I am a medical reviewer, Division of Dermatologic and Dental Drug Products.

DR. JUHL: Thank you.

Our next order of business is the reading of the conflict of interest waiver by our executive secretary, Igor Cerny, who is taking care of details somewhere.

Jane Peterson, who will actually be our executive secretary for our next meeting.

**Agenda Item: Conflict of Interest**

MS. PETERSON: The following announcement addresses the issue of conflict of interest with regard to this meeting and it is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee

participants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and research, which have been reported by the participants present pose no potential for an appearance of conflict of interest at this meeting, with the following exceptions.

Since the issues to be addressed by the committee at this meeting will not have an impact on any particular compound, but rather may have widespread implications with respect to this industry, in accordance with 18 USC 208, the participants have been granted a waiver, which permits them to participate in today's discussion. Copies of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In the event that the discussions involve any other compounds or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose

compounds they may wish to comment upon.

DR. JUHL: Thank you.

Well, at our first meeting in October to just review a little bit, we began the process of developing the bulk list of drugs that will be available for pharmacists to compound with. There were, I guess, two things that we did there, not only review some individual drugs, but to begin to feel comfortable with the criteria of doing the same.

There were a number of drugs that we had on the list to consider last October that we were uncomfortable with making decisions on for reasons of their complexity or the lack of information. That leads us to our task today. We did the easy ones then. These are more difficult.

So, during our sessions for the next two days we will consider a variety of compounds for a variety of different maladies with a variety of different safety issues.

To kind of start us off, I would like to have Jane Axelrad make her introductory remarks.

**Agenda Item: Introductory Remarks**

MS. AXELRAD: First, I would also like to welcome everybody here. It was very difficult I understand for several of you to get here today and we

really appreciate, you know, the effort that you made to get here. I would also like to introduce before I get into my remarks the other FDA staff who are in the room, some of whom we may be calling upon to answer questions. So, I would ask them to go around and introduce themselves.

DR. JUHL: Except we will need a microphone for them to do that.

DR. BROWN: My name is Paul Brown. I am a pharmacologist from the Division of Dermatologic and Dental Drug Products in CDER.

DR. VIDRA: I am Jim Vidra, the review chemist for DNCB. I am also in the Derm and Dental Division.

DR. HATHAWAY: I am Dr. Steve Hathaway, a chemist with Derm and Dental.

DR. DeCAMP: Dr. Wilson DeCamp(?), chemistry team leader, Derm and Dental.

DR. COSMOS: Mary Jean Cosmos(?), supervisory project manager, Division of Dermatologic and Dental Drug Products.

DR. JACOBS: Abby Jacobs, pharm tox team leader, Derm and Dental Drug Products.

DR. O'CONNELL: Kathryn O'Connell, medical officer, Dermatologic and Dental Drug Products. I am filling in for Dr. Wilkin(?), who is the division

director and he is out of town.

DR. TENNELLI: Good morning. Bob Tennelli, CDER, Office of Compliance.

DR. CHAMBERS: Wiley Chambers, deputy director, Division of Anti-Inflammatory Analgesic and Ophthalmic Drug Products.

DR. RICHMOND: Fred Richmond, team leader, Adverse Drug Reaction and Compounding Team within the Office of the Compliance.

DR. MITCHELL: Wayne Mitchell, Regulatory Policy Staff here in CDER.

DR. BROWN: Ron Brown, pharmacist in the Office of Compliance.

DR. SCOTT: George Scott, pharmacist, Office of Compliance.

DR. HEINER: Betty Heiner(?), Federal/State Relations, Office of Regulatory Affairs.

DR. BASAT: Martha Gottem(?) Basat. I am chemist in the Dental Derm Division.

DR. JONES: Mike Jones, pharmacist, Office of the Center Director.

DR. LANDISH: John Landish, Office of Planning and Evaluation.

MS. AXELRAD: Thank you. I really wanted them to introduce themselves. Many of them are members of the

Pharmacy Compounding Steering Committee and others are from the division that you will be hearing from this morning, who were involved in the reviews. Over the course of the next two days, you will be hearing from many other Center staff, who have been involved in reviewing these individual compounds because we have had the review divisions involved this time to a fairly extensive amount and they have done a lot of work, but they will introduce themselves as they come.

But I really wanted to recognize the people who have been contributing to our implementation effort. I also want to thank the committee sort of more broadly for being willing to serve on this advisory committee. I know that it is really a lot of work for you all to prepare for the meetings and to come, but it is really very helpful for us to have a panel of distinguished experts to consult with as we work on implementing the law.

I am looking forward to productive discussions over the next two days.

It has been six months -- sorry -- seven months since we last met and we have been very busy during this interim period, working to implement Section 503(a) of the Food, Drug and Cosmetic Act, which was added by Section 127 of the FDA Modernization Act.

I would like to spend a few minutes bringing you up to date on our efforts over the past months and then we will begin our presentations on the drug substances that were nominated for the bulks list.

On January 7th of this year, we published the proposed rules in the Federal Register that would include a list of bulks drug substances that may be used in pharmacy compounding under the exemptions in Section 503(a) of the Act, even though they are neither the subject of a USP or NS monograph nor a component of an FDA-approved drug.

In that Federal Register notice and proposed rule, we proposed 20 drug substances for inclusion on the list, based upon the recommendations we received from the committee at the October meeting. We indicated in the notice that ten additional substances were still under review by the Agency and we solicited comments on these substances. These are the substances that will be discussed with the committee today and tomorrow.

The proposed rule also included and requested comments on the criteria that the agency is proposing to use to determine whether a nominated substance should appear on the bulk drugs list. We discussed these criteria with the committee in October and the criteria proposed for comment reflected the deliberations of the

committee.

The comment period for the proposed rule ended on March 23rd, 1999. The proposal generated over 190 comments from individuals or organizations. The vast majority of these comments, about 86 percent, were submitted by multiple sclerosis patients, friends of multiple sclerosis patients, physicians and other individuals in support of the drug substance 4-AP.

These comments were letter or e-mail testimonials about the benefits of 4-AP. Unfortunately, the comments did not include as much scientific or technical data about the use, safety or efficacy of 4-AP as we had hoped. But you will be hearing quite a bit about that this afternoon from our Review Division and a number of outside speakers.

The remaining comments on the proposed rule addressed a wider variety of issues. For example, several expressed support for one or more of the bulk drugs under consideration, especially the dermatological drug products, like chemtheradine(?), DNCB and squaric acid. Several expressed opposition to drugs under consideration, such as mild silver protein or poracetan(?) and several raised larger policy concerns about the Agency's overall efforts in this area.

We are in the process of evaluating these

comments and preparing the final rule. The discussions today and tomorrow of the nominations of the substances to be included on the bulk drugs list that may be used in compounding will be considered when we develop the final rule. And, of course, this rule will never be actually final because it may continue to evolve as substances are added or removed from the list.

When the committee last met, we discussed 60 drugs that were being considered for inclusion on a list of drugs that have been withdrawn from the market, because they have been found to be unsafe or ineffective. When we discussed that list, we were concentrating on drugs that have been withdrawn from the market for safety reasons.

As you know, Section 503(a) provides the drug products that appear on a list of drug products published by FDA in the Federal Register, that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective may not be compounded under the exemptions in Section 503(a).

A proposed rule containing this list was published for comment before our last meeting on October 8th, 1998, and a final rule containing a list was published on March 8th, 1999. The committee has been

provided copies of the final rule in background packages. And I believe there are copies available elsewhere.

The only comments concerning specific substances that we received on that rule were comments recommending against inclusion of adrenal cortex and neomycin sulfate on the list of drugs that could not be used and comments in favor of including dexphenfluoramine(?) and phenfluoramine(?) on the list.

In the case of adrenal cortex, the Agency decided that the substance should be included on the list that could not be compounded and we included it in the final rule because of our concerns about significant risks associated with the substance, both in terms of bovine spongioform(?) encephalopathy, BSE, and the associated risks of getting Creutz-feldt-Jakob disease and in terms of the risk of under treatment of serious conditions and our rationale is laid out in the final rule.

The Agency decided to postpone final action on parenteral drug products containing neomycin, neomycin sulfate, because of the pendancy of various administrative actions concerning that drug. The preamble to the final rule indicated that neomycin sulfate may be added to the list at a later date.

Therefore,, the final rule contains 59

substances that may not be used for pharmacy compounding under the exemptions in Section 503(a) of the Food, Drug and Cosmetic Act. The list may be updated periodically if other drugs are removed from the market for safety reasons. We hope, of course, they aren't, but we will take that into account.

With regard to drugs that have been withdrawn for efficacy reasons, you may recall that at our last meeting, we mentioned three drugs that were nominated for inclusion on the list of bulks drug substances that may be used in pharmacy compounding under the exemptions in Section 503(a), but that had been withdrawn from the market for efficacy reasons.

Those three were betahistine, hydrochloride, cyclandelate and pentylenetetrazol. We deferred consideration of these because the Agency had not yet determined how we would handle drugs that had been removed from the market for efficacy reasons.

We have now concluded that we do not intend to devote Agency resources to compiling a list of drugs that have been withdrawn from the market only for efficacy reasons. Instead, we have decided that we are going to only focus on drugs that are nominated for inclusion on the list of bulk drug substances that could be used in compounding.

The reason is that if a drug substance is a subject of an approved drug application for at least one indication, it can be used in compounding. If the drug substance is the subject of a USP or NS monograph, it can also be used in compounding. And if it doesn't meet either of these criteria, it can't be used unless it appears on the bulks list.

Therefore, we don't plan to develop a separate list of drugs that may not be compounded because they have been withdrawn only for efficacy reasons. Instead, if something is nominated for inclusion on the bulks list, the fact that it may have been withdrawn for efficacy at some previous date will be considered, along with other information and the other criteria that we have developed to make a decision as to whether it ought to appear on the bulks list.

That is the approach that we are planning to take for those three compounds. In November of last year, we published a guidance concerning our enforcement policy during implementation of Section 503(a). The committee has been provided with copies of that guidance. At our last meeting in October, a number of questions were raised about what was going to happen in terms of the transition period, while we were developing the many documents that we had to develop to implement the

statute.

This guidance recognizes that implementation of the new law requires us to develop many different rules and other documents that were not going to be in place when the statute took effect last November 21st. The guidance that FDA will not action to enforce certain provisions of the compounding statute until the related regulation or other document is completed.

