The positive aspects of this course of action would be that the drug would remain available to men and women who really need it. The negative would be, and I assume this would be a negative, would we accomplish what we would hope, that the drug would be used more cautiously, and with a reduction or elimination of fetal abnormalities.

We know that the labelling can be improved in a number of different areas, and I am sure we will hear about this later. In the area of packaging, in the area of warnings to patients, as well as changes on the bottle and patient and physician package inserts. The silhouette of a pregnant patient with a red line through the figure was used by one firm to indicate the drug should not be used when pregnant. This would be useful for patients who do not read or do not take the time to read. Informed consent, of course, could be used in conjunction with any of these labelling changes. Obtaining the consent signature would emphasize to physicians and patients the serious nature of Accutane therapy.

Finally, I would like to mention the drug distribution program which was used for AIDS patients when AZT, now retrovere, was in short supply. I mention it because there has been in-house discussion

about the feasibility of initiating such a program for Accutane. This could only be initiated however, if Roche were interested in supported the project.

The plan worked as follows. Interested persons would call the AZT hotline which was federally funded at a toll free number for information about obtaining AZT. A packet was mailed to the physician who submitted evidence that the patient fitted the criteria obtained for the use of the drug. A determination was then made by the persons at NIH and at the distribution house according to earlier criteria. The determination was made to send or not to send a drug or whether more information was needed. If approved, a one-month supply of AZT was sent to the pharmacist, and this was only sent on a monthly basis when it was determined that the patient should get a further supply.

In ending, I would like to again indicate to you how pleased we are that so many of our invited guests and members of the panel came. We want you to know that we view this as an extremely serious problem, and you testimony and your comments will weight heavily on our final decision. Thank you.

DR. BERGFELD: I am going to stop for a moment and ask the Committee, the panel, if they have any

specific questions. We will be moving on after two more presentations to discussing our options but we should stop a moment to see if there are any specific questions of any of the presenters. Elizabeth? Dr. Abel?

DR. ABEL: I just had one comment or one question for Dr. Lammer. He referred to the studies that were done using a decreased dose of Accutane, that this would not reduce the teratogenicity risk. I wondered if he had any thoughts about the decreased duration of the use of the drug and whether that would effect adverse outcome.

DR. LAMMER: We are still in the process of reviewing that data, but there have been children born with multiple birth defects whose mothers took as little as three capsules so that I am not sure if that is what you were looking for.

DR. BERGFELD: Thank you.

DR. BERGSTRESSER: Let me address that in addition. But you would agree that the duration of the risk exposure would be reduced, if instead of five months as is current, if Dr. Peck's system were useful, that a one month exposure would decrease to some extent the risk of fetal abnormalities.

DR. LAMMER: On the surface, that seems

logical. That will not address the problem of people who are pregnant when they start taking the drug, but perhaps that might reduce the number of people who have pregnancy failures on it.

DR. BERGFELD: Dr. Stern?

DR. STERN: This is a bit of a rhetorical question, Ed. It is my feeling that what we have heard here is that there is a real problem. However, I do think in terms of thinking about what remedies to take, while we cannot precisely know the numbers, we know it is a real problem, but having some idea of the magnitude of the problem should in part guide us about what recommendations to make because after all, we are balancing risk and benefit to both the unborn and to parents and I just cannot accept the idea that no teratogenicity for any drug is acceptable or we would not have Dilantin on the market, would we?

DR. LAMMER: I think that is a different situation. Most mothers who go into pregnancy taking medications like Dilantin know what they are getting in for. They make a decision whether, most of them make a decision whether or not to take the drug during the pregnancy as opposed to this drug which virtually all of the, I have not run across a single mother who was not aware that she should not take this drug during

pregnancy. These women all know that they should not be taking the drug during pregnancy as opposed to the example you used of Dilantin where many of those mothers have no choice but to take the medication during pregnancy or risk the potential consequences of their seizure disorder.

I guess your question really gets at the point that I thought I was trying to make which is really what are the objective criteria or subjective criteria even for making these decisions for drugs that are relatively non-toxic to the mother, they have a high absolute risk with fetal exposure, and there is nothing that is comparably efficacious for the particular category of disease they are marketed for. It is an unusual situation, and it is, I think part of the responsibility of the regulatory agency is to deal with developing criteria for helping to make those decisions and I have not heard anyone get up here and talk about what are the important criteria. I personally do not feel that body counts is the relevant issue, and I hope, I do not think that is what you were saying either.

DR. STERN: No, that is what I want to clarify. It is not a matter of body counts. It is a real problem, and we need creative ways to make it as

small a problem as it humanly possible given human behavior in terms of warning patients, in terms of all the things that have been talked about in terms of prevention and ways that will be truly effective in doing it but we cannot hope in any way to completely eliminate the problem. We can only reduce it to its minimum.

DR. BERGFELD: Excuse me, does Dr. Gary Peck have a comment to make to Dr. Lammer? You will have to use the microphone.

DR. G. PECK: Just the comment that I made this morning that by using the one month treatment period I would assume that since the drug is washed out so rapidly from the body, it has a very short half life, that it would reduce, it would obviously reduce the duration of risk, the teratogenicity if you use a one month course versus a five month course.

DR. BERGFELD: Dr. Graham, do you care to respond?

DR. GRAHAM: Just one piece of information that bears on this which is that we have not looked at it for our induced abortions yet in Medicaid, Michigan Medicaid, but we did look at it for the first trimester deliveries, and of the 13 first trimester delivery exposures, eight of those occurred with one

prescription for Accutane so that I think that any system that is based upon presumption that minimizing the exposure to one prescription will still have to accept a fair amount of pregnancy exposure with the drug, and I think that is coincident with the information that was presented by Dr. Lee earlier on contraceptive failure where the rates of contraceptive failure are higher in the first year than they are in subsequent years.

DR. BERGFELD: Thank you. Dr. Penneys?

DR. PENNEYS: I was not clear on the logic of why multiple and increasingly frequent pregnancy tests will help the problem once you determine that a subject is not pregnant and given the medication, all you are doing is making a diagnosis of contraception failure earlier by having, for example, weekly pregnancy tests.

DR. BERGFELD: Dr. Miller, if you wish to address that.

DR. MILLER: I agree with you that you are diagnosing it earlier, but what you are introducing into the system as with methadone is a behavior modification that is weekly sensitizing the patient to the risk that we are talking about so it serves two purposes of the follow up as well as the earlier detection.

DR. BERGFELD: Thank you. No other questions by the Committee? Then we will move on to Hoffman-La Roche's presentation. Dr. Del Vecchio, you are going to present this?

DR. DEL VECCHIO: Yes, I am.

DR. BERGFELD: Excuse me, what is the length of your presentation?

DR. DEL VECCHIO: About 30 minutes.

DR. BERGFELD: I would have to confine you to that length please.

DR. DEL VECCHIO: Okay. Could I have the slide projector on? To begin our presentation, I would like to reiterate the goals that we put forth this morning. These are our goals. We wish to restrict the use of this drug to patients with severe recalcitrant cystic acne, particularly in this target population, the population at risk that we are talking about, whether or not it is 4,300 patients or 61,000 patients. I agree that it is not the issue. The issue is we do not want it used for anything other than severe recalcitrant cystic acne.

We wish to exclude pregnancy when the prescription is written. We wish to insure that contraception is communicated, and will work. It is paramount in assessment of how to deal with this issue

that we believe these goals be kept in mind. Our three part proposal we believe will accomplish these goals best at the same time preserving the opportunity for the 60 to 70 percent of the patients who cannot become pregnant to obtain the drug without undue hindrance.

The Roche proposal takes three approaches, a regulatory educational approach, a patient approach and a physician approach. We are proposing a radical change in labelling. We are proposing expansion of the contraindication be written in the present box warning which reads that Accutane is contraindicated in women of childbearing potential unless all of the following conditions apply. All of the following conditions must be met before prescribing the drug, and there are five of them. First, we brought the indication into the contraindication. The patient has severe, disfiguring, recalcitrant, cystic acne. We have added the term disfiguring in order to further emphasize the need for these patients to be the most severe type of recalcitrant cystic acne. Second, the patient is reliable in understanding and carrying out instructions. It is up to the physician. It is his or her responsibility to determine if that patient is reliable. He has to be sure that the patient can comply, and, third, that the patient is capable of

complying with the mandatory contraceptive measures. We have proposals which we believe will help the physician to carry out these conditions.

Fourth, the patient has received both oral and written warnings of the hazards of pregnancy and has accepted her understanding and acceptance of those warnings in writing, and we have a proposal, again, to help the physician carry that out. Fifth, pregnancy has been definitely excluded through a negative pregnancy test and appropriate history and physical examination. We believe that is certainly essential. We have heard information this morning that a large number of patients who have had congenitally malformed babies and a large number of exposed pregnancies are women who were pregnant at the time they received the prescription. We believe that this, we have to address that very definitely.

Those are the five conditions under which a physician may now prescribe Accutane if it is acceptable to the Committee and to the FDA. In order to help the physician to implement this, we proposed a patient consent kit. We will supply a standard form for a patient consent that will contain all the necessary information, all the explanations. There will be an explanation for the physician and for the

patient as to what this means. It will be delivered to all dermatologists and all known prescribers of the product. It will be offered to all other physicians who wish to have it, either through our sales representatives and it will be reinforced on every sales visit. Although we do not have the final wording on it, and I will not try to read this to you, we have begun to work on it with our law department. Tentatively, the form will be in duplicate so that the patient when she signs the form will leave one with the physician and will keep one with her as a reminder, and perhaps we will talk about a pharmacy option later on, perhaps even to show to the pharmacist. We will before we issue this have focus groups to deal with this with patients and with physicians to be sure that we are on the right track, and that this form and the concept itself is, in fact, acceptable.

The second major portion of our program is our new packaging. We think it is a unique packaging configuration. We are just passing around two samples to the Committee. I would like to be sure we get those back, please, because those are not active ingredients so therefore those are misbranded packages, but they are, in fact, the package as they will appear. As you see on the screen, it is a blister pack of 10 capsules

of Accutane. The portion of the package which unfolds from around the blister contains all of the copy of the patient leaflet which we current are providing to pharmacists and physicians to supply to patients. The patient will now receive that leaflet as an integral part of this package, and even as the blister pack itself, even if she cuts off the portion that is the leaflet, the blister pack itself will say, warning to female patients, Accutane may cause severe birth defects. You must not take Accutane if you are or may become pregnant during treatment. That is in red. Every portion of the patient leaflet that deals with pregnancy and contraception is in red. The patient, before she takes the first capsule, and every time she takes another capsule out of this package, will see those warnings. We believe this is as close as you can get to guaranteeing that the patient will receiving the warning every time she takes the capsule.