For example, it says that FDA will not take action against a pharmacist who compounds a difficult to compound drug product until the agency promulgates the regulations required by the statute identifying what are demonstrably difficult drug products.

In this guidance, the Agency also establishes a specific transition scheme for bulk drug substances that are under consideration for inclusion on the bulks list. In the guidance, FDA gives compounders a one-year period to nominate new substances for the bulks list and that period was from November 21st, 1998, when the statute took effect, until November 21st of 1999.

We indicate that we will exercise enforcement discretion and will not normally take regulatory action against a drug substance that has been nominated during this period while that substance is being evaluated and as long as the substance does not appear to present a

significant safety risk.

For those substances that are nominated after November 21st, 1999, FDA will evaluate the substances, but they may not be used in compounding unless and until they are placed on a list if the compounding is going to qualify for the exemptions.

On January 21st, 1999, we announced the availability for comments of a draft standard memorandum of understanding to be entered into by the states that implements the provisions of Section 503(a), that addresses the interstate distribution of compounded drug products.

The comment period on this draft has been extended until June 1st, 1999, and we have received many comments on it, I think, over a thousand comments on this. So, we will be very busy analyzing the comments and doing what we need to do to get that out.

We will finalize the memorandum of understanding in consultation with the National Association of Boards of Pharmacy after evaluating the comments.

We are also working hard on the general pharmacy compounding implementing regulations and on the third list that we were directed to develop, the list of difficult to compound drug products that may not be used

in compounding if it is to qualify for the exemptions under Section 503(a). We expect to present the first portion of the list of difficult to compound drug products to you at our next meeting sometime this fall.

Finally, you should know that the day before Section 503(a) took effect, seven compounding pharmacies sued FDA in Federal District Court in Nevada, challenging the constitutionality of certain parts of Section 503(a) on First Amendment grounds. The suit challenged the constitutionality of the provision that states that to qualify for the exemptions under Section 503(a), a pharmacist may not advertise the compounding of particular drugs or classes of drugs, but may advertise the compounding service.

The suit also challenged the provision that for compounding to qualify for the exemptions, it had to be based on an unsolicited prescription. The court issued a temporary restraining order preventing FDA from enforcing these provisions, while the lawsuit is pending and the parties briefing the case said that the court can decide whether to impose a permanent injunction.

Before I turn this over to our first speakers on specific drugs, I would like to briefly mention that three drugs have been nominated for the list that we do not intend to present to you in formal presentations at

this meeting.

The first is pentylenetetrazol, one of the bulk drug substances that was deferred after our last meeting because it had been withdrawn for efficacy reasons. Our Review Division searched the literature for articles regarding the use of this compound in humans and was unable to find any information on it. The drug is apparently used in animal testing to induce seizures in animals so that anticonvulsant medications can be tested.

I checked with the International Academy of Compounding Pharmacists, who nominated this substance for inclusion on the list and they were unable to identify any literature on this subject. Therefore, we decided that we really had no basis for including on the list and really nothing to present to the committee on it. So, we won't be presenting anything further on that.

The second compound is chloramine-T. The Agency received a single nomination for this substance. The nominator reported the use of the substance by only one pharmacist at a rate of up to twice a year in a dental office for a root canal procedure. Our review of available data indicated that chloramine-T is an antiseptic agent and possibly an antibacterial. It has some uses in veterinary practices, which is not relevant here because the compounding exemptions only apply to

human drugs and not veterinary medicines.

Very little literature could be found on chloramine-T. In reviewing the dental literature, chloramine-T is mentioned in a 1984 edition of Accepted Dental Therapeutics under "Root Canals and Cavity Preparations. However, the current edition of the American Dental Association Guide to Dental Therapeutics, 1998, does not mention chloramine-T. Similarly, chloramine-T is not mentioned in a current endodontic text.

Based on our review of the literature, it appears that this is an outdated therapy for human use in dentistry and that its use is extremely limited. Lacking data on its historical use and with a lack of any evidence of widespread use, we don't believe that the substance should be included on the list of bulk drug substances and we don't intend to present any additional information about this to the committee.

The third compound that we are going to talk about is Peruvian balsam. We received a single nomination for Peruvian balsam. The nominator reported use of this ingredient by only one pharmacist in dermal and dental preparations amounting up to 16 ounces per year. Our review of available data indicated that Peruvian balsam is a gum resin used as a protectant in

most cases. It is also an active ingredient in a product licensed as a biologic, used to test for allergic reactions to the balsam.

Because we could not document widespread use of this substance and because of its high potential for producing allergic reactions, CDER believes that this substance should not be consider for inclusion on the list for compounding and do not intend to present a formal presentation on this substance at the meeting.

Of course, if anyone on the committee or any member of the public can supply us with additional evidence that any of these three compounds are widely used in pharmacy compounding or additional information supporting their placement on the list, we will be happy to consider it.

That concludes my prepared remarks. I can take any questions that you might have on what I have said before I turn to the first substances on the agenda.

DR. JUHL: Questions for clarification?

Hearing none, we will move to our first topic of conversation, dinitrochlorobenzene. There will be a series of FDA presentations by Dr. Vidra, Dr. Brown and Dr. Okun.

Please.

**Agenda Item: Dinitrochlorobenzene**

DR. VIDRA: Good morning.

As previously mentioned, my name is Dr. Jim Vidra, review chemist from the Division of Dermatologic and Dental Drug Products.

This chemical has several names; however, the easiest name to pronounce might be DNCB. The generic chemical name is 1-chloro-2,4-dinitrobenzene or 2,4-dinitro-1-chlorobenzene. This beige colored chemical has its physical and spectroscopic properties well established since its initial synthesis in 1875.

For you compounding pharmacists, its solubility properties include insoluble in water, slightly soluble in ethanol and soluble in benzene and ether and other organic solvents.

DNCB is considered stable at normal temperature and pressure conditions. During a fire, irritating and toxic fumes may be generated, such as hydrogen chloride, chlorine gas, nitric oxides, carbon monoxide and carbon dioxide.

DNCB is incompatible with strong oxidizing agents and alkaline bases.

Several published synthetic routes exist for DNCB. There are multiple impurities identified in bulk DNCB obtained from various sources. DNCB's impurity and yield may vary depending upon its route of synthesis.

This table from Wilkerson, et al., summarizes the impurities found in DNCB, sold by each of these six commercial sources. To briefly explain this table and using the Aldrich 98 percent pure DNCB as an example, the Aldrich sample contains 1-monochloro, mononitrobenzene isomer, 2-dichloro mononitrobenzene isomers, plus a dinitromonochlorobenzene isomer, other than the DNCB itself.

As a contrast, the ICN 98 percent pure DNCB contains only one isomer. The analytical method used was a gas chromatography mass spec analytical procedure. This method could not differentiate between the ortho, meta or para isomers, simply due to the method of the mass spec itself.

To summarize the chemistry in Assessment 1, DNCB is well characterized physically and spectroscopically. It is stable under normal use conditions. The acceptability of any DNCB lot for compounding should be based upon knowledge of these two specific impurities, the 1-chloro-4-nitrobenzene, as well as the 1-chloro-2-nitrobenzene. These impurities could present carcinogenicity concerns.

The DNCB used in compounding could vary significantly from the DNCB used in literature studies due to its varying concentrations and types of impurities

present. Altered clinical properties and toxicities could result from these variations.

Thank you.

DR. BROWN: My name is Paul Brown and I am a pharmacologist from the Division of Dermatologic and Dental Drug Products. And I will summarize safety information available from the literature on dinitrochlorobenzene.

Dinitrochlorobenzene and some of its possible impurities are mutagenic in the Ames assay and this mutagenicity appears to be due to direct interaction of dinitrochlorobenzene with DNA, since metabolic activation is not required. Dinitrochlorobenzene also induces -- is also genotoxic in human skin fibroblasts in vitro at low doses, similar to those that would be used in vivo.

Dinitrochlorobenzene did not induce tumors in rats or mice in an 18 month feeding study, although the dose of dinitrochlorobenzene in this study had to be decreased after four months for mice and two months for rats because of toxicity.

The carcinogenicity of dinitrochlorobenzene by the clinically relevant topical route has not been assessed and this is an important point since the outcome of carcinogenicity by the topical route may be very different than the outcome from the oral route.

Two possible precursors of dinitrochlorobenzene did cause significant elevations of tumors in mice in the same study in which dinitrochlorobenzene was evaluated.

Dinitrochlorobenzene is absorbed through human skin. For example, in one study, approximately 53 percent of radiolabeled dinitrochlorobenzene applied topically to humans was recovered in the urine over five days. In animal studies, dinitrochlorobenzene was shown to be irritating to the skin and cause the depletion of the important cellular protectant, glutathione in the skin.

In one study, it was shown that dinitrochlorobenzene activated the long terminal repeat promoter of the human immunodeficiency virus in transgenic mice, carrying this promoter.

This is a table that summarizes safety information about dinitrochlorobenzene, again, bacterial mutagenicity was positive. Mammalian genotoxicity was positive, as measured in human skin fibroblasts. Dinitrochlorobenzene was negative for carcinogenicity for the oral route, while some possible impurities were positive. Topical carcinogenicity hasn't been evaluated, as I mentioned, and information on other aspects of dinitrochlorobenzene toxicity, such as chronic toxicity, reproductive toxicity, photocarcinogenicity have not been

reported.

And the Assessment 2 that is in the written review also summarizes this information. Dinitrochlorobenzene is genotoxic and at least two of its potential impurities are carcinogenic in mice. Since other studies have not been conducted, teratogenicity or other toxicities cannot be excluded.

DR. OKUN: My name is Marty Okun. I am a medical reviewer in the Division of Dermatologic and Dental Drug Products. I am here to summarize what is known about the human safety and efficacy data pertaining to DNCB.

This slide has a cartoon of a poison ivy plant because the cutaneous reaction induced by DNCB is analogous to that induced my contact with poison ivy. Typical local side effects associated with DNCB application at the application site include burning, itching, blistering, crusting, urticaria, eczema.

The following systemic side effects have been reported: fever and malaise, painful cervical lymphadenopathy, eczema at distant sites, not where DNCB was directly applied. Case reports also describe edema of eyelid and face requiring hospitalization and dyspnea characterized as of near tracheostomy severity.

There is limited long-term safety data

available from use of DNCB. Our review indicates that a published follow-up of longer than six months duration is available for only 135 patients, most of whom were adults. No published reports on pregnancy outcomes are available. No cancer cases have been attributed to DNCB, but the duration and completeness of follow-up is not reported.

Pharmacists, physicians and other health care workers are potentially at risk for DNCB sensitization. Furthermore, although unreported DNCB treatment may sensitize to related compounds, such as nitrobenzenes, which are commonly used in agricultural industries. So, there is the potential for sensitizing workers in those industries.

If applied at home, concerns include the possibility of serious adverse effects from application without proper monitoring and possibly sensitizing of family members.

Our assessment of the human safety is that there are human safety concerns and since there is significant transcutaneous absorption in humans, systemic safety cannot be assured.

Before discussing the effectiveness of DNCB, briefly describing its target diseases as appropriate, we have here a clinical slide of a wart. Warts are scaly

papules caused by infection with the human papillomaviruses. They cause cosmetic disfigurement, pain on walking if they are on the feet. They can interfere with manual tasks and are potentially infectious.

Safe, effective treatments are available, such as condylox, podofilin, salicylic acid, cryotherapy, lasers. All practicing dermatologists recognize that despite the availability of these treatments, warts are frequently recalcitrant to any or all of those modalities.

This is a clinical slide of two patients with alopecia areata, which is an immune-mediated non-scarring hair loss disease, which can affect patches of the scalp or the entire scalp, in which case it is called alopecia totalis, or the entire body, in which case it is alopecia universalis.

This disease causes cosmetic disfigurement and can also cause functional impairment, especially if eyebrows or eyelashes are lost.

For treatment of alopecia areata, there are treatments available that are reasonably safe and reasonably effective; corticosteroids administered a variety of routes and, again, a common experience is that despite the availability of these treatments, alopecia

areata is frequently recalcitrant to treatment.

Our assessment of the approved alternatives for treatment is that available approved products have been demonstrated to be safe and effective for the treatment of warts and alopecia areata and that some cases are recalcitrant to treatment, despite the availability of these alternatives.

This slide shows the dates of the first reported use and number of reports in the English language literature for a variety of indications that have been treated with DNCB, including warts, alopecia areata, melanoma, immuno-diagnosis and HIV. It is noteworthy, if you look at the year of last report, that the most recent studies of DNCB use for treating warts and alopecia are approximately ten years old.

Most dermatology texts and recent review articles caution against DNCB use, principally because of the positive results on an Ames assay, or warn about the hazards of mutagenesis or generalized sensitization reactions. Other immunogens that are evaluated, such as diphenylcyclopropenone, and squaric acid dibutyl ester rate more favorably.

Some pioneers in DNCB use have switched to other topical immunogens, principally because of these safety concerns, but, nonetheless, a few clinicians

continue to use DNCB for treating alopecia areata predominantly for patients with more than 50 percent scalp involvement.

Our assessment of historical use is that evidence of widespread use of DNCB is not apparent. Reports of DNCB use have declined in recent years, even in reviews of immunomodulatory treatments.

Typical method of use for alopecia areata and warts involves two phases. The first is a sensitization phase, a relatively concentrated solution; 2 percent in acetone is applied to normal forearm skin. The next phase, the elicitation phase, lower concentrations, ranging from .001 percent to 2 percent, depending upon the report is applied weekly or biweekly to lesional skin.

The concentration is titrated with the goal of inducing a brisk allergic response in lesional skin.

This slide shows a photograph of a hypersensitivity reaction, triggered in non-involved following a topical application of DNCB. You can appreciate the redness, the edema of the skin and microle vesiculation. This is the goal, to induce this kind of brisk allergic reaction.

In considering the efficacy of a proposed treatment for alopecia areata and warts, it is important

to keep in mind the natural history of these diseases and, most importantly, that they can resolve spontaneously, depending upon the Lugia(?) Report, warts have been reported to resolve, about two-thirds of them resolve by two years of follow-up without any treatment and alopecia areata, the spontaneous resolution rates range from as low as 38 percent by five years to as high as 94 percent by one year.

Nobody really understands the prognostic features that dictate the probability or the rate of spontaneous resolution of either of these two diseases.

The reviewed studies of DNCB for treatment of these disorders are largely uncontrolled or self or internally controlled or non-compliant patients are the control group. The problem with interpreting these studies is that without a control group of patients, it is very unclear how much improvement can be accredited to treatment effect, rather than to the spontaneous resolution that is possible with these disorders.

Nonetheless, assessing efficacy in alopecia areata, the percentage of patients with cosmetically acceptable response that persists off treatment ranges from 0 percent to 36 percent with a weighted average of approximately 9 percent and the duration of follow-up in these patients ranges from 3 to 18 months. It is unclear

whether DNCB is more effective in those patients who are recalcitrant to the other treatments that we already mentioned.

The efficacy in warts, percentage of patients with complete resolution of treated warts ranges from 45 percent to a hundred percent, with a weighted average of 70 percent. Most studies were open label, with all warts treated. In the one internally controlled study where some of the warts on the patients were treated and some were observed, the resolution of the treated warts was not statistically superior to untreated warts.

Again, it is unclear if DNCB is more effective in treatment of warts in patients who are recalcitrant to other treatments. We requested a consultative review by our colleagues in the Oncology Division to evaluate the effectiveness of DNCB in the treatment of recurrent melanoma and they concluded that the available studies are relatively small and non-randomized. They have short follow-up periods. They utilize several application techniques, such as topical or intralesional administration and that they are descriptive or anecdotal in nature.

Of note, no current standard oncology textbook recommends DNCB for treating melanoma. Further, our oncology colleagues reviewed the use of DNCB as an

immunodiagnostic agent with the principal purpose of testing immune competence in cancer patients. They concluded that no well conducted randomized trials validating its use have been performed and, frankly, that the prognostic significance of reactivity is unknown.

A consultative review was performed by our colleagues in the Antivirals Division on the effectiveness of DNCB and HIV treatment. Their conclusions were that there was no consistent benefit on CD4, CD8, natural killer cell count or progression to AIDS.

There was a statistically significant reduction in HIV viral load seen in one study of eight patients, but they felt that this was a fairly confusing result because these patients did not have any change in their CD4 count that is typically observed in response to decreased viral load.

They were concerned about potential interactions between DNCB and other approved anti-retroviral therapies and the potential interactions are unknown and potentially of concern.

Our assessment of the evidence of effectiveness is that there is limited evidence that DNCB is effective for the studied indications. With specific regard to alopecia areata, DNCB may provide an increase in hair of

variable cosmetic quality, but such hair may be lost despite continued therapy or upon discontinuation of therapy.

And our conclusions are that we have concerns about placement of DNCB on the list of bulk drug substances for compounding. And these concerns include concerns related to safety, limited evidence of efficacy and in clinical use, DNCB has largely been supplanted by other topical sensitizers, because of the concerns about mutagenesis.

Thank you.

**Agenda Item: Questions From the Committee**

DR. JUHL: Do we have questions from the committee, either for Dr. Vidra, Dr. Brown or Dr. Okun?

MR. TRISSEL: One of the statements that was made was that there was a significant remission rate that occurs naturally. Does that include HIV patients, whose immune systems may or may not recover?

DR. OKUN: You are referring specifically to the remission rate of warts?

MR. TRISSEL: Yes. I am sorry.

DR. OKUN: There is no information in the published literature concerning the spontaneous remission rate in HIV patients with warts. The studies I cited to you were actually done before AIDS appeared in the

community.

There is actually no published literature concerning the -- although it has been reported for treatment of warts in HIV patients, there is no published literature on the efficacy of DNCB in HIV patients, who have warts.R We looked rather thoroughly for that.

MR. TRISSEL: Elizabeth, do you have any input on that?

DR. MC BURNEY: I agree with Dr. Okun's comments that there are no published data on that and I would really like to reserve my comments to the other immunogens that we are going to be discussing later. I feel at this point that I would like to be able to have the drug available for those few patients. There are two groups. One, the ones that he pointed out with alopecia areata with diffuse, extensive, greater than 50 percent of their hair loss. I think there has been data to show that using some of these topical agents in those patients, that perhaps we may be able to offer them something when they have exhausted all the other means.

That would be my concern for those particular patients. Then the second group of patients are those with very widespread warts, involving all the tips of their fingers, around all their nails, and these are patients that have severe immunosuppression, whether it

be due to infection with the AIDS virus or due to iatrogenic inducement of loss of ambient system through chemotherapy agents.

These patients are frequently unresponsive to many -- to all the therapies that were listed. But as far as DNCB particularly, I would rather direct my comments to the other two immunogens that we will be discussing.

DR. LIEBMAN: Randy, we have two physicians or groups of physicians in Baltimore who use it. One of them is a pediatric dermatologist at Johns Hopkins and the other one is a community physician dermatologist, who also teaches on the faculty at the University of Maryland.

The general consensus is why do you use this because no one else seems to be using it. And across the board, the answer is we have exhausted all other possibilities. We have gone through everything that we could have gone through and nothing has been successful. This is my last resort.

It would appear that it is successful because again and again they come up with new patients for it, knowing that it has potential downside, but somehow feeling, again, it is the only other -- if they don't have this, then they have nothing left.

I guess, somewhat with what Elizabeth said, at least they want the opportunity to have a fallback position. Their position is if you take it away, then I have got nothing to offer my patients.

MS. AXELRAD: Dr. Juhl, I was wondering if we could take questions on any of the information that was presented and then hear from the American Academy of Dermatology before we get into a sort of generalized discussion. It was sort of our feeling that the committee might want to hear the information on all three substances and ask questions about that and then discuss all three substances together after it has heard all the presentations, if that is okay?

DR. JUHL: I think that is good. Let's differentiate between items of clarification and questions for discussion. So, are there items of clarification?

MR. TRISSEL: One more.

DR. JUHL: Larry.

MR. TRISSEL: I just have one concern about the use of apparently only published literature to establish use in the community because really you are establishing how much interest there is in publishing on this particular material, rather than how much it might be used. Now, on this case, of course, there are hundreds

of papers in the literature. In others, there may be only a few, but rubbing alcohol is widely used, but I doubt if there is a whole lot of published literature in recent years on researching it.

So, I am not sure about the validity of establishing widespread use, using only published research articles.