What we are attempting to do is to interpose ourselves between the patient and the capsule so that even if there has been a failure on the part of the physician to determine whether or not the patient is pregnant, even if there has been a failure on the part of the physician and pharmacist to give the patient the necessary information, or even failure on the part of

the patient to listen to that physician or pharmacist, there is one last chance to get to her before she takes that pill, and, in fact, if she thinks she may be pregnant, at least there is an opportunity for her to have another last chance before she continues to take the medication.

Nothing is guaranteed. We cannot guarantee that these will not be taken out and put into a bottle, but we believe that this is probably the most unique attempt at getting warnings across that has ever been undertaken. We expect that this will be a major cornerstone of the program. It will have a major impact on reducing pregnancies. The wording on this, of course, has not yet been approved by the FDA. It has not been submitted as a supplement although we are prepared to do that. This will be the only way you can get Accutane. That will mean that men and women who are not of childbearing potential will have to have the packages this way. The pharmacists will not like this. It will take up more room on the shelves. It takes up inventory space. I am afraid that is the way it will have to be because we feel there is no other way to do that.

This packaging will be accompanied by an intensive educational promotional campaign which will

be devoted to nothing other than this packaging, the new contraindication as well as the programs that you have yet to see. You are welcome to take a look at that package and I will be happy to take any questions on it later.

We are also proposing, as part of that packaging, a pregnancy symbol or perhaps better, an anti-pregnancy symbol that would appear on both the packaging as well as educational material that would be available to physicians, pharmacists, and patients. I am not sure that this is the final graphic, but it is pretty close to it, and we are going to propose something very close to that to the Agency.

The third part of our program is a peer program, a far reaching, peer professional program. We have contacted and have tentative agreement from the American Academy of Dermatology to enter into their standards of care program through which the Academy will develop a set of standards of care for the treatment of acne including the use of retinoids like Accutane in that treatment. We hope that the focus, the major focus of that program will be on patient selection and contraception. The program will be distributed by the AAD through its members and through other professional outlets through other physicians who

may be apt to prescribe this drug. Again, we expect that this will influence the physicians who are members of the Academy and even others who are not members by the weight of the professional reputation and the importance of this Academy. Obviously, we will support the program but we do not intend to have any editorial control over what happens in that program. This is going to be for dermatologists by dermatologists, an certainly for other physicians as well, and we would hope to include in this some of the issues that deal with contraception, some of the things that have been brought up here, the issues of double contraception, the issues of abstinence and some of the other possible ways of dealing with contraception, perhaps in collaboration with the ACOG if they are willing to enter into this program, we would certainly encourage that as part of the program. We have contacted the AAD, as I said, and we have tentative approval from them pending final approval from their Board of Directors.

And, as part of that peer program, if the dermatologist or prescribing physician is uncomfortable with the diagnosis of pregnancy, the counselling of the patient on contraception, the dispensing of a contraceptive prescription or procedure or device, then

we will agree, on his or her request, and on his or her volition that we will reimburse the patient for an initial consultation with a gynecologist or with any other appropriate family planning physician for the purposes of obtaining laboratory tests, including a pregnancy test, an appropriate history and physical examination, whatever else is necessary for that patient to be prepared to take Accutane appropriately. This is not a mandatory program. It is entirely voluntary. A physician who wishes to prescribe Accutane who feels that he or she can handle this certainly is free to do that on their own, but we feel that if a physician feels uncomfortable, wishes help, we are going to provide that help and we will arrange for that.

We do not have the details of this program as yet. Again, I will be happy to try to deal with any question that may come up. We will coordinate this with the appropriate professional organizations to be sure that we are not doing anything that may violate them in any way. I would say that we have already had one focus group with a group of 15 gynecologists, all of whom felt it was a very innovative and excellent program and felt that it would be accepted very readily in the gynecologic community, and we believe that this

is a very unique and a very important portion of our total program.

Just to summarize the major points in our program, first of all, we are proposing the major labelling change, the contraindication to be expanded with the five conditions that I mentioned before. As part of that, we are proposing, and this is part of the contraindication, a signed consent form, and we will help the physician with a sample form, a unique packaging configuration which you have all seen which we believe will get to the patient with all the warnings, and a peer education program through the AAD in addition to the contraception consultation program.

Now, I am sure there are many questions about our program, but before we get into that, I would like to briefly discuss some of the other options that we have considered, several of which have been discussed here. Dr. Evans alluded to several of them. I am going to go through each of those six categories briefly. What we have done is lump some of the different ideas into these categories rather than take individual ideas. I have listed them all with consequences and issues. Dr. Evans called them positives and negatives. You may want to call them pros and cons. We feel that consequences, that is,

results in issues, that is problems, is a more appropriate way to go, and I would like to start with the physician prescribing restriction.

What am I referring to there? A program that, for instance, requires a double signature on a prescription. Two dermatologists to sign off on the prescription, a gynecologist to sign off on the prescription before it can be written, Roche to sign off on the prescription before it can be written, perhaps restriction to dermatologists in terms of only dermatologists being able to write a prescription or submission of the prescription to some sort of board for verification. That is what I am referring to. The prescription would not be valid unless something else happens to it.

What would be the consequences of such a program? There would be a reduced number of prescriptions. Any time you have a second opinion, you are going to reduce the number of prescriptions. There would certainly be an increased awareness of hazards. The patient would know that she would have to go to more than one physician in order to get the drug. It puts the burden on the right person we think, and that is the physician. That prescribing physician is the person who really has the responsibility in terms of

prescribing Accutane. There is a double check on that physician's choice as a validation, and there is an increased patient dialog. Obviously, there has to be some sort of dialog because the patient knows there is something different about this drug.

What are the issues of such programs? Well, there are several. As far as we know, this type of program is not enforceable except through state boards of medicine, and that is 50 different state boards and legislature to go through. We cannot mandate controls on prescriptions. It would not directly have an effect on the pregnancy rate, although it certainly would have an impact on the pregnancy rate at the time that the prescription is written. It would reduce the use in appropriate patients of child bearing potential. There is certainly the possibility that patients might decide it is just not worth going through that, or physicians might decide it is just not worth going through a second opinion. I am not sure if that is good or bad, that is why I have not said it is a pro or a con.

The potential for conflicts with the second party, the second dermatologist, the gynecologist, Roche, whoever it may be, are certainly major. It would encourage physician dispensing, physicians who do not want to go through all of this, would just buy the

drug themselves and dispense it. It might encourage the use of other drugs or other sources of the drug, perhaps some of the drugs that were mentioned before, such as retinol, and it would be an increased patient expense in terms of an additional consultation, travel and so forth.

Let me go on to the second category, that is, pharmacists dispensing restrictions. Now, in this case we are talking about restrictions that would in some way would prevent the pharmacist from filling a prescription that is already written. For instance, a requirement that you read the patient the hazards of pregnancy before filling the prescription, that he check that the pregnancy test is negative, that he check that she signed the consent form, that he somehow verified the diagnosis and so forth.

What would be the consequences? There would be some reduced filling of prescriptions. Obviously, not all of them would be filled. It fits the role of the pharmacist as an educator. Again, an increased patient awareness of hazards I think is obvious. There would be some sort of ordered or verification of a physician compliance with the contraindication requirements, and the pharmacist is the final gatekeeper before the patient gets that prescription

filled. If you want to call those pros or positives, they certainly could be considered that.

But what are the issues? Again, not enforceable except through state boards of pharmacy. We cannot make the pharmacist do that. The prescription is already written, and I think that is the major issue here. That prescription should not be written if that patient is not a candidate. It puts the burden on the wrong person. We believe the physician has the major burden here.

We have studies that show that in anywhere from 50 to 60 to 80 percent of cases where the studies have been completed, that the purchaser of the prescription is not the patient. It is the patient's mother, brother, aunt, uncle so of course our system falls flat on its face when that happens, and, in addition, as you heard earlier this morning, the pharmacist may never even talk to the patient. As you may be aware, in major chain pharmacies, which are becoming bigger and bigger, they, in fact, discourage the pharmacist from coming down to the counter. The pharmacists are to stay up behind the plexiglass and to deal with compounding prescriptions and the patient or the purchaser deals with a clerk. There is certainly the opportunity for a conflict with a physician-patient

relationship. Imagine a pharmacist saying to a patient, I cannot fill this prescription because your physician should not have written it for you. It would certainly do this, that is, encourage dispensing, the issues of patient confidentiality and pharmacists quizzing them about contraceptive methods and so forth, is an issue and certainly the liability, the potential that physicians, I am sorry, pharmacists, are one way or another entering into the practice of medicine is certainly an issue.

This is the option that we have had the most discussion about, and certainly has been most discussed here at FDA and perhaps by many other people. We hear the term limited distribution a lot, and when you ask someone what do you mean by that, you usually do not get much of a response because we are really not quite clear. The most common ones that come up are AZT type distribution, as Dr. Evans mentioned, or and IND type of distribution. Whatever it means, limited distribution would entail the following. The drug would not be openly available on the market. All treatment, all prescriptions would go through Roche or another third party, and it would be distributed to pharmacies only upon approval of that third party. I think all limited distribution options would somehow

fall into those categories.

What would be the consequences of that? Complete control of our job by the company, distribution of Accutane, certainly a marked reduction in prescriptions. Physicians are not going to go through all of that, no matter how appropriate the patients are, not for the numbers of patients that they are going through now. There would be a high awareness of the pregnancy hazard, as there will be anyway, with all of these proposals. There would be a second opinion or validation of the physician's choice by someone else, and it would make data gathering a little bit easier, the possibility at least for registration and more information.

What are the issues? The logistics of restriction of distribution of a drug of this size and this popularity, I hate to use that word, but that is what it is, are immense, and frankly, do not have a distribution system in place that would enable us to go to 55,000 pharmacies in order to have this happen. We would have to invent a new system. It would be an inappropriate restriction on the 60 to 70 percent of patients who cannot become pregnant, who are not at risk. They would have to go through the same system. The problem of drug diversion, illegal imports, and a

black market I think then become very viable. The drug is available in other countries. The drug can be made. I can be made, I would not say easily, but it can be made by chemists. I do not want to overplay this, but again I think it is a consideration.