DR. ALLEN: I have, I guess, a question. When we look at the conclusions -- and this is just kind of for my information as we look through all of these -- there were safety concerns, limited evidence of efficacy, et cetera, if we look at human safety, I guess I was wondering how that conclusion came because there are limited long term safety, but that is going to be common, you know, with a lot of these things; no published reports on pregnancy outcomes.

There is obviously not going to be any pregnancy studies. No cancer cases were attributed to DNCB. Pharmacists, physicians, other health care workers would be at risk for DNCB sensitization, but that is no different than working with doxyrubin(?), 5FU, et cetera, et cetera. I guess another couple of things, DNCB treatment may sensitize to related compounds. That could be true to other things.

If applied at home, concerns include, you know,

family members. I guess my question is at what level are we looking at areas of safety and even efficacy, because there are studies where it has been efficacious, for the conclusions to be drawn that there are safety concerns and limited evidence of effectiveness? Where would be the line for not saying there is limited evidence of effectiveness and what would be the line for -- or what level of safety concern would be acceptable? Does that make sense?

In other words, where did the conclusions come from based upon what we have seen and read in our background materials?

DR. JUHL: Anyone want to comment on how the A led to B?

DR. DeLAP: If I could just comment briefly, and I think this is partly the broader discussion that Jane was just alluding to after we have looked at all the three compounds, I would just like to separate out the issue of whether a compound should be available period versus how it should be available because I think those are two different questions.

I think as we are looking at safety and effectiveness kinds of concerns and when a product becomes a kind of product that you would like to have more widely available with perhaps less safeguards and

under the prescription or investigational mechanisms. Those are the kinds of things we have to weight. What do we know about the safety? What do we know about the effectiveness? Is it still really more in the area of an investigational drug? Is there enough safety concern that that alone would make it something that should be out there?

So, these are all kind of judgment issues that we would like to really hear the committee's input on, but, again, I wouldn't want this to be a discussion of whether it is something that should be available or not available, so much as if you think it is worth having, then I think it becomes more of a discussion of how it should be available, as opposed to, you know, a "yes" or "no." Is it appropriate for compounding or is it more appropriate to still be under INDs with all of the things we can do to try and make that as user friendly as possible or should it be -- you know, should it be prescription?

DR. JUHL: Sarah.

DR. SELLERS: I would just like to clarify that this -- for both indications, these are being used chronically, so patients will be seeing long term exposure to this agent potentially.

DR. JUHL: Is that your experience, Dr.

McBurney?

DR. MC BURNEY: No, it is not at all. What we usually do is we try to induce, as Dr. Okum showed, 2 percent solution on the skin and induce an allergic reaction or an immune reaction. Then we paint it on the individual lesions, say the warts or the area of loss of hair of alopecia, depending from once a week to as frequently as twice a week or even three times a week in some patients, generally on a once a week basis, until we get a response or until you decide that there is no response.

But this is not done over a year's period. This is done over weeks or months, rather than in terms of years. Then it is usually discontinued. Now, if there is a recurrence, there may be a decision to reuse that therapy later, but it is not like, for instance, you would take a heart medication for the rest of your life or high blood pressure medication. It would be used in a time-limited fashion.

DR. JUHL: Okay. I don't think we will abandon the issues by going on to the next drug. So, let's do that.

Dr. Rodriguez.

DR. RODRIGUEZ: We heard about the drug being, quote, unquote, absorbed from the skin and 53 percent in

the urine. How long does it persist in the body? I am just trying to think in terms of the -- we know some drugs that may stay for weeks after that or something like that or is this an acute type sort of exposure and then the drug sort of disappears.

DR. VIDRA: The data that I talked about with the 53 percent, that was in the urine after five days. So, they looked -- in that particular study, they did look over, I think, a 24 hour period. I think the majority of the drug was eliminated early on, like in the first 24 hours, but, again, that is 53 percent in urine. In that particular study, they didn't look at the PCs(?) or anywhere else. They don't know where the other 47 percent is.

Since it does interact covalently, some of it might be bound in tissue and it might not get out in the urine.

DR. MC BURNEY: I would like to just point out one thing that was mentioned in the presentation, that we have safe effective treatments for alopecia areata and they list underneath that corticosteroids intralesionally, meaning they are injected under the skin topically, which would be a lotion or a cream, and then systemically.

I must state concern about it being listed as

safe, effective, systemic steroids because we are all familiar with the many side effects and that particularly is a problem with long term use in our pediatric patients of long term use of systemic steroids.

DR. JUHL: Okay. Let's move on to diphenylcyclopropenone. Dr. Hathaway is doing the chemistry and then Dr. Brown and Dr. Okun are back for their presentations.

**Agenda Item: Diphenylcyclopropenone**

DR. HATHAWAY: Good morning. I have been asked to speak about what is known about the chemistry of diphenylcyclopropenone, also known as DPCP. Diphenylcyclopropenone is a low molecular weight, small ring organic compound, whose physical and spectroscopic properties have been described in a number of published reports in the literature.

It is possible to confirm the identity of the bulk material from various sources by comparison of the properties and the spectra. The stability of diphenylcyclopropenone has been evaluated by examining the known chemical reactivity as published in the literature. DPCP is unstable to heat at temperatures near its melting point, around 120 degrees celsius.

Carbon monoxide is emitted leaving behind diphenylacetyline and other unidentified products. DPCP

is also light sensitive and appears to decompose in a manner similar to that of heat. Note that DPCP is affected by light of any type, natural or artificial and including ultraviolet light.

DPCP is unstable in alcohol solutions of base and rapidly decomposes to form a number of products, some of which are unidentified. It appears to be stable in neutral or acidic solutions of alcohol. It is not soluble in water. And DPCP is also chemically reactive, forming addition products with a number of materials.

There are several published synthetic methods for producing DPCP or similar compounds. There is also a second solid form known, the monohydrate, which may come into play regarding identification or amounts. There are also several commercial suppliers. However, it is not known what methods are in use for production of DPCP by these suppliers.

Literature reports are primarily concerned with the methods of synthesis and little or no information has been reported regarding the identification and characterization of any synthetic impurities or degradation products in the bulk chemical.

Lastly, quantitative methods of analysis have not been published in these literature reports. Thus, we are unable to determine how well, if at all, impurities

are measured.

This is our assessment for the chemistry. The physical and spectroscopic properties have been adequately established in the published literature. This material is unstable to heat and light under a variety of conditions. It is also known to be unstable in alcohol solutions at basic pH, thus, limiting a choice of compounding material.

It may also be unstable due to reactions with other materials. Numerous sources and methods of production indicate that the impurity profile may differ with the source and the uncertainties of analysis may be a concern here.

Thank you.

DR. BROWN: Now I will summarize some safety information that is available from the literature on diphenylcyclopropenone. Diphenylcyclopropenone is mutagenic in the Ames assay but only in the presence of light. Alpha, alpha-dibromodibenzylketone, which is a synthetic precursor and, therefore, a potential contaminant of DPCP is mutagenic in the Ames assay both with and without metabolic activation.

The potential for absorption of diphenylcyclopropenone is not clear, although diphenylcyclopropenone was not detected in the serum or

urine of humans treated topically in the only reported study. The techniques used in that study did not exclude the possibility that diphenylcyclopropenone was rapidly absorbed and metabolized.

This is a table then that summarizes safety information from the literature about diphenylcyclopropenone. Again, it was mutagenic in bacteria with light and, unfortunately, other aspects of toxicity have not been reported in the literature.

Then, again, the Assessment No. 2 in the written review also summarizes the information that diphenylcyclopropenone is photogenotoxic. But given the lack of additional studies, it is not known what toxicities diphenylcyclopropenone may have or whether it may be teratogenic.

This slide shows a list of the recent reports describing side effects associated with the use of DPCP and several are listed here. There have been more published reports of side effects associated with DPCP use and for either DNCB or squaric acid, which will be discussed next.

Our assessment of human safety is that there has been limited characterization of human safety. There have been local side effects described, typically a burning, itching, blistering, clustering, urticaria and

eczema, analogous to what is seen with the DNCB. A less commonly vitiligo is induced, which sometimes can be persistent and also something called dyschromia in confetti, which is hyper-pigmented areas with islands of hypo-pigmentation. That also can be quite persistent.

In reviewing the literature, the following systemic side effects have been reported, fever and arthralgias, disseminated bullous erythema multiforme, which is a skin disease characterized by a bruise-like blistering, wing-shaped lesions scattered over the body and generalized vitiligo and generalized eczema, vitiligo and eczema not confined to the sites where the DPCP was applied.

Pharmacists, physicians and other health care workers are at risk for DPCP sensitization. There is a report that three out of five medical and nursing staff members developed severe local dermatitis and irrigation of the eye and nose and generalized pruritus from incidental exposure to DPCP.

Apparently, these staff members experienced symptoms simply by entering a room where DPCP had recently been dispensed or mixed up.

If applied at home, sensitization of family members is possible. There is a case report, which attributed incidental exposure of DPCP as the cause of a

case of eczema and persistent vitiligo in the wife of an alopecia areata patient being treated with DPCP. In that case report, parenthetically, DPCP was applied in the clinic. So, this was exposure from the material that had rubbed off of a patient after he had gone home and vitiligo had been persistent.

Our assessment of the approved alternatives for treatment, if I may follow up on Dr. McBurney's comment, we agree that a long term systemic, corticosteroid treatment is not safe and it is on this list as reasonably safe when referring to comparatively short burst in papers of a month's duration, which has been used in literature to reverse alopecia areata. Used in that manner, you can avoid many of the side effects associated with long term use, but, clearly, a long term use is not safe.

We have already discussed previously that there are safe, effective treatments available for warts and I will just reiterate that despite the availability of these alternatives, there is no question that some cases are recalcitrant to all of these treatments.

Historical use, our assessment, the first reported use of DPCP for treatment of alopecia areata was 1983. There are at least 18 reports in the literature on using DPCP for alopecia areata. Five reports use this

treatment in warts. Evidence of widespread use is not apparent. The point is well-taken that the published literature does not necessarily capture the totality of the clinical experience, but that is the basis of our review. This is a summation of the published reports.

The typical method of use of DPCP is -- it is applied in the provider's office. A relatively concentrated solution is used to sensitize to uninvolved skin and a much more dilute solution is used to sensitize -- after sensitization has occurred, much more dilute solution is applied to trigger reaction in lesional skin.

The largest study characterizing DPCP use in warts, 134 patients were treated for eight weeks and the response rate was 37 percent; all warts resolved, 37 percent of the patients had all their warts go away and 13 percent, at least some of the warts resolved.

This was an open label study.

Assessing the effectiveness of DPCP in alopecia areata, which has recently been reviewed in a review article and their conclusion was that the response rate, which in their assessment included cosmetically acceptable or partial regrowth. The response rate ranged from 9 to 85 percent, with a weighted average response rate of 58 percent.

In the larger study, response rate was 50

percent, but the relapse rate is approximately 50 percent. As with the DNCB, it is unclear if use of DPCP is more effective in patients who are recalcitrant to other treatments.

Most cited review studies were uncontrolled or self or internally controlled. In a randomized, placebo-controlled study, no significant difference in outcomes was observed between patients treated with DPCP and patients treated with placebo.

Our assessment of the evidence of effectiveness is limited evidence that DPCP is effective in the long-term treatment of alopecia areata or warts. Treatment of alopecia areata may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.

In our conclusions is that there may be variations in the impurity profile of bulk DPCP. There is comparatively limited evaluation of the safety of DPCP, specifically with respect to long term toxicity, dermal and systemic, reproductive toxicity, carcinogenicity and photocarcinogenicity, especially given that there is a positive assay in the presence of light and microsomes.

There is variable effectiveness with limited evidence of long-term benefit.

Thank you.

**Agenda Item: Questions from the Committee**

DR. JUHL: Questions of clarification for our speakers?

Bill.

DR. RODRIGUEZ: I have some questions. Maybe I misunderstood it, but there is quite a number of reports of, quote, unquote, side effects in here of recent vintage. That suggests to me that there is, quote, unquote, an objectionable ratio of side effects to use or aquatic use of the medication. So, I was wondering about that part.

The other one that I was wondering about is in some of these studies where it has been used for alopecia areata, have they reported the number of side effects in those groups because at least you get a general idea. I am not sure that -- obviously, this is not my field, but I am just looking at it from the scientific point of view.

The third thing is a study that compares 20 versus 35, the power of that study must have been very, very, very low. You know, from other areas of the literature you have anywhere within 9 percent and 50 percent. So, again, I have questions about random trials

that are that small.

I am not -- I don't use this medication, but I am just raising this concern from a curiosity point of view.

DR. OKUN: Your points are certainly well-taken. It is very hard to assess from a review of the literature what the denominator is. In other words, how many patients are using DCPC and not having any problems. Nobody is going to write up a case report of a patient who doesn't have an adverse event.

All we have a sense of are the numerator, rather than the denominator. Your point also about the randomized trial is also quite valid. In general, I am not sure how much weight you can put on a single trial with relatively small numbers. Again, our responsibility is to look at what is out there.

This is the only randomized placebo controlled trial. Everything else was open label.

DR. LIEBMAN: I am concerned about the fact that you keep talking about long-term use, long-term use. Repeatedly, you have heard Dr. McBurney say it is not used long term and with respect to hair loss, if you discontinued the medication. Is that not true with menoxidil(?) also? And is that not true of rotepropecia(?)? Would you say is that then a downside

of those two drugs also or is that just a reality that says when you are taking hair growth medicine, hair grows sometimes when you stop taking the medicine.

The hair that has grown tends to not continue growing. I mean, it sounds like it is presented as if that is bad. I think that is just part of the drug. It goes with other drugs in the same light. The same kinds of drugs give those same kind of side effects.

DR. OKUN: I think Dr. McBurney has characterized the natural history of alopecia areata very accurately. Individual episodes may not necessarily be very long and individual treatment may only need several months to reverse the loss.

However, my impression is that alopecia areata is a long term disease in which there are periods where disease activity has remitted and periods where that exacerbates. Each individual treatment duration may be several months, but most patients who were in the literature, reviewing their case reports, they may need several treatments over the course of an extended period of time as their disease waxes and wanes in severity.

DR. LIEBMAN: You are right, but you keep saying "it may," as opposed to there is documented evidence that it does cause. My concern is that there is kind of the, I guess, implied threat -- and I know that

is not what you are saying -- that maybe if you use it long term, maybe you will have side effects.

To me, that skews it a little bit and I am not sure that is not what you are trying to do.

MS. AXELRAD: If I could just make a comment and you might respond, but, basically, I think for approved drugs, for drugs that are approved treatments that we have reviewed, they have been put through an extensive battery of tests to show what the consequences are of whatever use it is going to be put to on the label.

There are, you know, reproductive toxicity tests, carcinogenicity tests and all that -- our experts, you know, elaborate on that, but basically these compounds, we don't have any of that kind of evidence on. I think that is the contrast between the approved drugs and the ones that we are considering here.

DR. O'CONNELL: Dr. O'Connell, Department of Dermatology and Dental Drug Products.

That is essentially what I was going to point out. With an approved drug, there is informative labeling for the physician and the patient so that they can make a judgment, based on the evidence for efficacy and the strength of that evidence. And the known risk, true, all risks aren't known at the time drugs are

approved, but at least the risks that are known at the time of approval and then labeling is updated.

But the other point I would like to make, since I am filling in for Dr. Welkin, I am going to steal a statement that he likes to point out to us when we discuss things. The absence of evidence is not evidence of absence and the fact that we don't have this information certainly, I think, weighs at least as heavily as the facts would weigh if we had evidence that they were unsafe. See what I am saying? We don't know is the bottom line.

All we have is what is published, but that doesn't mean that because things aren't out there, that they are not occurring, because it is not published that it is not occurring.

DR. JUHL: I believe we are bouncing back and forth between safety questions and questions of effectiveness that we don't have good information for. I believe if we took Assessment 6 that Dr. Okun presented to us, it says that there is limited evidence of long-term effectiveness. There may be a variable cosmetic quality of the response and the hair may be lost if therapy is stopped. We could put any of the drugs that are used to treat that malady in there and have the same criticism be made of them.

The difference between those drugs that had been labeled as safe and effective, it is more on the safe part and the effective is with quotes around it, I guess, the regulatory meaning of "safe" and "effective."

So, I think we really have a difference in safety and a safety in chemistry and controls and so on that we have with commercial products as the major focus here. We aren't going to have good information. We are not going to have the kind of information you folks are accustomed to looking at, but we are dealing with those patients that didn't fall within the whatever percentage of response. The question we will have to deal with then is is there a way to make other alternatives available for people, but above all, we don't want to do harm and it would be nice to know we had some indication that they worked.

Are there other questions or clarifications? Yes, go ahead.

DR. PECK: I will be probably be going back to this on other compounds. It is a little of a concern to me about multi-commercial sourcing. Then we get into the second thought about poor analytical procedures to evaluate the particular compounds.

The statement about well-characterized physical properties, I am not sure that there are well-

characterized chemical properties. Some are mentioned, but it is not that complete.

A good remark is made about the impurity profile may vary with source. That, in turn, will carry over to the patient response if the material is not, quote, as good as one would like to have a clinical application.

So, my thoughts are about the inability to have a good feel about sourcing.

DR. JUHL: We shall then move to our third drug in this category, squaric acid dibutyl ester. We have the same cast of characters from the Agency, please.

**Agenda Item: Squaric Acid Dibutyl Ester**

DR. HATHAWAY: Again, I am Steve Hathway, Derm and Dental Drug Products. Now I am speaking about squaric acid dibutyl ester.

Squaric acid dibutyl ester is a low molecular weight small ring organic compound, similar to DPCP. And the physical and chemical properties resemble those of carboxylic acid esters. A number of reports published in the chemical literature have established the physical and spectroscopic properties of this compound. It is, therefore, possible to confirm the identity of this material from various sources by comparison of its properties with these known values.

The stability of SADBE has been evaluated by examining the known chemical reactivity as published in the literature. Squaric acid dibutyl ester does not appear to have sensitivity to moderate amounts of heat or to exposure to light, though its structure suggests that there may be a photochemical reactivity.

Squaric acid dibutyl ester has been reported to be unstable in water solutions. This hydrolytic activity varies with the pH and is fastest in basic solution. The hydrolysis also occurs in acidic and neutral pH.

About the synthesis, there are several published methods for synthesis of squaric acid dibutyl ester and related compounds and there are also several commercial suppliers. However, it is not known what methods are in use for the production of this compound.

The literature reports are primarily concerned with the methods of synthesis and there is little or no information reported regarding the identification or characterization of any synthetic impurities or degradation products in the bulk compound.

Finally, quantitative methods of analysis have not been published. They are typically semi-quantitative in the published literature. Thus, we are unable to evaluate how well, if at all, impurities are measured.

Lastly, our assessment of the chemical

properties and behavior, squaric acid dibutyl ester's physical and spectroscopic properties are adequately established in the published literature. The material is stable to heat and light under normal conditions. It is known to be unstable in aqueous solutions at all pH's and also in solutions where there is a trace presence of water and, thus, this would limit their choice of vehicle.

And numerous sources and methods of production indicate that the impurity profile may differ with the source and the uncertainties of analysis may be of concern.

Thank you.

DR. BROWN: I am Paul Brown, still. I will summarize the safety information available from the literature on squaric acid dibutyl ester. Squaric acid dibutyl ester is not mutagenic in the Ames assay and it does not cause transformation of hamster kidney cells in vitro.

There are at least two synthetic precursors of squaric acid that are potential contaminants of squaric acid dibutyl ester, hexachlorobutadiene and tetrachloro-2-cyclobutene-1-one. Hexachlorobutadiene is carcinogenic in rats and tetrachloro-2-cyclobutene-1-one is carcinogenic in mice.

Squaric acid dibutyl ester has been shown to penetrate human and mouse skin in in vitro experiments and experiments in hamsters have shown that the dibutyl ester of squaric acid is a more potent sensitizer than the diethyl ester, demonstrating that the different esters are not toxicologically equivalent.

Then this is a table that summarizes the safety information about squaric acid dibutyl ester. Again, the bacterial mutagenicity is negative and information on other aspects of squaric acid dibutyl ester toxicity has not been reported, although there may be some carcinogenicity of potential impurities.

Then Assessment 2 in the written review also summarizes the information that two potential contaminants are carcinogenic and given the lack of additional studies, other potential toxicities and teratogenicity of squaric acid dibutyl ester are not known.

DR. OKUN: Our assessment of the human safety of squaric acid dibutyl ester is that its characterization is limited. There have been side effects described in the case reports. Some are local, manifesting as blistering, itching, eczema. That is fairly common; less commonly, pigmentary changes occur.