It would have no direct effect on the pregnancy rate. All it would mean is at the entry point, at that single check point into the system, the patient perhaps could be guaranteed to have severe recalcitrant cystic acne, and perhaps could be guaranteed not to be pregnant. I am not even so sure of that. Those of you that are familiar with the AZT system are aware of the fact that my understanding is that the average turn around time was about two or three weeks for a request to come from the field, to go through burroughs, welcomes, third party, go back to the pharmacy with authorization or shipment. If you picture what we are talking about here, the dermatologist examining a patient, ordering a pregnancy test or getting a gynecology consult, deciding that the patient is not pregnant, starting her on contraception, sending in the request to the company or to the third party, waiting for whatever processing time, and I suspect it would be longer although obviously we try to make it as short as possible but I suspect it would be

longer because this is a much bigger program than it would be with AZT, and then the drug finally gets back to the patient. Now what? Do you do another pregnancy test? Do you bring the patient back to the gynecologist again? We want the drug to be started on the second or third day of a normal menstrual period. What if the patient comes in and has that first visit on the second or third day, and she gets the prescription and she waits a couple of weeks and finally the prescription arrives. Now, she is in the latter portion of her menstrual cycle. Is she going to wait until the second or third day? I do not know. The patients are not doing it now. We have evidence that show that a large number of patients are not starting the drug on the second or third day of their menstrual cycle, but whenever they get the prescription whether or not they have a pregnancy test.

The other issue, of course, is that we have to totally rely on the requestor, that he or she is giving us the appropriate information. There is nothing in a system like this to stop someone from saying yes, this patient has severe recalcitrant cystic acne, and they may not have it. I think the important point, the most important point by far is that this kind of system will certainly cut down on the numbers of patients who will

receive the drug, but it does not address the goals that we are after. It does not address the goals except maybe the goal of restricting the use to severe, recalcitrant, cystic acne. In and of itself, it does nothing to deal with the issue of safety beyond the initial prescription. That was not an issue with AZT. The issue there was limited supply making sure the most severe patients go the drug, but one they got it, there was not an issue in regard to the distribution system. That would be the same effect here. At the point of distribution, you might achieve something but what about the rest of the three or four or five months during which the patient has to get the drug? That, in fact, is the danger period. We believe, in fact, that our proposal will eliminate that first checkpoint. That is, the pregnancy at the time that the prescription is written, and still do something for the rest of that time that she receives the drug.

Let me just go quickly to a couple of other possible options that absolute contraindication in women, period, without conditions, without any of the conditions that we mentioned before. The consequences would be a significant reduction in prescriptions certainly and a decrease or an increase in pregnancies, and let me try to explain what I mean by that. If this

is contraindicated in women, the warnings and the packaging are not applicable. Yes, it is certainly true that the FDA has the authority and responsibility as we would to put warnings into such labelling that says that this drug should not be used in pregnancy and so forth, but the more warnings you put in, the more details you put in, the more of the voluminous material that is available now that you put in, the more that you give a double message which says, well, it is contraindicated but you are going to use it, here is how to use it.

I would submit to you that what we would end up having is perhaps the possibility of more pregnancies with less of the appropriate material being available. The issue then of diversion from other groups and sources become major. How do you stop a male from giving the drug to a female. I have no idea how to stop that. There is no way to do that, and this kind of contraindication is not enforceable as far as we know except through liability on the part of the physician who may risk the liability exposure if he does not comply with this.

Finally, and I think very importantly, an absolute contraindication is clearly discriminatory against reliable female patients who, if they are

completely informed and agreeable, and make a conscious decision, can take this drug and take it appropriately, and take it under the proper conditions.

The final option I would like to discuss is withdrawal. We do not think this is a very appropriate option, and there are some obvious reasons for that. The consequences of that will be the drug is not legally available. That is pretty clearcut as Dr. Evans said. The issues? Denial of the drug to the non-target, the not-at-risk population, 70 percent of the patients who get Accutane right now. The rights of informed patients to make decisions, similar to the previous slide, the use of inappropriate alternatives such as retinol or other drugs which may be, may carry many other hazards to the fetus and to the mother as well as perhaps teratogenicity hazards, and without the same kinds of labelling that Accutane has.

Again, drug diversion, import, illegal drug production, again, I do not with to overdramatize those, but with a drug that has been on the market for six years, a major drug like this, to take this drug off the market, I think it would be foolish to think that this would not happen. If you consider what is happening now with non-approved drugs like menoxidil and how difficult it is to control the distribution,

the import, the illegal manufacture of that drug, I think you can consider what may happen with a drug like Accutane.

Finally, I would like to go back to the Roche proposal, and the consequences and issues there. The warning to the patient is as close to guaranteed as we can get it. Yes, it is possible to circumvent the packaging, but I think it is very unlikely. We are establishing a standard of care, or supporting that establishment of a standard of care, both on a corporate and regulatory level through the contraindication and through the consent program as well as on a peer professional level through the major professional organizations. There will clearly be an increased awareness of hazards. I do not see any way that the patient could miss that, even if she does not sign the consent form, she certainly is going to see the packaging, and in order to sign the consent form, there has to be increased patient-M.D. dialog.

There will be a reduction in prescriptions. I believe that some patients will not take this drug when they see all those warnings in packaging that they may not have seen before. I believe some physicians will elect not to be bound by those restrictions and the contraindication, and they may elect not to prescribe

it. There will be no interference with the non-target, the not-at-risk population, that is, males and females who cannot become pregnant.

What are the issues with our proposal? Again, the labelling portion is not enforceable. Again, except through liability on the part of the physician. It depends on voluntary compliance. There may be resentment or protest by physicians. I will tell you that some of this has been presented to one group of physicians already that we have heard considerable protest that this placing too much of a burden on the physician, too much of a restriction on the physician. There will not be as great a reduction of prescriptions as with the other options, but I have to go back again to what are our goals? Are we just trying to reduce prescriptions or are we trying to prevent pregnancies? I think that is what we are trying to do. That is what everybody in this room is trying to do.

One other point. The value of regulatory intervention in education has been raised, and demeaned to some degree here. We do not agree with that. We think we have shown data, we think we have other data that says, in fact, that regulatory intervention in education is, in fact, effective.

Just for emphasis, I would like to repeat the

primary goals. We want to limit the use to severe recalcitrant cystic acne. We think the contraindication is going to do that because it includes the indication itself right now, and the consent form. We want to exclude pregnancy at the time the prescription is written. We think a combination of the contraindication, the consent form, the packaging, are all going to do that, as well as, of course, the contraceptive consultation program. And for the same reasons, we want to insure contraception during the period of treatment. We believe that our proposal is designed to meet all three of those goals.

I would like to ask Dr. LaBraico to now step up here for just a few minutes to briefly discuss some possible studies designed to measure the effects of our proposal.

DR. BERGFELD: Could we limit these to a very few minutes, please?

DR. DEL VECCHIO: Yes, they will be.

DR. LABRAICO: Yes, it will be very limited because I think that whatever type of monitoring program we are going to use will depend on the decisions that are made by this Committee today and, in fact, Dr. Faich and I have already discussed that as soon as we have some idea as to what we are going to

do, drug safety at Hoffman-La Roche and the epidemiology group will get together to develop a monitoring system because obviously, whatever you do, we have to have some way of measuring the effectiveness of the program that has been discussed, and I really do not have anything else to say about it at this time.

DR. BERGFELD: Thank you. We have two other presenters --

DR. DEL VECCHIO: I just have one more statement. I just want to reemphasize that we are certainly ready, and I have already spoken with Dr. Faich with regard to working with the Division in terms of any monitoring program that may be necessary. I would just like to speak to our implementation, and this will just take literally one minute.

In terms of our implementation of the proposal, we are ready to file supplements with the FDA for both the packaging and the labelling. We will be prepared to send out a "Dear Doctor" letter to health professionals in regard to the entire programs, and we will have the promotional educational campaign which will be devoted solely to this program. There will be no positive promotion for Accutane. There will also be a public media campaign to alert both the health media as well as the public to the fact that this is

happening. We have made the contacts with AAD, and as we said, preliminarily they have agreed to work with us. Our target date for all of this, assuming the supplements can go through reasonably rapidly would be to have most of it if not all of if in place by June of this year.

Finally, in summary, I would just like to say that we believe we have presented a proposal which will restrict the use of the drug to severe recalcitrant cystic acne, will reduce pregnancy exposures, and will reduce congenital malformations to the minimum possible consistent with maintaining the rights of the patients to receive an essential drug, and maintaining the ability of physicians to prescribe the drug appropriately without undue restrictions. Thank you.

DR. BERGFELD: Thank you. We have two other presentations. The next one is by Dr. David Erickson, Centers for Disease Control, on prevention of Fetal Abnormalities.

DR. ERICKSON: Good afternoon. I am Dave Erickson, and I am grateful for the opportunity to be here to discuss with you the important issue of birth defects caused by first trimester exposure to Accutane.

I am Chief of the Centers for Disease Control Birth Defects and Genetic Diseases Branch. The

Mission of our program is to search for causes of birth defects, and to prevent unnecessary morbidity and mortality due to these diseases. I am here today because we believe that the birth of babies with defects cause by fetal exposure to Accutane is unnecessary. Obviously, if this drug was not available, these defects would not occur. While the drug is available, it is incumbent upon physicians who prescribe the drug, and on women who use the drug to see to it that we do not have more babies born with the severe problems caused by in utero exposure to Accutane.

As we have been made aware today, the current approach has not prevented all fetal exposures. We believe it is time for a new and effective approach to preventing fetal exposure. CDC has been involved in the issue since 1983 when my colleague, Ed Lammer, and others from CDC, saw a baby in Atlanta who had serious malformations subsequent to a maternal exposure to Accutane. Dr. Lammer went on to publish, with the help of scientists at the FDA, and Roche, a major study on the effects of first trimester fetal exposure. Our program staff have continued to follow the issue since that time, and we recently assisted the New Jersey State Health Department to publish in CDC's Morbidity

and Mortality Weekly Report a report of four cases of Accutane embryopathy that occurred between 1983 and 1987. Each member of the Committee should have a copy of that article.