The following systemic side effects have been

reported: fever and arthralgias, severe generalized dermatitis, distant local dermatitis, generalized pruritus without dermatitis. Clearly, these side effects do not necessarily have to be localized just to the site of application.

We have a clinical picture of a typical blistering reaction with squaric acid dibutyl ester. I think in this case, the health care provider has overshot his or her goal of inducing allergic reaction. This is a little too much. It is hard to titrate.

We have already covered this. Approved alternatives for treatment are the same as with the DNCB and DPCP. So, I think we should skip this.

Historical use of squaric acid, the first reported use in 1980 for treatment of alopecia areata and it has been used as an experimental treatment alternative for alopecia areata, 14 reports in the literature and for warts there is one report.

Evidence for current widespread use is not apparent.

The typical method of use, again, is analogous to what was described for DNCB and DPCP, a sensitization and then an elicitization phase.

Review of its use for treatment of alopecia areata response rate, which includes a cosmetically

acceptable or partial regrowth rate, ranges from 29 to 87 percent, with a weighted average of about 59 percent. In the largest study, the response rate was 65 percent, a relapse rate of 50 to 70 percent, even with continuation of treatment.

Again, these studies were predominantly open label, internally controlled.

It is unclear if squaric acid is more effective in patients who are recalcitrant to other treatments.

The same study that was mentioned earlier for the DPCP, another arm compared efficacy of squaric acid against placebo and the numbers are comparatively small, 44 patients on squaric acid, 20 patients on placebo; no significant difference in outcomes.

Our assessment of evidence of effectiveness, limited evidence that squaric acid is effective in the long term treatment of alopecia areata or warts. Treatment may provide increase of hair of variable cosmetic quality during treatment. The hair gained on treatment may be lost even with continuation of therapy.

Our conclusions are that there may be variations in the impurity profile of bulk SADBE. There is limited evaluation of the safety in terms of long-term toxicity, both dermal and systemic, in terms of reproductive toxicity, in terms of carcinogenicity and

the photocarcinogenicity.

There is variable effectiveness with limited evidence of long-term benefit.

Thank you.

**Agenda Item: Questions from the Committee**

DR. JUHL: Additional questions of clarification?

Elizabeth.

DR. MC BURNEY: I don't want to get technical and bogged down in studies, but I would like Dr. Okun to elaborate a little bit because the study you mentioned by Antonelli Tosti in 1986 that compared the difference immunogens, that is, the topical agents versus placebo, I believe that particular study dealt only with very patchy alopecia areata. There was less than 40 percent of the hair loss.

The real use of these agents are in patients that have very widespread alopecia, recalcitrant alopecia areata. I certainly would agree with your conclusion and that is that people with very limited areas of alopecia areata are the patchy areas, say, one to ten areas less than the size of a dollar, a silver dollar, are going to have a normal response of resolution. Whether you treat them or not, they are going to get better.

I certainly concur with your point, but I do

think we need to realize that there is a smaller subgroup out there of patients with very severe widespread non-responsive alopecia areata. I want to make that point and please correct me if I am not portraying that accurately.

DR. OKUN: My recollection is that most of those patients in that study did have comparatively little hair loss. I am trying to recall the details of the entry criteria. I can't remember off the top of my head.

Your point is well-taken. I am not certain that one can be confident that the responsiveness in limited cases is substantially different than responsiveness in widespread cases. But certainly it is a small study. I am not sure how generalizable the results are. That is what is out there.

MR. CATIZONE: Mr. Chair, I have a question of clarification but not to the technical aspects of the products, but more in general of process and the committee's responsibility. So, I don't know if you want those now or at the end of the discussion?

DR. JUHL: Is it something that someone could answer in two sentences or less or will this lead to a discussion? I guess I will let you use your judgment.

DR. OKUN: More than two sentences.

DR. JUHL: Shall we save it for our discussion session?

I would like to move now to the presentation by the American Academy of Dermatology, nominators of these compounds, Dr. William Rosenberg, professor in the Departments of Medicine and Preventive Medicine at the University of Tennessee.

**Agenda Item: American Academy of Dermatology Presentation**

DR. ROSENBERG: Thank you very much. I appreciate the chance to represent the American Academy of Dermatology. I would like to say that I also serve on the Medical Advisory Board of the Alopecia Areata Foundation, which is a patient advocacy group of people concerned with this disease, which can be devastating to many of them. They have asked me also to speak for them in support of the wish that the practicing community will still have the opportunity to use this treatment when possible.

I want to make a few comments, a little bit of historical review and then be available, I hope, to answer questions from the group.

Of course, benefit to risk is at the heart of regulatory decision-making and in terms of the benefit here, I would point out that we are dealing, certainly at

the alopecia areata aspect of it, with some patients, who really carry a very heavy burden of disease. The pictures that were shown of widespread disease are not unusual. People will lose more hair than that.

Many of them are young and terribly upset by what they face with this during the difficult periods of adolescence and childhood. Dr. McBurney, I think, speaks for most of us, who are interested in practice in this area, that systemic steroids are not an acceptable treatment for alopecia areata.

The hair that grows with systemic steroid comes right out after you stop this systemic steroid, which is not the case with this kind of treatment. And the potential side effects and relapsing and remitting disease are well-known and almost the worst thing about the corticosteroids by mouth is that they almost always work while you are taking them. So, there is a great temptation for patients to want to keep taking them, keep taking them while they do themselves further harm.

Most of us who are interested in this disease do not consider that safe and effective. Intralesional corticosteroid is safe and effective, small shots of atriumcynelone(?) asetinide(?) suspension, usually somewhere around 5 milligrams per ml, sometimes 10, will grow hair in a very limited area. This has a limited

applicability to people with small area of alopecia areata. It is not suitable for widespread areas.

So, this is a treatment that in terms of alopecia areata, that we would miss very much if we didn't have it. Just a little historical review about this, I suppose I have more experience with this treatment than anyone else. I was, to my knowledge, the first to have used it and it was a patient 25 years ago or a little bit more, the wife of a surgeon, whose office was around the hall from where I was practicing in the sixties, 30 years ago, who had long time alopecia areata and was taking systemic corticosteroid on her husband's prescription.

We got to be talking about it and I told him that intralesional steroids had been introduced since she had been started on that other treatment and that these were much safer. She was a grown woman. She taught high school French. So, we began a relationship with this patient where I would see her two or three times a year and inject five or six new spots every time.

One day in the office after five or six years of this, she said to me, Bill, why is do you think that I have to keep coming in and getting these new spots treated? Why do I keep getting it? And I said to her, Betty, I said, probably the more interesting question is

is why most people who get alopecia areata recover spontaneously and have it again maybe once or twice or frequently never again, but don't have the trouble that you have.

And she said why do you think that is. I said I don't know. I said, the trouble, of course, is these lymphocytes that appear around the hair and then the hair goes away. We don't know what the lymphocytes are attracted to there. I said maybe what it is, most people the lymphocytes are able to get the trouble away and then the hair can regrow and there is no more reaction.

And she said is there any way to get more lymphocytes there? I said, well, actually there is. There is an allergist who works in the same office, has a product called DNCB that he puts on people's arms. They are supposed to become sensitive to it and it will bring lymphocytes in most people.

She said, you want to try it? I said sure. So, we put some -- sensitized her to DNCB and put some weak DNCB on her alopecia areata and it grew hair and we reported that or presented her case to a -- at the time, the Archives of Dermatology used to present the transactions of dermatologic society meetings. Dermatologic society meetings worldwide are always -- frequently, one brings a patient to the society meeting

and the members of the society see the patients and discuss their case and then those cases always used to be reported in some of the journals.

So, this single case report, which was not really a case report, but what was the transactions of a meeting of the Memphis Dermatological Society was published in the Archives of Dermatology. Rudolph Hopley, a dermatology professor in Germany, read this and began doing this on an organized and thoughtful and extensive way.

We began also to do some larger studies. Hopley then told us that the West German regulatory agency told him not to use it because of the Ames test, but said that these other -- he said that the other two drugs -- first, the SADBE, later the DPCP, had passed that review and that is what most of us started using.

So, on the basis of, as I say, 25 or 30 years and lots of patients personally, I can tell you that it would be very hard to not to have this to offer to patients who come in with this terrible disease. One of the sad things about this kind of disease is parents and patients have been told that it is due to stress and dysfunctional family life and so forth. And that is not true either.

Whether it is autoimmune disease or whether

there is actually some antigen there in the form of a virus, it is not at all clear. Hopley feels that it is autoimmune disease and SADBE brings suppressor cells. I still in my heart think that there is some evidence for a virus and the related disease vitiligo also, there is evidence of a virus.

So, the issue is unclear. The fact is that this treatment is helpful for a lot of patients. I brought along a statement from Jim Davis, who is a pharmacist who has been mixing it for me for 25 years. I asked him for that a week or so ago and he said he would, but his wife was ill. He was going to take her to Florida for a couple of weeks to try to recuperate and he left a statement, which I am not sure I understand exactly, but from the point of view of the practicing pharmacist, this is not only something that he can do in the office, but that he feels is important to him and it has been a very gratifying aspect of his career as a compounding pharmacist, the ability to work with these patients.

DR. JUHL: I wonder if I could ask you to clarify. You said that this treatment -- and I assume you talk about the method of the treatment, but we have three compounds. Could you clarify which --

DR. ROSENBERG: I have not used DNCB, again, as

Dr. McBurney said, many of us have not used DNCB for a long, long time, since really Hopley first presented these other two chemicals to us. So, my experience is with SADBE and DPCP, apparently is a little more stable in acetone, although I am not sure of that. We have both of them available at the pharmacy.

Patients will sometimes become tolerant of one and need to be sensitized to the other, but I would hate to lose both of them. In terms of the efficacy statement, it does not have a commercial sponsor. It has not had that kind of a study, but Hopley has published numerous pictures and we have seen the same treating one half the head and the hair grows on that half of the head and not on the other half.

Then the other areas will grow hair sometimes, it seems that -- in the same that in the same way they treat few warts successfully and sometimes they all go away, the immune system is certainly active in this disease and it has become now legitimate apparently in clinical immunology to talk about immune modulating substances, which means that it is a very complicated system and we don't exactly know what we are doing but sometimes benefits accrue and I guess we can use that kind of a term here in terms of whether it is an immune suppressor or an immune adjuvant. Certainly, in warts

most of us think it is an immune adjuvant.

DR. JUHL: I wonder if I could ask you to offer an opinion on the quality of science, at least as we would like to have -- we would like to have all the answers -- doesn't seem to be there.

The question I have is: Is it possible to know more if we had a better system of collecting information or is this illness so unusual and so patient specific that it is hard to do research on or is it the lack of funds to do research on? But from our perspective, we need to decide if they are to be available or to recommend whether they be available and if so, how they would be available.

I am wondering if a more systematic collection of information would yield anything, either in terms of how well the drugs work or how safe they are.

DR. ROSENBERG: I am sure that could be done in terms of priorities. I am sure it would probably not be on anybody's list. As I say, it has no commercial sponsor and I think the -- I would be surprised if the NIH wanted to do a placebo study. As far as the efficacy is concerned, I think -- again, as Dr. Okun pointed out, the Tosti study, the power was too low in a disease with a high spontaneous cure rate or recovery rate to show a benefit over placebo.

In terms of efficacy, I would say that the practicing community of dermatologists and the medical board of the Alopecia Areata Foundation, which presently includes the dean of the University of Rochester College of Medicine and a couple of very -- really distinguished serious scientists. The efficacy is there. Dr. McBurney can speak from her perspective.

I think there is no question -- certainly, it doesn't work every time, but certainly it will help some people. In terms of the safety, I think the fact that this community is concerning itself with safety must be welcomed by everybody, the Academy of Dermatology, the Alopecia Board, all the patients and all the practicing communities. That is something that none of us wish to treat patients with unsafe products.

DR. JUHL: I guess in a way I consider for lack of other sponsors, the practicing dermatologists and compounding pharmacists to be the commercial sponsors of this product. What I would like to have a feel for is could we get more information from that group if there was an organized effort amongst them to do so.

DR. ROSENBERG: I don't know how it would be organized. The Alopecia Areata Foundation raises funds and it has been giving away -- making grants of two to three hundred thousand dollars a year, but -- and, again,

the board looks -- reviews the requests, but the feeling has been that science-based research, laboratory work into a function -- interreactions between the immune system and the hair follicle and some aspects of hair regeneration are more likely to move this forward and then would be a large clinical study.

There have been requests for monies to do these kind of clinical studies and they get low scores so that they have not been done. We have been looking for an animal model and there now are animal models and which may or may not be exact, but, I mean, it is that type -- in one very recent study, one of these agents worked in one of the animal models. I am sorry I don't have that reference. I don't know if you saw that.

DR. JUHL: I guess I am more looking from a practical point of view, from our decision-making process, would the academy be interested in sponsoring an IND such that when people are using this amongst your association of dermatologists, they would have a standardized product that comes from one manufacturer that we know more about, that there be a standardized collection form of adverse effects and a registry almost.

DR. ROSENBERG: I couldn't speak for them. I am not sure that I recall that kind of activity ever having been done.

DR. JUHL: I don't think it has, but I am asking would that be of interest to the academy?

DR. ROSENBERG: I don't know. For those of us that care about this disease, of course, many of our colleagues will refer patients so that I think in terms of everyday practice, lots of people could get along without it, but for the patients with alopecia areata, it is really necessary that there be some doctors who want to do this and some medicine that they can look to with some hope. They really would like to be able to continue this kind of treatment. They find it helpful and we find it helpful.

DR. JUHL: I have no argument with that. The patients have to come first, but we don't have enough good information. We could use more information. I guess I am wondering is there the will amongst --

DR. ROSENBERG: As I say, in terms of safety, we would yield absolutely to your judgment. I certainly would and I am sure everybody would. In terms of efficacy, I think we could -- if you would accept that publication of a randomly controlled evidence based placebo study in a refereed journal is the only kind of evidence, that -- and some people think that about a lot of things, we just don't have that. The nature of this would make it extraordinarily hard.

It seems to me that reasonable people looking hard, of a panel of reasonable people looking hard at the published -- even the published material, not just anecdotal, the pictures of patients and the weight of evidence that these things work in alopecia areata would conclude that they are effective for growing hair in a certain percentage of these patients.

I think -- I would not accept evidence-based criteria, as they now exist in the practice of medicine for the refereed journals and so forth and so forth. We are talking about a sort of a little by -- backwater area here of medicine that for those of us that are in it and have it, it is very important. I truly think that I would not -- would urge this committee not to assume that these things are not effective.

DR. JUHL: Other questions for Dr. Rosenberg?

Dr. Sellers.

DR. SELLERS: How many patients are affected by this and what is the breakdown of peds to adult patients?

DR. ROSENBERG: I don't know that answer. It is a high -- of those that want treatment, it is a high percentage of adolescents and some children. I should know the answer but I don't.

MR. CATIZONE: Maybe if you get a clarification of the question, of your patients, the patients which you

see and treat, total patients, what percentage of your patients require the use and treatment of the two products that you use?

DR. ROSENBERG: A small number. I could get by with one of them.

At the meeting of the Alopecia Areata Foundation Medical Board, which was just the last week in March in New Orleans, I asked -- I told the group this meeting was upcoming and asked them just what their experience was with it and, first, everyone there uses this treatment. Everyone there uses this treatment, which is something to say.

The second was they felt it worked about half the time. Again, this is -- a lot of experience, though, in that room.

DR. RODRIGUEZ: I just have a simple question.

Since you have a foundation that you are associated with and you have just told us that at the meeting that people say -- 50 percent say it works, one of the questions that we are concerned about is safety. Most of these products have been used for over 20 years plus and even though anecdotally, do we have any way of -- I mean, that -- these people who are highly interested in the disease and who are supporting a foundation and associated, do we have any information that might assure

us of, quote, unquote, the safety of this product? It might be anecdotal, but at least it is more than what we have on hand.

DR. ROSENBERG: I am unaware of any serious problems from it. I mean, the contact dermatitis, of course, but it goes away. Jim Davis, who wrote this thing, I said, how about the problems for the compounding pharmacist. So, he rolled up his sleeve. He said, well, here I have got a little redness here. He said I was mixing someone Tuesday and he said I am allergic to it and he said every once in awhile it will bother me a little bit, but it doesn't upset me.

So that I -- one would hate to, you know, bring historical evidence that it doesn't hurt patients, but I continue to -- I think it is safe. I certainly -- compared to the systemic corticosteroid, it is not a contest. It is safe. Compared to puva(?), where there elevations of soralin(?) UVA, of melanoma 15 years later, I think it is safer than puva.

Topical steroids don't work either.

DR. JUHL: Elizabeth, Larry and Bob.

DR. MC BURNEY: Dr. Rosenberg, I have two questions, one of which you have somewhat answered. Of the three agents, which one do you think has been the most effective and is used the most frequently by

dermatologists?

DR. ROSENBERG: I don't know that. To my knowledge, at least up to a few years ago, the Mayo Clinic was still running DNCB. They just never changed and then that was -- I was surprised when they told me that is what they were having. I think it was Sig Muller(?) was still there when they were doing that. But I didn't know anybody else was using DNCB anymore.

Do you?

DR. MC BURNEY: No. My impression is that it has fallen off since the other two -- in your practice, do you use primarily the squaric acid or the DPCP, would you say, equally or one over the other?

DR. ROSENBERG: Interchangeably. Mostly, I think, Hopley uses most mostly DPCP now. So, I use mostly DPCP now. He is very good. I am sorry he didn't come to this meeting. He is very, very good. He is very organized and does it in a very organized way.

DR. MC BURNEY: My second question is, and realizing this is anecdotal, just on -- but which I think is extremely valuable coming from someone like you who has treated many patients with alopecia areata, do you feel that of those two agents, the DPCP versus the squaric, do you feel of those two that one is more effective than the other?

DR. ROSENBERG: No. I think if this committee was more comfortable with the safety of one than the other and thought it would be useful to have one and just one, I could live with that, but there are patients who will become tolerant and no matter how strong you -- they say, well, it doesn't seem to make me pink anymore. Nothing happens.

Hopley has his patients come to the clinic once a week, where his -- actually, it used to be his wife painted it on when she was a nurse. My practice all along has been to write the prescription and teach the patient how to use it by -- we won't go into that -- dipping a cotton applicator into this acetone solution and waiting until it is dry and then touching it lightly and so forth for home treatment. So, both of those techniques are possible and patients will come in and say that it doesn't work anymore. They get a fresh bottle. Maybe it has gone off and they get a fresh bottle and that doesn't work and then so we will make it stronger and make it stronger and that doesn't work.

It is evident that they have become tolerant of the chemical. So, it is useful in those cases to have a second one. But that is not very common. That is rare in a rare disease with an unusual treatment. I think we could live with one.

MR. TRISSEL: A couple of points. One is I would suggest to your compounding pharmacist that he should wear some protection, particularly gloves, just as a matter of common sense.

Let me ask the people from the Agency, is there any precedent -- are there precedents set for advocacy groups -- let me ask someone from the Agency, are there examples of interest groups or foundations holding INDs to evaluate some, say, orphan drug, for lack of a better term?

DR. DeLAP: Well, there are some products that have different than conventional approaches to IND process, I would say. Not every product that is under IND is being sponsored by a commercial organization that wants to market it eventually and, of course, a lot of them that aren't held by commercial organizations of that sort are held by individual investigators, but then there are still others that are held by organizations that are interested in having a particular product available.

We do have -- there is precedent for having INDs that aren't necessarily going to lead to a product in the marketplace, where really what it is is serving as a mechanism for having a product available to people in the U.S. for a disease that is perhaps so rare in the U.S. that there is never going to be a commercial

development.

I think that the reason that people are interested in that or, you know, the value added, I guess, is the way I would express it for the Agency is that then we are looking at things like how is the product produced and manipulated before it goes to the patient. So, we look at things like what is the source of the chemical? What is the purity? What are the impurities?

That is looked at under the IND process and there is at least some intent to learn as much as possible, understanding -- I certainly respect -- number one, I respect Dr. Rosenberg's experience. I also respect his -- it would be impossible to perhaps get a traditional gold standard kind of randomized control trial out there in this area. But, nonetheless, when we see these things under INDs, even if they are not headed in that direction, a lot of times there is an ability to collect some information that advances the state of the art over time, such that we can develop more experience to the best recipe, as it were, for using the product, the best way of -- you know, for compounding purposes, I mean, what is the best solvent and way of doing the compounding so we preserve the stability of the product and you get the least possible side effects from the

patient.