We have watch this situation develop with ever-increasing concern. I think in retrospect we were naive to believe that fetal exposures would be prevented by the publicity surrounding the publication of Dr. Lammer's article, and the papers of others, along with the strong warnings made to physicians by FDA and by Roche. I think manifestly the approach has failed to prevent the birth of babies with major handicapping defects. In fact, as you heard earlier today, there is evidence to suggest that the rate of fetal exposure may not have declined to any marked degree even after the renewed warnings were made in 1985. They were strong warnings, but they obviously have not done the job.

As a result of this, we believe that it is time for a new, much more aggressive approach to preventing babies being born with defects due to Accutane exposure. So why do we feel so strongly about this? I guess very simply, it is a matter of our perception of the balance between risks and benefits. Most of the Committee members are probably well aware

of the benefits of Accutane use. From what we personally know, what little we know, Accutane is remarkably successful in the treatment of cystic acne, and we also understand that it is more than a cosmetic problem in many instances.

On the other hand, I think we are concerned that the public and the profession may not be fully aware of the magnitude and severity of the risk to the developing fetus. I think it is a tremendous challenge to you to make a fair accounting of the risks and benefits of Accutane use, to balance the interests of the unborn with the problems of older persons with skin disorders. I think it will take much introspection on the part of each of you to decide how to advise the Commissioner about how many persons cured of cystic acne is a fair and equitable balance for each baby born with serious, physical and/or mental deficit. My own perspective is that babies should not have defects caused by Accutane.

Simply stated, I believe that tragic situations are wholly avoidable, and that we should do whatever it takes to see that they are avoided. The only way that we can be fully confident that this will happen is to have the drug removed from the market because, as Dr. Lee pointed out this morning, there is

no perfect contraceptive. So long as fertile women use the drug, there are bound to be babies exposed in utero during this sensitive period of development.

While I personally advocate removal of the drug from the market, I concede that the birth of all but a small number of babies with defects would likely be avoided by a very restricted drug distribution scheme. An example of a restrictive drug distribution scheme is that that is used for thalidomide that you heard Dr. Grabowski speak of earlier. You all know that thalidomide is a potent teratogen, has about the same teratogenic potency as Accutane, and it has been available in the United States for treatment of leprosy complications since the early 1970's through an IND at the Hansen's Disease Center in Louisiana.

Thalidomide is available for outpatient treatment of males and non-fertile females, and as I understand it, it is rather readily available for males and non-fertile females. It is also available for potentially fertile females in a highly restrictive environment. My understanding is that admission to the Hansen's Disease Center is necessary for potentially fertile women to obtain the drug. According to staff at the Center, about 300 patients per year are treated with thalidomide, but only a handful of potentially

fertile women have received the drug under this IND. This is a very restrictive approach, and apparently it has had the effect of making the drug essentially unavailable to potentially fertile females.

I want to share with you CDC's ideas of what would be an acceptable limited distribution plan that would make Accutane available to potentially fertile women. If I could have the slide please, Jose, and most of you sitting around the Committee table should have a copy of this slide. We would suggest that the drug should be available through just a limited number of centers, regional centers perhaps, that there would be a Distribution Center Review Committee that would require certification by the physician who wishes to use the drug, that the patient has severe acne that is resistant to other forms of treatment before releasing the drug, that the manufacturer in cooperation with the distribution centers, would devise innovative approaches to educating professionals who want to prescribe Accutane, about the dangers of the drug to the unborn, and about the facts of contraception, and I think some of the suggestions made by the representatives of Roche go a long way to helping out with this particular point of our recommendation.

We think that there should be a distribution

center oversight procedure to require certification that women who are treated are at minimal risk for becoming pregnant during and shortly after treatment. Dr. Lee this morning suggested approaches to effective contraception with particular emphasis on the young women who are often candidates for Accutane treatment.

Ideally, the physician prescribing the Accutane would coordinate the use of the drug with another physician. For example, an obstetrician who would be responsible for helping the woman to manage an effective method of contraception. Basically, we see this as a two specialist problem, that the obstetricians need to get involved in this.

Prescriptions, we think, should be limited to one month supplies of the drug. To receive continuing treatment, the patient would need to return to have a reliable pregnancy test performed, and to received further counselling. The system would be designed so that women would also return at an appropriate time after the completion of treatment for a final pregnancy test. Finally, even though the goal of our plan is to prevent fetal exposures, failures are bound to occur, and each center should have a system for adequate counselling of women who do become pregnancy while using the drug.

We also believe that it is extremely important that any prevention strategy be accompanied by a follow up. For example, a national registry of patients who have had exposures during pregnancy with a follow up of pregnancy outcome, so that there is an evaluation of whatever is done.

I just want to briefly want to relate a case history that I think illuminates some of the points made here today, both by CDC and others. On April 21, that is last Thursday, I received a call from a pediatrician in the Southwest United States who had recently seen a baby who was born on October 31, 1987, with Accutane embryopathy. The baby's mother is 16 years old. The pediatrician's call was to inquire, on behalf of the baby's grandmother, as to whether we knew if the government or the company had a fund to help provide support for babies damaged by Accutane. The pediatrician also inquired as to whether there was still anyone interested in learning about new cases, and I believe that this case has now been reported to the FDA.

Initially, apparently, the mother was given a six month course of treatment with Accutane. I think she was about 14 at the time. Before starting the treatment, the dermatologist apparently had given

extensive warnings to the baby's mother, and to the grandmother about the dangers of Accutane to the developing fetus. The teenager was given a pregnancy test, and started on birth control pills along with the Accutane. Later, sometime after completing the first course, the mother's acne apparently worsened. She began another course of treatment, but this time she did not have a pregnancy test, nor did she use the birth control pills. This mother stopped taking the Accutane sometime we think around the sixth week of pregnancy. She stopped taking the Accutane because she remembered the dermatologist's warnings. She did not inform her mother that she was pregnant until she was allegedly in the seventh month of pregnancy.

This baby is alive today, has bilateral microtia, and appears to be severely developmentally delayed. I think this case, as I said earlier, illuminates many points. People do not know that there is still interest in reporting. Women, apparently women are given warnings by dermatologists but for one reason or another are unable to follow them or decide to ignore them, and that contraception is a problem. There will be problems with contraception, either failure or reluctance to use contraceptive methods on the part of some women, and lastly, some women will not

know or let on that they are pregnant until a time in pregnancy when they do not have full options for management.

Finally, I want to just close on a note of concern about other retinoids that have been mentioned here today. For example, Tegison, and I think it is our point of view that Tegison, along with other retinoids that might be approved for marketing at some time in the future, ought to be treated with the same type of restrictive approach as we believe Accutane should be. I thank you very much for your attention.

DR. BERGFELD: Thank you, Dr. Erickson. We have one other guest speaker that wishes to return to the podium. I would have to restrict you, Mr. William Schultz, he is presenting for the Health Research Group, to five minutes at most.

MR. SCHULTZ: We agree with the goals that Hoffman-La Roche put up on the screen, the goals being to limit the prescribing of Accutane to cases of severe recalcitrant cystic acne, exclude pregnancy and insure contraception but these are not new goals. These are already the goals that are in place and the current labelling is already designed to accomplish these goals. Thus, the current labelling limits the indication to severe recalcitrant cystic acne, and it

has a very explicit warning about pregnancy, and the whole point of this hearing, and the whole point we are all here, is because the current labelling has not worked, and a major reason that it has not worked is because doctors are consistently prescribing outside the labelling indications, and secondly, the word is not getting to patients.

Therefore, in addition to the measures that Roche has suggested, particularly the information consent measures, we believe that it is essential to adopt some method of limiting the distribution of Accutane, and that could be done either in the manner suggested by the CDC in the comments that just preceded me, or it could be done as we suggested, by limiting the distribution, limiting the prescribing to dermatologists, but the reason I wanted to come back here is to emphasize that we do not believe that any of these measures are going to work unless the distribution is limited, and unless the doctors are required to execute some sort of affidavit or representation essentially swearing that they will live by the indications of the drug.

Now, the Roche presentation acknowledged this as a possibility, and then flashed up the arguments against it, and the presentation, that aspect of the

presentation was so brief that I think it is probably hard for all of us to recall exactly what was on there but the most important point that was on there, and the one that was emphasized in the presentation was that this sort of limitation is of questionable legality and somehow could only be enforced by state medical boards. I am here to say that is not true. We cited in our testimony at page 20 a case where the Food and Drug Administration prosecuted a doctor in a hospital for prescribing a drug consistently outside the indication. We also cited a 1972 Federal Register notice where the Food and Drug Administration says it has the authority to limit prescribing in this manner, and finally, the example of thalidomide obviously shows another approach of limiting prescribing.

The other point is that this sort of limitation I think is essential even to Roche's plan because Roche's plan depends on getting these information packets to the doctors who are going to be prescribing the drug. They say they will send it to all dermatologists and other doctors that they are aware of, but obviously the plan is not going to work if every doctor in the country is allowed to prescribe the drug. I recognize that the FDA has historically been reluctant to get into the area of regulating what

is called the practice of medicine, and thus this kind of limitation has not often been considered, but this is a very special case, it is a very difficult case, and we believe it demands the kind of solution that we are recommending here. If there are no questions, that is the end of my presentation.

DR. BERGFELD: Thank you. The FDA did invite 14 guests to be here, about half of whom have spoken. I would like to ask if any of the other guests who were invited have a prepared presentation at this time. If not, we need to move on to the options that are posed to the Committee and the questions posed to the Committee. At this time, I would like first to set the scene. I think what we ought to do is to have a few minutes in general comments, and then we should take up the questions as posed to us somewhat generally and then specifically so I would like to ask any of the Committee members if they would like to make a general statement, pose a general thought, ask a question of any of the presenters that preceded and to do it at this time if this be the case. Dr. Drake?

DR. DRAKE: I would like to ask, first let me make a comment. As a general rule, I am very apprehensive about restricting drugs to any certain specialty because I would suggest that there are, one

of the pediatricians who testified today is probably every bit as qualified to understand the problems and the precautions that should be taken with Accutane as are the dermatologists so that concept makes me a little bit nervous, but I would like to ask if anybody on this panel or any of our guests know of other drugs that are specifically restricted by virtue of specialty board certification.

DR. BILSTAD: Some of the anti-cancer drugs are limited to use in hospitals and, in fact, are dispensed only through hospital pharmacies and the labelling states that they should be used only by oncologists who are familiar and experienced with using the drug. I am not familiar with other situations in which it is limited to specialties.

DR. BERGFELD: Any other questions of any other Committee members? Dr. Stern.

DR. STERN: Dr. Tabor and I were talking at lunch, and it seems to me what would be highly desirable it to have, if this were only a drug that came under the DEA controlled drug kind of legislation, what we need here are some kinds of controls. After all, we do this for morphine, we do it for codeine, to prevent abuse, prevent the wrong kind of people. It happens to be the Department of Justice rather than the

Department of Health and Human Services that does it, but are there available mechanisms to put this into the category of the controlled drug just as one needs to have the right to dispense controlled drugs in addition to your physician's license to practice.

DR. BILSTAD: Currently, for a substance to be, to come under the Controlled Substances Act, it has to meet certain criteria which include effects on the central nervous system. This was recently raised as a possibility for controlling the distribution of growth hormone and anabolic steroids. I know specifically with anabolic steroids that it was considered and was after considerable reflection and legal consultation, was rejected as a possibility at least under the law as it currently exists.

DR. TABOR: As Dr. Stern said, we had some discussion about this at lunch, and it seems to me that there is a gap in the regulations or in the regulatory scope available to the Food and Drug Administration. There clearly are some situations that arise where a little more control is necessary for non-narcotic drugs, and it would be certainly desirable, at least theoretically, to have some mechanism by which you could schedule non-narcotic drugs. In the Roche presentation, there were some mention about

discouraging the number of prescriptions if there were to be some kind of limited distribution system, and I would like to just put on the table the fact that there are certainly some fairly commonly prescribed scheduled drugs that are perhaps less frequently prescribed because they are scheduled, but certainly widely used, and I think we all know what some of these drugs are. They are used in the practice of medicine, pediatrics, and so forth.

I would also like, while I have the microphone, to just correct for the record, the story about thalidomide. Thalidomide is distributed under IND but it is a, the limited distribution is partly because of the IND, partly because the European manufacturers last year cut off distribution to the United States because of litigation. It is a distribution that was limited to about 300 patients as was stated, and it was also distribution that was done at federal expense by a federal agency at Carval in Louisiana, none of which is really applicable to Accutane.

DR. BERGFELD: Dr. Stein, do you have any comments generally?

DR. STEIN: No, I was just wondering, an additional issue I want to bring up, perhaps it is a

little early to do it, but I think that we perhaps need to do something in the interim until further steps are taken, whether is it blister packs or further education, I think we ought to consider restricting or halting distribution of the drug, at least in new patients in the interim.

DR. BERGFELD: Dr. Abel.

DR. ABEL: Dr. Wolfe referred to two concerns, and that is the prescribing outside of the strict indications for cystic acne, and the word of the risks not getting out to the patients. I think that these issues are addressed in large degree by the new package labelling by Roche. In addition, though, I would like to refer to that idea of the consultation or consultation with OB-GYN for every patient, and perhaps we should consider that appropriate in every case, and perhaps even post-signature for the initial prescription but I think that needs to be discussed and I agree that it is behavior modification, increased interaction between the patient and the physician, dermatology and OB-GYN person is essential.

DR. BERGFELD: Thank you. Dr. Minus?

DR. MINUS: Just a couple of comments. I think on the Roche presentation, they mentioned something about preventing pregnancy. I think I would

like to see something more in the goals that what we want to do in the instance of Accutane is to prevent birth defects or either add that to your goals. I think that with all the changes that have already been made in the labelling, that for us to add additional changes in the labelling is not going to get to the heart of the matter. I know personally that Accutane is a wonderful drug. I have used it. I have used it in female patients with wonderful results. However, being in an academic institution, I have seen a number of cases which Accutane has been prescribed for by non-dermatologists as well as by dermatologists who really have not followed the guidelines so I really feel that there is a problem, and personally speaking, I would like to see some kind of limited distribution of the drug as a way of controlling the use of Accutane much better than changing the labelling.

DR. BERGFELD: Thank you. Dr. Osterhous?

DR. OSTERHOUS: Somebody once said this Committee was being Solomon in trying to decide one way or the other, you know, somebody is going to get hurt one way or the other. As a unit physician for the full term nursery in our center, I do not like to see babies who have birth defects. I do not like to tell mothers about this. I think it is horrible, and we have

already agreed that we should not count bodies, but there is not one of us here who does not have a picture of that baby in our head as well as a picture of someone with acne as well as known people who have had children with anomalies and known people who are suffering abuse bigger than cosmetic problems so I think it is time to put aside bodies and body counts as almost impossible in describing this issue.

The problem with the Committee as I also run a poison control center, and I happen to know that there are physicians who are giving this drug who are non-dermatologists who are giving it for diseases for which it is not intended, that there are people who are getting it, I recently talked to a 19-year-old girl who is getting it for a rash. No, it is not acne, she told me. She has been on it three months, and no one told her about the problems of getting pregnant.

I read this little brochure that was in our packets. It scared me to death, not just about getting pregnant, I am kind of out of that range, but you cannot wear contact lenses, there are people who could not live without contact lenses. Your skin turns yellow, you might have mental derangements. I mean, everything in here is scary enough but then on every page we have a warning. Well, I happen to like the new

little packets that they put out, and I happen to like the warnings, but again, as a director of a poison control center, when we get children who come in who have gotten into lye that have safety containers, have skull and crossbones, and you tell the mother, why did the child get into it. Oh, I do not know, I did not know it was dangerous. So there are people out there who warnings mean nothing or why would we have pregnant women who still smoke and who still drink, and people who still do not use seat belts with their own babies?

DR. BERGFELD: Dr. Fleiss?

DR. FLEISS: I am sorry that there were no definite plans proposed by Roche for monitoring for surveillance for that over the next year or year and a half of whatever reasonable amount of time we agree on. There is an ability to assess, is the new system, whatever it is, working or is it not. I would love to hear some specificity.

DR. BERGFELD: Dr. Del Vecchio, to you have a response to that?

DR. LABRAICO: One of the questions that comes up about having a sufficient data base of information, one is what do we start the comparison with? If we start the program today, what will be our baseline of measurement for the future. In other words, where do

we, we are starting here at this point, and how will we know the effectiveness of the program, and what will be the baseline that will fall from. Now, we have recently become aware of some additional data bases that appear to have more females in it than some of the previous mentioned data bases. It is an HMO with multiple cities, and we are going to start to look at this to see if it can give us the kind of information we want. There is considerably more females of childbearing potential in it than either one of the data bases that have been mentioned today, probably somewhere in the realm of 3,000. We can look at the previous experience in that group and then use that same group to monitor forward.

DR. FLEISS: On page 61 of the Roche document that we got, there were some data indicating by year, from 1982 through 1987, the pregnancy exposures for 1,000 patients. There was a nice drop between 1983 and 1984 or thereabouts, and then it is pretty well plateaued so there is some background.

DR. LABRAICO: That is the spontaneous system of course, yes. We can continue to monitor that system. That system can stay in place, but I think we are looking for other systems, too. Obviously, the spontaneous system will continue being monitored, but I

think the idea is to look for other systems also.

DR. BERGFELD: Does that answer your question?

DR. FLEISS: Yes.

DR. BERGFELD: Dr. Bergstresser?

DR. BERGSTRESSER: Four quick comments that have come to mind during the deliberations. The first one is a personal one. We have heard statements that the overutilization of Accutane may be as low as three percent or as high as 85 or 90 percent, compared with those for whom the indications are certain. My own personal feeling is the number is clearly in between, that neither number whatsoever. Those of us in practice and those of us in the centers know that in fact that both dermatologists and general practitioners and others who, in fact, have overutilized the drug, we have no idea what that number is, but it is not zero.

The other one has to do with expense. I am very much concerned about any remedy for this problem which drives the price so high that the males and the women who cannot become pregnant can no longer afford this drug. Obviously, one cannot expect Roche to lose money on the drug, and therefore I think there is going to be an entire middle class that is going to be driven out of the market, and I am concerned very much about these people. The third item that I think should be

dealt with is that about contraception failure. I am certain the data that was presented earlier today related to failure, and under the best of circumstances, the rate per year is one in a thousand, and most circumstances are not ideal, rising to perhaps one percent. I looked at the Puget Sound data, and found that, in fact, their rate of failure was approximately one percent so in fact, that may be an absolute limit for the decrease that one can get so in fact, no matter what we do, there will be some failures so to expect to go to zero is not fair.

On the other hand, that test is not applied to any other drug that is used in the United States so in fact, we are going to have to look at comparisons between drugs before we can reach a sound decision.

Finally, I think it is absolutely necessary that the data now be accumulated to find out what we are going to be doing in the next six months because I would hate very much to come back a year from now and once again have totally inadequate data to base our decisions on. Thank you.

DR. BERGFELD: Dr. Penneys?

DR. PENNEYS: I have three comments. One, a general comment regarding the submission of material to panel members prior to the meeting. I kind of think it

is unfair for us to have this information, information that is incomplete and only really represents two-thirds of the FDA's presentation. I realize that data collection is dynamic but I think it is also a little unfair for us to review incomplete information prior to the meeting.

The second point I have is regarding incorrect usage versus creative usage. I am not sure the limitation of access to the drug to a specialty will address the point of giving it only for the correct package, label, requirements. For example, Dr. Peck presented a long list of several conditions that all of us, as dermatologists know are really medical conditions that require this drug as the best form of treatment, and in fact the FDA suggests we use medication that is not approved according to the package insert to replace Accutane as alternative therapy so I think you have to separate incorrect use from creative application of the medication. That also is my third point.

DR. BERGFELD: Okay. Any other comments to be made? Then let us look at our questions that we have before us. I do not think that we have to summarize where we stand. We seem to feel that Accutane has high efficacy, and that we are really concerned with the

at-risk group, and specifically in this group, the teratogenic effects. The first question, do you recommend that Accutane be removed from the market? I would like to go around the table and call for an individual vote on this. Dr. Drake?

DR. DRAKE: Realizing that we do have a problem with birth defects, and acknowledging that up front, I think to remove Accutane from the market would be a disservice to the 70 percent or so of the individuals who still can benefit from the drug. I would prefer to see us be a little more creative with our educational programs and try to ascertain other methods with which to solve this problem so I would be opposed to an overt withdrawal of Accutane from the market.