You know, we can learn more about those kinds of things over time with the more organized research effort under an IND. So, you know, I think that that is very interesting concept and I would like to hear further as to what people think about that. I don't know if the academy would be interested in sponsoring that kind of an effort. It is not a trivial thing to do, but we always try and work with people when we know that they are trying to do something like this for a special population of people that we need to be careful to serve.

We try and work with people that are interested in organizing these kinds of efforts to make sure it is not more onerous than it has to be.

DR. JUHL: Joan.

MS. LA FOLLETTE: Speaking of these other types of INDs that aren't from a commercial manufacturer or company, might be a private physician, I am not familiar with that type of IND, as far as what type of documentation goes in, but does that mechanism provide -- some of the concerns, where we are concerned about the source of the drug substance.

I mean, is that filed as I am going to use this supplier and then that is what it is limited to, such as the way a commercial IND would be.

DR. DeLAP: Yes, we do look at the source of the product and what is known about the purity and impurities and whether there are any issues that come to the fore from that. I think you got the sense from some of the presentations that our chemists made that there is a fair amount known about some of these products and there are different impurity profiles, some of which are probably better than others in some bulk products, we would rather people use if they are going to do this, and others, we would rather they stay away from perhaps because of levels of carcinogenic impurities.

So, we do look at that and we do look at that and we do regulate that under an IND to ensure that we are getting an acceptable quality product.

MS. LA FOLLETTE: I had one more question for the speaker, the presenter. I understood in your talk, you were talking about Dr. Hopley and you said in Germany they had made some decisions based on positive Ames tests to ban -- this is what I understood you to say --

DR. ROSENBERG: That was my understanding, yes.

MS. LA FOLLETTE: Are some of these compounds available in Europe or are they also compounded?

DR. ROSENBERG: I think Hopley compounds it. He buys the chemical and compounds it. I don't think they are available as therapeutic agents, I mean, you

know, from a pharmaceutical supplier, but I think they have passed -- my understanding was that the squaric acid and the DPCP had passed regulatory review there. They were two that he could use at that time.

MS. LA FOLLETTE: That may be interesting to this committee to know what source of drug substance and maybe there is a history of it being used in Europe. I mean, it just might be another avenue to collect more information since nobody enters into an IND here.

DR. ROSENBERG: It certainly is used in Europe. Just without going over it again -- just what I hoped I was able to get across in three points. One is that alopecia areata is an important disease to people and one not to be dismissed just -- it is much more important than male pattern hair loss, in my opinion -- much, much more important than male pattern hair loss. I would not contribute to a male pattern hair loss foundation or serve on their board.

I voted against propecia when I was on the Dermatology Advisory Committee last year. It is an important serious disease for some people.

Two, I would submit that if you are not convinced it is effective treatment, that it -- we could put together a group of people who would come here, admittedly not with a gold standard peer review journal,

double blind placebo, evidence-based, pass all the hoops of standards, but we could come in here with enough data to convince you that this stuff works, at least some of the time.

I have no question about that. I have no question that the committee would be satisfied and I would be -- if you wanted that, I am sure we could put it together.

The third is the safety. We are very grateful that this committee is considering the safety and it shouldn't be there unless you think it is safe. We appreciate the time and effort and thought that is going into this concern very much.

DR. JUHL: Thank you, Dr. Rosenberg. I think we will stipulate to points 1 and 2. Our question is how do we make this available for the benefit of patients in the safest way and at the same time begin to move the science a few inches forward.

The suggestion that I had made earlier that that would be a -- in my opinion, it would be an excellent venture for the academy to be the sponsor of an IND and collect patient information, not in the scale of a full-fledged trial that we would like to see if we had all the money in the world, because we don't, and a kind of a registry, maybe a registry of pharmacists.

Maybe after 20 years, we find all these people develop something and we have no way of knowing because there have been no records kept. It seems to me we could bring more order to the process, which should in the long run benefit patients.

Thank you, again.

DR. ROSENBERG: Thank you, sir.

DR. JUHL: We are seven minutes over our time budget. We will take a brief break and we will start the open public hearing at 10:45. So, please be prompt.

[Brief recess.]

DR. JUHL: Let us reconvene with a few helpful suggestions from our AD man. First of all, when handling the mike, handle it from the base, not from the top. Please don't touch this, meaning the top of the microphone. And also make sure that you pull it so that it is as close to you as it is to me. If it is some distance away, he turns up the power so that you can be heard and that is where the feedback comes from. So, if we could follow good microphone etiquette, we will see if we can improve on the quality of the sound from here on in.

**Agenda Item: Open Public Hearing**

We now have the first of several open public hearing speakers that we will have during the next two

days. During this session because we want to ensure fairness to all, we will have timed presentations. Our first guest is Larry Sassich from Public Citizen, who will make a presentation to the committee and he will have ten minutes.

Larry, welcome.

MR. SASSICH: Thank you very much.

I am Larry Sassich, a pharmacist with Public Citizen's Health Research Group in Washington, D.C.

Public Citizen strongly urges that the Food and Drug Administration's Pharmacy Compounding Advisory Committee consider the following four important issues: The nominated bulk drug substances appearing in the FDA's January 7th, 1999 proposed rules as substances that may be used in pharmacy compounding should be reviewed by appropriate agencies -- divisions in a manner similar to the drugs that will be discussed today and tomorrow and then be discussed by the Pharmacy Compounding Advisory Committee before this rule is finalized.

I would like to commend the Derm and Dental Products Advisory Committee on their rigorous review of what is known about these three sensitizers that was presented this morning. Even though some members of the committee might not feel that rigorous science is necessary, I think the public does and I think the

reviews that were done this morning will make excellent newsletter articles for our consumer news letter that goes out to about 130,000 people.

My second point is five of the above mentioned 20 bulk drug substances are currently ingredients in commercially available products and, thus, should not be included on the list of substances that may be used in compounding. These are ferric sulfate, ferric sulfate hydrate -- and I think the FDA considers this as one compound -- phenindamine tartrate, phenyltoloxamine and taurine.

The third point, there should be clarification of the reasons for including currently marketed nutritional substances on the list. Three of the above mentioned substances are currently sold as nutritional supplements. These are choline bitartrate, glutamine and taurine. Taurine is also an ingredient in an FDA approved product as mentioned above.

Choline bitartrate is advertised heavily on the Internet as a brain stimulant. Glutamine as the -- will be the successor to creatine for body buildings and taurine, if I remember, is sold as to normalize the pH in the central nervous system. Ads for these products appeared on pharmacy Web sites on the Internet.

My last point and the most important, I think,

is the use of abuse of pharmacy compounding. We feel that there is evidence for the abuse of pharmacy compounding. The nomination of DDMPS, a chelating agent, and piracetam, a brain booster, on the list of substances that may be used in pharmacy compounding are clear examples of this abuse.

The suspect use of DMPS is discussed in Public Citizen's comments submitted to the docket regarding the list of bulk drug substances that may be used in compounding. Examples of how piracetam is being promoted and what use it is being promoted and sold for are given below.

In considering the bulk drug substances that may be used in pharmacy compounding, it was the FDA's expectation that "fraudulent or quack remedies will be less likely to be included on the list because the practice of compounding such drugs is not expected to be sufficiently prevalent or longstanding."

Unfortunately, the misuse of pharmacy compounding for exploitation of the public may contribute to a significant segment of pharmacy compounding.

There is a an unprincipled symbiotic relationship between some compounding pharmacists and exploitative practitioners of complementary/alternative medicine movement, each requiring and using the other for

their own economic well-being.

The Web sites for the International Academy of Compounding Pharmacists and the Professional Compounding Centers of America link to the Web site of the American College for Advancement in Medicine or ACAM in Laguna Hills, California, an organization that claims on its Web site to be "dedicated to educating physicians on the latest findings and emerging procedures in complementary/alternative medicine, with special emphasis on preventive/nutritional medicine."

ACAM has been involved with the promotion of chelation therapy that involves the intravenous injection of EDTA, approved by the FDA for the treatment of heavy metal intoxication. We have been informed that an action is pending between ACAM and the FTC over charges that ACAM made unsubstantiated and false advertising claims that non-surgical EDTA chelation therapy is effective in treating atherosclerosis and that this has been proven by scientific studies.

Two weeks ago, the editor of Public Citizen's Health Letter, a newsletter for consumers, received a complementary copy of the March/April 1999 issue of the International Journal of Pharmaceutical Compounding, a publication, as Dr. Loyd Allen mentioned -- he is the editor-in-chief of this particular publication and a

member of this committee.

He was also listed as a consultant to Professional Compounding Centers of America in August in 1998, though, this announcement no longer appears on the PCCA Web site.

The International Journal of Pharmaceutical Compounding was delivered to our editor bundled with print and promotional materials from Smart Publications of Petaluma, California, an organization that proudly announces on its Web site, "We're the people who created the classic, international best seller, Smart Drugs & Nutrients, pioneering the concept of cognitive-enhancing substances.

A cover letter draws attention to an enclosed press release entitled "Natural Testosterone: Good for Your Heart." This is a chapter in a recently released book entitled Maximize Your Vitality and Potency: For Men Over 40, published by Smart Publications, a book that "covers natural testosterone and other supplements to reverse the effects of aging."

The cover letter goes on to say, "Also enclosed is a recent copy of the International Journal of Pharmaceutical Compounding in which the 'Heart Health' chapter is excerpted. What's the connection? Natural hormones must be custom prepared by compounding

pharmacists because they are not available from drug manufacturers."

The cover letter also invites our editor to "Please consider reviewing our new book or writing a story on these topics." The press release announcing the book says in part, and it is very similar to the above statement, "The key chapter on heart health from this book has been excerpted in the current issue of the International Journal of Pharmaceutical Compounding. What's the connection? Natural hormones, like natural testosterone, are available from compounding pharmacies represented by this journal."

At the end of the "Heart Health" chapter published in the journal is the following advertisement. Maximize Your Vitality and Potency can be purchased direct from Smart Publications. Wholesale pricing is available for pharmacies wishing to resell the book to customers (a good way to educate about the value of natural hormones.).

Also in the materials received by our editor was a newsletter entitled Smart Publications Update, apparently written for distribution to the general public. The newsletter advertises products, such as deprenyl citrate drops, piracetam liquid and triple natural estrogen cream as anti-aging products. On page 6