DR. BERGFELD: Thank you. Dr. Stern?

DR. STERN: I abstain.

DR. BERGFELD: Dr. Stein?

DR. STEIN: I would be opposed to removing it from the market.

DR. BERGFELD: Dr. Abel?

DR. ABEL: I would also be opposed to removing it from the market. There is no question that it is highly teratogenic and we are all aware of the risks, yet I think we all know of the efficacy of this drug

for a certain segment of the population, and I think that to remove it from the market, I agree this would be a disservice to that group.

DR. BERGFELD: Dr. Minus?

DR. MINUS: I do not think it should be removed from the market because of several reasons, not only severe cystic acne, but being in Washington and having Dr. Peck as a ready referral, for all of the other diseases that he has listed that we see create misery in patients, we are able to send them up to Dr. Peck, and he is able to treat them with Accutane. It is a marvelous drug, not only for cystic acne, but for another host of diseases that we see in dermatology and I would be opposed to removing it from the market.

DR. BERGFELD: Thank you. Dr. Osterhous.

DR. OSTERHOUS: Despite what I said earlier, I do not think this drug should be taken off the market until something at least creative, as Dr. Drake said, had been done to effect it. I am afraid that there are too many other alternatives and too many black markets that especially teenagers would get into that you are not going to eliminate the problem of fetal malformations. They would just be coming from something else.

DR. BERGFELD: Thank you. Dr. Fleiss.

DR. FLEISS: No.

DR. BERGFELD: Thank you. Dr. Bergstresser.

DR. BERGSTRESSER: Abstain.

DR. BERGFELD: And Dr. Penneys.

DR. PENNEYS: No.

DR. BERGFELD: And I vote no. So we have two abstaining and the rest of the Committee voting to keep this drug on the market.

Moving then to question two, it states, if the answer to the above is no, what other actions do you recommend? In general, they are listed A, B, and C, change physician's package insert labelling, B, change patient labelling and other. I would like to go around the table again and I would like each of you to address all of these at one time, and then we will come back and vote on them individually. Under other, you may add other that you may not see here listed so we will allow for a list to begin. Dr. Drake.

DR. DRAKE: I think that I am in favor of part A, and under part A, I am in favor of one and two. I do not think we should, absolutely, I am not in favor of part three because I do not think we should contraindicate the drug in women of childbearing potential because there are those women who do have childbearing potential who are willing to abstain or

use adequate birth control, and who might benefit a great deal from the drug. With respect to other changes, I think the approach through education is still a very strong approach. I would like to see us look at that more carefully. With respect to part B, change the patient labelling, although it has been pointed out that the labelling has been adequate, but not maybe as adequate as it could be, I think the bright red labels that Roche has proposed certainly is a step in the right direction so I would vote yes to try to do that, and I happen to think that blister pack is very useful.

With respect to the other, I clearly think that we need additional publicity and we need additional education, not only for the doctors who might prescribe it, but clearly for the consumer. As with many things, education is going to be the key. I think we have seen that in AIDS. Education is the key to treating that disease. People still are abusing IV drugs, even though it is fairly obvious that this is the problem so I think education is our major key here. With respect to signing a statement, I have no problem with that. I think I would be opposed to restricting distribution.

DR. BERGFELD: And you have no other

suggestions then to make under other.

DR. DRAKE: I guess I have a lot of suggestions, but my main one is education would be my number one key.

DR. BERGFELD: Fine, thank you. Dr. Stern?

DR. STERN: In terms of suggestions, in the package insert, I think rather than restricting it to to specialty, I think much as has been mentioned with chemotherapeutic agents, I think there should be a very strong statement that this drug should only be prescribed by those physicians who are expert in the treatment of the indicated conditions, and who are, and the alternative treatments in addition to this drug, to really focus in so physicians are aware that it should be used wisely and so there is the extra burden on the physician that they realize they are taking a responsibility.

I think also that one of the things we have not heard enough about, and I think if the pharmacist is still a professional and I believe he or she to still be so, I think another potential for greater interface is to think about not only educational material to be distributed in a mandatory fashion by the pharmacist, but also the possibility of consent. I understand there are problems with consent because it

it not always the person who is going to take the drug who obtains the drug, but perhaps in Accutane, we should require that the prescribee be also the person to obtain the drug as another, second way to have an interface with the professional.

Under other, and I do not think this is really an FDA consideration, but I think it is important as a public policy consideration, some of my differences with the presentation this morning is that I think that the magnitude of this problem varies among different groups who use this drug who vary according to the sophistication, their adherence to recommendations, their likelihood of becoming pregnant during the six month crucial period, and perhaps with respect to their quality of medical care as well. Certainly if I, on the basis of the data presented today, if these data from Michigan were reaffirmed and verified by the appropriate follow up steps that we talked about, if I were the Director of the Michigan Medicaid program, the first thing I would do is put in a second opinion option that is for women that this drug requires a second opinion. If I were to administer that program, I would put in a second opinion program, and there will be differences between physicians but I think in cases where there are risks as well as benefit, having two

physicians look over risk patients is good clinical practice, and when you consider the costs of that second opinion versus the cost of the care that goes on without it, I think it might well be justified, especially for certain populations.

DR. BERGFELD: Thank you. Dr. Stein?

DR. STEIN: I would agree with most of the recommendations given by the company and some of the additional ones already discussed. I have some other suggestions. I am wondering about the physician who does not read the package insert, and unfortunately, that probably is a problem. There may be a mechanism to have physicians as you referred to already, be called on by representatives of the company. Perhaps consideration should be given to additional publicity, even broadcast media. I do not know if that has been done, both to the patient and to the physician. A minor point, a package should be developed in Spanish, a blister package if you have not already done that, and I really am tempted to agree with some of the recommendations to restrict distribution, and I think we ought to give that further consideration. I am not sure of the best way to do that.

DR. BERGFELD: Thank you. Dr. Abel?

DR. ABEL: I would agree with the

recommendations so far, and especially with the changes in the package inserts by Roche as far as the physician's package and the patient. I do not feel the drug should be contraindicated in women of childbearing potential because it eliminates those women who are conscientious and will insure contraception.

I agree also, I would like to emphasize this need for the continued interface, interface between the pharmacist and interface between the obstetrician-gynecologist, and I think certainly a consultation is indicated before starting a patient, a woman of childbearing potential on this drug. I also think that we have to monitor the impact of all these changes and have follow up data on what the effect has been of this increased educational effort, and changes discussed today, and additional publicity, etc.

DR. BERGFELD: Thank you. Dr. Minus.

DR. MINUS: I would say that I would answer yes to all of these recommendations except number three, contraindicate the drug in women of childbearing potential because, as has already been mentioned, that would exclude as a matter of fact, most of the patients that I have seen have been in this category who have responded quite well to the drug. I am concerned, however, about a couple of things. Number one, not

only the cost, but I am worried about the poor and the undereducated. With the ability with all of the education we are talking about, it still is very difficult to get across to the patient a lot of whom I see about the dangers and the hazards. We see an increase in the use of cocaine during pregnancy and the problems relating to that, and I do not really feel that education in terms of packaging labelling is going to get to the heart. I do think if a physician is able to have the drug, to distribute to the patient, can have a better intellectual conversation with the patient to get down to the nitty gritty so that the patient understands the ramifications of the medication that they are about to take.

So, for that reason, under other, I would include of suggest that there be a redistribution or restricted distribution. The exact manner, I am not sure.

DR. BERGFELD: Thank you. Dr. Osterhous?

DR. OSTERHOUS: I would certainly vote yes for number A, but also feel that if the physician prescribing this does not feel that the patient is reliable or capable of not becoming pregnant, and there is no way to get an adequate gynecological consultation, then perhaps the doctor himself could be

made very well aware of restricting the use or denying that patient in the childbearing age the use of the drug. The labelling, yes, everything is fine if people will read it, if even doctors will read it, and I think again having what Dr. Stein said about having someone go and tell doctors, because I happen to know doctors do not read package inserts, and this is something that perhaps you have to stick in front of their faces and someone used the expression, behavior modification. Maybe this would be a good way to teach them again more awareness about the drugs that they are using.

Under other, Dr. Minus said it very well, and I would agree with him, that I think restricted distribution should be looked into.

DR. BERGFELD: Dr. Fleiss.

DR. FLEISS: I am in favor of A-1 and A-2, not A-3. Likewise, B-1 and B-2. Likewise, C-1. With respect to C-2 and the signed consent, I do not think it would do any good. It will not do any harm, but if this is like patients signing an informed consent form for participation in the research study, a day later they will forget what it was all about. But what is lacking here, and what I think is essential, reinforcement. Reinforcement every time the woman comes back and maybe more frequently, and those repeat

pregnancy tests, I was frightened by those data this morning on the mistakes, when they can occur, and it is too late, one day later even so repetition and reinforcement are so important.

DR. BERGFELD: Dr. Bergstresser.

DR. BERGSTRESSER: I will not be voting when it comes up to the vote. As I have gone through these, I think they are appropriate ideas. I am afraid that ultimately, none of the remedies are going to be satisfactory to various people who think that one failure is one too many. I think ultimately we are going to come to restricted distribution, and I am not quite sure of the system, but it will be obviously through experts who are tuned to the details of the treatment. I think that will limit exposure, it will allow for the systematic attention to the details prescribed in the drug, and also for data collection so I think the Committee may choose to recommend that today or maybe a year from now.

DR. BERGFELD: Dr. Penneys.

DR. PENNEYS: I agree with Dr. Fleiss so I will not repeat my vote. The only thing that I can think of that might be considered creative in the other category would be to include some restriction on refill of prescriptions and perhaps to have a maximum

allowable number of days per prescription. I realize that a physician could prescribe for three times the dose, and give a patient a three month dose on a one month prescription, but for most of us limiting the time period of a prescription and its refillability I think will one, have a behavioral modification on the physician and the patient, and two, might allow better follow up of these patients.

DR. BERGFELD: Thank you. I would like to call for a vote since the FDA will need a vote. I understand that Drs. Bergstresser and Stern will not be voting, and we will first call for a vote under Roman numeral II. The recommendations to change physician's package insert labelling, items one and two, all those in favor of those two recommendations, if you will show us by a sign of hand. Those abstaining? Those against. [The vote was seven for, two abstaining, and zero against.] So we are recommending A one and two. Under A three, contraindicate the drug in women of childbearing potential, all those in favor of that recommendation to contraindicate the drug in women of childbearing potential, please raise your hand. Those opposed. Thank you. [The vote was zero for, seven against.] The vote is to oppose number three.

Moving on to question two, Roman numeral

two-B, change patient labelling. I think we can put together items one and two. All those in the Committee that are able to vote in favor of items one and two, please show by sign of hand. Those opposed. [The vote was seven for, zero opposed.] Thank you. We are then recommending that Roman numeral two, B-1 and B-2.

Moving on to C, I think we will take up only C-2, which is to require patients to sign a statement acknowledging that they understand the serious adverse effects of the drug. All those in favor of requiring such a statement, please show a sign by hand. Those opposed? [The vote was seven for, zero opposed.] This is also recommended to you.

Taking up item under C-3, restrict distribution voluntary on part of drug manufacturers. This recommendation is under consideration. All those in favor of restricting distribution of the drug itself --

DR. MINUS: Can I ask you a question before you vote on that?

DR. BERGFELD: Certainly.

DR. MINUS: Exactly what do you mean when you have in parenthesis voluntary on the part of drug manufacturers?

DR. BERGFELD: Dr. Evans will answer that.

DR. EVANS: It is my understanding that we cannot require to restrict distribution. If the company agrees to it, that is fine, but we cannot require that that be the case. Jim, I would like for you to make more comment if it is appropriate.

DR. BILSTAD: I think that is the opinion that we have gotten previously from legal counsel. However, we certainly can revisit that issue further.

DR. BERGFELD: It would be appropriate at this time if we dropped that, and have the consensus of the vote be to restrict drug distribution, and leave it up to the FDA as to how they would do that. Dr. Abel?

DR. ABEL: Are we going to have a chance to discuss other changes that were recommended which may have an impact on the drug distribution such as the second opinion option that Dr. Stern referred to. This may help to restrict its use to its appropriate, restrict the drug to its appropriate indications and also limit its use if a second opinion were required before it is prescribed by another dermatologist, two signatures or by --

DR. BERGFELD: Correct. I think it would still follow under the category of restricting the drug's distribution though so why do we not take up the general category and then come up to the specifics of

our recommendation? All those in favor then of restricting the drug's distribution, if you will show by sign of hand. Three. Those opposed. Three.

DR. MINUS: Madame Chairman, I am still not happy with the way this is put. Part of what our recommendations, at least the way I feel about it, agreeing to or answering yes to number two and all the ones we have already voted on, if the company decided not to distribute it, I would be very unhappy with whatever else I have agreed on. I do not see how we can get around that, or is there a way to do it? I want distribution or the restricted distribution but if it is going to be voluntary, if the drug manufacturer chooses not to do that, then a lot of what we have already said yes to will be negated as far as I am concerned.

DR. BERGFELD: Commissioner Young?

DR. YOUNG: Maybe I could reply, let me reply in this way. The most important thing that we have to do now is, on this question, to be sure what our opportunities are through General Counsel, on the restriction of prescription drugs. It may be that when we revisit this that we will get a different opinion than we have had all along. To date, the advice that we have had from our legal counsel is that it is not

possible to restrict. We shall investigate that very carefully following this meeting.

If we are not able to restrict this in a mandatory fashion, then we would have to resort to either a change in the law which would enable us to restrict it, a modification in regulations which might enable us to deal with that, or a voluntary compliance, and since there is one manufacturer, we might be able to focus on that but we are in the midst of a legal analysis right at this time. Thank you.

DR. BERGFELD: It appears to me that the Committee, by consensus, feels that there should be restriction of this drug by some method. I would like to go over the things that were mentioned during the comment period to state some of the restrictions that you have actually put on this. We have dealt with four different areas, restriction of the actual distribution of the drug, restriction of two special physicians for distributing the drug, restriction of special patients who get the drug, and the necessity of having a second opinion in those high risk females. I see those as four different restrictions that we have discussed. Is there any comment about those four, or additions? Because we are making recommendations to the FDA, and even though, Dr. Minus, we do not have to say

specifically what restrictions and we do not have the ability to actually put this into being, we can still make recommendations how we think they ought to approach the restriction so I wonder if you make another comment, would it be satisfactory for you or have us present to the FDA that yes, we believe that this drug should be restricted in some manner, specifically to the high risk female who might receive this drug, and we are recommending expiration of four different methods if not others.

DR. MINUS: That is fine.

DR. BERGFELD: Any other discussion?

DR. DRAKE: Madame Chairman, would you please repeat the four options you just outlined?

DR. BERGFELD: These were options taken from all of your conversations. Specific drug distribution restrictions; restrictions on special physicians dispensing the drug; restrictions regarding special patients who receive the drug, and a restriction recommending a second opinion in those high risk females.

DR. BERGSTRESSER: Would you like a vote as to how various members feel on each one of these individual issues? Would that be helpful to the FDA?

DR. YOUNG: Yes, it would.

DR. BERGFELD: I would assume at this point there are no other restrictive clauses or categories to explore. Dr. Drake?

DR. DRAKE: I keep coming back around, instead of trying to define this by who can do what, I guess I would still like to come back to subject of education. Would it be appropriate to include in there a category whereby physicians who want to prescribe the drug must complete an appropriate CME course showing that they, in fact, have knowledge of the drug, knowledge of the adverse effects, knowledge of the whole thing. I mean, we might solve, I would still like to try to keep the focus on education and if they can show that they are knowledgeable, then I think that might solve some of our problems.

DR. STERN: In fact, I think Lynn makes a very good point. One of Sid Wolfe's group's recommendations was that only dermatologists who register with the company be allowed to prescribe the drug. Perhaps a more appropriate kind of thing is a registration based on not only saying I am a board certified dermatologist but in fact, completing a brief test, open or closed book, that you send in that you know and show that you have some knowledge of the indications and counter indications and the necessity for screening patients

appropriately. If you are going to do registration, you may as well do it based on demonstration of knowledge and just not on demonstrating what characteristics you have in terms of your past education.

DR. BERGFELD: Thank you. Any other comments regarding education? Dr. Drake, I think that is a marvelous addition to this list of four.

DR. YOUNG: Only because that is possibly a precedent, would you feel, Dr. Drake, that in general, in the prescription of medicines, that for each medicine in specialties, where there are risks, substantial risks, that physicians should have some sort of a signed affidavit before using it? I only raise this because you are recommending something which is different than has been done before. I do not want to prejudice the issue one way or another, but wanted to get your feeling on it.

DR. DRAKE: I think that is a very good point. I do not want to set a, I am not attempting to set a precedent, but I think there is some vague precedent in that doctors have to had a DEA number before they can prescribe certain controlled substances. I would like, I think I sort of just tie this in to Dr. Stern's comment that we have some kind

of program whereby we know who is prescribing it, and that we know they are conscientious with it. I do not think, as a general matter, it is practical. However, I think this drug is special. It is special because we clearly need it for a certain set of patients. There is no adequate substitute. This drug is also special because it does cause birth defects which none of us want, and I am just trying to find a common ground whereby we can still serve those patients who need the drug, and yet make some attempt to protect those patients who might suffer birth defects if they are not properly educated so I would like to make it clear that I am speaking with reference to this drug and this drug only. Clearly, it is special or we would not be here today.

DR. BERGFELD: Dr. Penneys.

DR. PENNEYS: I would like to ask Dr. Drake what her feelings are about doing the same thing for giving methotrexate to psoriatics who can develop serious consequences from that treatment. Are you implying that we then have to take course credits in order to administer a drug that can have serious consequences in that instance?

DR. DRAKE: Neal, if you look at the vote, I vote against restricting this drug, period. I think

restrictions of that nature are not useful. That is my personal opinion on it. But in fact, this panel voted to recommend some restrictions so in fact, if we are going to recommend some restrictions, I am just trying to put it in some mode that I think is more practical than just saying broad based, nobody of childbearing age can get the drug or broad based, only board certified dermatologists can prescribe it. I would like to see a little more rationale if we are, in fact, going to recommend restricting, I would like to see it based on some adequate rationale.

DR. STERN: What was the vote? I thought it was three to three.

DR. BERGFELD: The vote was three to three.

DR. STERN: So the Committee did not come out in favor of anything.

DR. DRAKE: Well, Madame Chairman just said the Committee voted to --

DR. STERN: She was incorrect.

DR. BERGFELD: I was incorrect. It was three to three.

DR. DRAKE: I am glad we got that clarified.

DR. BERGFELD: And we stepped away from having the chairman vote, and if I was voting, I would have voted to restrict it, and we went to a consensus

opinion that it appeared to be some consensus that we restrict.

MS. THOMPSON: Can you take a question?

DR. BERGFELD: Not yet. We will take your questions in a moment. We need to complete our agenda here. Again, let us back up a moment. It seems to me the recommendation of this Committee, these two, recommend to the FDA that they consider some restriction of the use of this drug, and we have illuminated five different areas. I would be hesitant in leaving this subject without stating that every one of the panel members mentioned education, and they mention education of the patient, the physician and the pharmacist, and I think it behooves us to again reiterate that statement or those statements.

It was also mentioned by the Committee that they felt that monitoring this drug now and in the future, was very necessary, and we would implore you, the company and the FDA, to continue your monitoring, and that you present to us at a later date the results of this and hopefully the conflicts of your base informations will not be so diverse because we are in a dilemma as Committee members trying to interpret your ability as statisticians to synthesize this material because we feel there is a problem but we do not think

your numbers are good. I think at this point we have completed the questions, and we have given our opinion as a Committee, and I would ask for any brief questions that might arise from the audience, and I would hesitate to say if you make them lengthy, I will cut you off. Are there any questions from the audience? Will you come to the microphone, state who you are and what your question is.

DR. LAMMER: Ed Lammer. I would like to make a suggestion, that assuming that these compounds are going to stay on the market, that especially all of the dermatology chairmen who happen to be present here incorporate into part of your training for dermatology residents how to talk to patients about contraception and particularly learn from the experience of pediatricians in dealing with young women who come in with their mothers to get prescriptions and that it be part of the training curriculum for dermatologists to learn how to deal with reproductive issues, and that is a place that we have to begin.

DR. BERGFELD: Thank you, Dr. Lammer. I would like to announce that this constitutes an open, public hearing.

MS. THOMPSON: I would like to know your definition --

DR. BERGFELD: Would you please give your name and who you are?

MS. THOMPSON: Marjorie Thompson. I am from Kentucky and I have been here in Maryland I think about six weeks --

DR. BERGFELD: We will need you to speak into the microphone. We cannot hear you.

MS. THOMPSON: I am from Kentucky. I am Marjorie Thompson. I have been in Maryland about six months. I would like to know your definition of dermatology. Is that a cosmetic of some sort? And I would also like to know if this is, causes birth defects in children, what then are the benefits of the drug, not only for childbearing women, but for maybe children, older people, and is this going to be restricted in what way?

DR. BERGFELD: I was hopeful that you had been here during the day since most of these questions have been answered during the day but I would like to respond to what a dermatologist is, and what the field of dermatology is all about. Dermatologist are medical doctors trained in medicine and have received their medical degrees. They are trained specifically in post-graduate training in diseases of skin, hair and nails, and again are medical doctors. The rest of your

questions, I am afraid, have been answered during the day, and we would be happy to give you a summary report but I do not believe we can address them all at this point.

MS. THOMPSON: Well, now, do you intend to limit this then if it has to do with skin and that sort of thing, and if it is harmful to childbearing women, or do you intend to restrict that in children under 10 or something and over?

DR. BERGFELD: I think if you been here today, you would know that this drug is used for severe acne, and it is limited to the use in severe acne and we are recommending as a Committee to the FDA that they consider restricting the use in the high-risk female who is the female in childbearing age. Thank you. I think that is all we can answer at this time.

MS. THOMPSON: Then the benefit is only for acne.

DR. BERGFELD: The benefit, it has many benefits, but it is specifically for acne at this point that we are considering it, and severe acne. Thank you for your comments. Are there any other comments? Yes, Dr. Del Vecchio.

DR. DEL VECCHIO: I would just like to make one or two comments in regard to some of the things

that have been proposed. I do not think, as a company, we would have any problem with the recommendation that this be used only by special physicians, specially-trained physicians. If the Agency feels it is appropriate, just dermatologists. We can say that, the only problem is, give us a way to enforce that or have the FDA develop a way to enforce that, the same with a second opinion on a prescription. We can make that recommendation. That does not carry the force of law. It just carries the force of pressure. Those are options that we have seriously discussed, and we think they may have some merit. The problem simply is there is no way that we know of at least that those are enforceable.

Some of the other things that have been suggested, I am not sure what is meant by restrictions to special patients. I thought that our proposal was designed to do that, but we are certainly committed to deal with the Agency on all of the recommendations in any way that they see fit, and we are more than willing to do what needs to be done to achieve the goals. If something needs to be done beyond our recommendations, if they achieve those goals, and we are convinced that there is no other way to do it, then we will certainly work in that area, and I just would like to express our

company's commitment to pursue that with the Agency under whatever umbrella the Committee wishes to leave this.

DR. BERGFELD: Thank you. We are making recommendations as an advisory committee to the FDA, and I am sure that you will hear later from them. This concludes the taking up of Accutane and its teratogenic effect. We are going to move on to our next agenda item. I realize that most of the audience will be departing. If you could do so quietly, it would be appreciated. We are going to be moving on to the update on the status of the patch test kits. In just a few moments, we are going to be hearing from Dr. Harold Baer, Chief, Laboratory of Allergenic Products. We will take only a few minutes so he can get to the podium and also so the group can leave the audience.

DR. YOUNG: If I could, just before all the meeting is adjourned on Accutane, I would like to just thank the Committee very much for joining in in this deliberation. I know it was a very rapid analysis of a large amount of data. It is an important issue. We will certainly take your comments under great advisement and consideration, and we appreciate immensely the opportunity for you and other members of the public to participate. Thank you very much.

DR. BERGFELD: Thank you, Commissioner Young. Dr. Baer will now present an update on the status of the patch test kits.

DR. BAER: A couple of years ago, it was decided that the kits used for patch testing should be subject to, pardon me? A little louder? It was decided that the kits which are applied to humans for patch testing should be subject to FDA regulation. A notice was published in the Federal Register, and it was supposed to be given to you, but unfortunately did not get here for some reason, which stated that these products would be subject to regulation, they would be considered biologics, and that they would be considered allergenic products. Consequently the primary reviewer of this product was the Laboratory of Allergenic Products.

There were just a couple of issues that we really were involved in. One is the question of labelling. Was the amount, could one show by analysis that the amount of drug claimed to be in the product really was there? The second issue was stability, to establish a dating period. Was it going to be there over some time course? The third issue was clinical, and that we wanted some data to show that the products actually work in target groups and to determine, if

possible, if there were any adverse effects. All of this information that has been included in the package enclosure, which will be part of the product. It will be sold, one product has been approved that manufactured in Germany, in Reinbeck, Germany, by Hermal, well, I do not know the whole name, it is a little complicated, Hermal to me. The information that they are going to sell, they have been approved to sell a kit of 20 chemicals which are listed in the package enclosure. They are sold as a kit not to be sold individually except as replacements for syringes which are currently in the kit, and I guess that is about it. If you have any questions, I will be pleased to answer them.

DR. EVANS: Dr. Baer, do you have one of the kits available, even with the --

DR. BAER: I did not bring a kit with me. It is a plastic box that contains 20 syringes. It is nothing very unusual about it.

DR. EVANS: Do you have the list of the allergens which you approved?

DR. BAER: The Committee had, it is listed in the package enclosure so the entire, those that have been approved, each of the members has that list of chemicals.

DR. BERGFELD: This list is in your package. Does the Committee have any comment to make at this time? We do have a couple of guests that would like to comment. Ed?

DR. TABOR: I do not know how much additional background might be of interest to the Committee. Dr. Evans, there was a lot of discussion that led to the decision of where to regulate this and how to regulate it, and perhaps you would like to outline that for them.

DR. EVANS: Well, as Dr. Baer indicated, we have had some oversight in patch test kits for since the mid-1970's, and there was a question as to whether we legally had this oversight, and as a result, we did not exercise it for long periods of time, and a number of companies were on the market and had the same allergens and we had no way of knowing whether there was any quality control in any of these ingredients, and through a series of circumstances that I will not go into in depth, but our legal folk were required to make a judgment on whether we positively had oversight over patch test kits or not, and they found out that we did. Since this judgment was made, of course, it meant that all of the ingredients had to undergo the same kind of quality control evaluation, that our drugs do,

and, of course, this took time, and of course that is information which many of the companies which had our patch test kits in the last 10 and 20 years simply did not have. It was further decided that Dr. Baer and his group in the biologics area had the experience with other kinds of allergens and they should be the persons who would evaluate the patch test kits so this has been ongoing with the folks from the North American Contact Dermatitis Society for, Dr. Baer, the last couple of years, would you not say?

DR. BAER: That is right.

DR. EVANS: And they have been very helpful to us and we have just reached the point where one patch test kit has been approved, and we have still got some ingredients in that which hopefully will be approved down the road, and we have others which are under evaluation.

DR. BERGFELD: Yes, Neal, Dr. Penneys?

DR. PENNEYS: I have a question. What about like orphan allergens? It is a dynamic field. Every day new chemicals are being introduced in our environment. People develop allergies to these chemicals. It is nice to have confirmed allergens that we knew were significant 20 years ago. What about the mechanism for addition and there are many, many

important allergens that are not in this list. Are we to continue to try to use them in a sub-rosa way, or is there some mechanism for introducing them?

DR. BAER: This is not a unique problem with patch tests. All allergenic extracts that we deal with, and that we regulate are in the same situation. There are basically two methods for getting those available. The quickest method is for somebody to apply for an IND, and to use it under those circumstances. The other is to have the manufacturer amend his license to include a new patch test material. I do not know of a third approach that is possible at this time although there is, in the regulations, one section that has an exception for certain cosmetics, and I do not remember what that section is, but there is such a section which exempts certain of those products from regulation.

DR. BERGFELD: Any other questions? Thank you, Dr. Baer. Dr. Thomas Jansen, the President of the American Academy of Dermatology, would like to make a statement.

DR. JANSEN: I would like to publicly acknowledge the cooperation of Dr. Baer and his group and Dr. Evans and his group for securing this improved report, a very important element of help to our

patients. I would recognize that there are additional antigens waiting in line to be approved that some of us perhaps consider to be more important than those that were approved, and would look forward to cooperating with you in every way, as in the past, to see that that can be accomplished very quickly. But again, I want to thank the cooperation that the Academy has received. Thank you.

DR. BAER: In terms of the importance of the ones that were approved, we reviewed those which the manufacturer submitted. This was their list, and we made no value judgment as to whether they were or were not the most important. We assume that if this is going to be sold that they would make a selection that dermatologists would like to obtain.

DR. BERGFELD: Thank you. Dr. Carnot Evans wants to make a remark at this time.

DR. EVANS: My only remark has to do with the fact that this is the last meeting of two persons, two doctors on the staff who have lent their efforts to us for the last few years, and they have done a superb job. I would like to thank Dr. Bergfeld, Dr. Rob Stern, for several years of great service, and I hope after you have an opportunity to catch your breath, maybe you will come back with us somewhere along the

road.

DR. BERGFELD: Dr. Peck?

DR. C. PECK: I want to add my thanks and appreciation to the Committee for I think an astoundingly well done job today. I asked you at the beginning of the day to provide us with, and I quote, reasoned, thoughtful, balanced advice, and we ask you to dissect and discuss the various points of view and to carefully advise us on the options, and in the Accutane area which was clearly a sensitive and topical area that had attracted the press, I think you really helped us to look at the issue straight on, and we will look forward to reacting to your advice. I would like to take this opportunity to thank Dr. Bergfeld for a masterful job at running the Committee for the day.

I would also like to acknowledge that this will be Dr. Tabor's last meeting with us in his current capacity, and I would like to acknowledge his several years of very productive and creative efforts in the center for drugs and in particular in the Division of Anti-infectives. Good luck to you.

DR. TABOR: Thank you very much.

DR. BERGFELD: I would like to say that I have most enjoyed my time at the FDA. I have not probably been one of the longest Committee members ever in the

institution since the early 1970's, and I think Rob thinks the same. We have enjoyed this, and we hope to be back with you sometime later. With that, I would say we are adjourned.

(WHEREUPON, THE MEETING WAS ADJOURNED)