just telling you that if you really think that they are going to have it in the office, and that is your intent, that is a mistake because they will not. If you are interested in making sure that it is a sensitive test, whatever fluid is obtained, then say so.

DR. NIEBYL: But the point is that the gynecologist might have the urine test in the office --

DR. HANEY: Absolutely.

DR. NIEBYL: -- and be doing the consultation for the dermatologist --

DR. HANEY: Sure. That is covered by a sensitive test.

DR. NIEBYL: I would agree. If you added the word "urine," you would have to add "sensitive."

DR. HANEY: Just say sensitive test.

DR. NIEBYL: Right.

DR. SCHROETER: At this point we have four proposals or four items. One has been brought up by Hoffmann-La Roche, recommendations for increased contraceptive efficacy. Is that correct? Does anybody want to address that? After that I think we ought to take up each one of these and focus on them. Does anybody have any recommendations on the last one?

DR. MCGUIRE: Since the representative of the Teratology Society brought up Norplant, I would like to suggest that that is probably not going to be terribly

successful in terms of compliance in the group of patients that we are dealing with. We are dealing with a population that needs to practice high quality contraception for a period of, let's say, five months, six months, and we are introducing a fairly expensive device that is going to provide contraception for three to five years. I do not think I am going to be successful in persuading patients to use that unless they are interested in long-term contraception.

DR. NIEBYL: Well, the main problem with Norplant is the problem we have heard presented here, that of irregular bleeding that occurs in at least 25 percent of patients. I think we have to educate patients about using effective contraception but, mainly, that is going over all the different ways of doing contraception and what is effective, and if the patient is using an ineffective method, counseling to use another one as well,for example, if she has an IUD, use condoms as well for those five months, or however you want to increase the efficacy. But it is through education about contraception.

I would think that increasing referrals to the gynecologists would probably do that as well as anything else. I do not expect a dermatologist to sit down and go through all the differential pregnancy rates with all the different contraceptives. But if more patients could have

the opportunity to discuss that it is absolutely critical that they not get pregnant for at least five months, they might choose to use either a more effective method or two methods at once.

DR. ROY: Perhaps the materials developed in conjunction with the American College of Obstetricians and Gynecologists could be updated in terms of at least mentioning Norplant. Some might use that as a contraceptive modality for the period of time for which it is intended.

DR. NIEBYL: But it has to do with patient compliance. If patients take birth control pills, that is usually more acceptable than Norplant. But if they admittedly tell you they miss their pills all the time and they will not use anything else Norplant might be an alternative.

DR. DAVIDSON: I personally believe that the current efforts at educating the patients about contraceptive use and choices, given the level of today's technology, are adequate.

DR. SCHROETER: At this time, let's focus on each of these four suggested changes and see if we want to make them specifically. Do I hear a motion -- and we will take the last one first since it is the most recent on our mind -- regarding changing the labeling for increased efficacy of contraception? Does anyone want to make a motion to change the labeling?

DR. MCGUIRE: From what to what?

DR. SCHROETER: From what is here. Let me read that for you. It is in the black box labeling: Effective contraception must be used for at least one month before beginning Accutane therapy, during therapy and for one month following discontinuation of therapy even when there has been a history of infertility, unless due to hysterectomy. It is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method.

DR. NIEBYL: There is no need to change that. That is pretty good.

DR. SCHROETER: Do I have a consensus? I see some heads nodding.

DR. SHUPAK: The recommendation is that in addition to abstinence one should use a condom?

(Laughter)

DR. SCHROETER: I think we should avoid comment on that. I will summarize and say that the two Committees, reflecting on the recommendation for increasing contraceptive efficacy as recognized in the labeling, feel it does not need changing.

Let's go to the sensitivity of pregnancy testing. Do I hear a motion to change the labeling? You will refer to the black box and I will read it as it is: ... has had a negative serum pregnancy test within two weeks rior to

beginning therapy. Serum. We will get to the timing in just a moment. Yes?

DR. SHUPAK: I move that the wording be changed to include a sensitive serum or urine pregnancy test.

DR. SCHROETER: All right. Do I have a second for that?

DR. TSCHEN: I would like to specify which sensitive urine for dermatologists' sake because we are not knowledgeable enough to know which ones are sensitive, which ones are not so sensitive and which ones are insensitive. So I think it should be specified.

DR. SCHROETER: And you said 15 mIU.

DR. DAVIDSON: But if we just say sensitive, won't the technical people deal with that? Are we supposed to put in the amount and what kind of test?

DR. SCHROETER: We cannot use brand names but we can specify sensitivity.

DR. NIEBYL: And type. We can say RIA or ELISA.

DR. DAVIDSON: But it may change.

DR. SCHROETER: Sensitive urine and/or serum testing. I have a motion to that effect by Dr. Shupak.

DR. MCGUIRE: Second.

DR. SCHROETER: Further discussion?

DR. FLEISS: How is it going to read?

DR. SCHROETER: Urine and/or serum pregnancy test.

DR. NIEBYL: Or it could just be "or."

DR. SCHROETER: And a description, 50 mIU.

DR. NIEBYL: If your argument is correct that the patient exposed two weeks after conception is still at risk, then it should be closer than two weeks.

DR. SCHROETER: We are coming to that.

DR. NIEBYL: Okay.

DR. SCHROETER: I want to focus on just the sensitivity thing. Are we clear on the motion? All those in favor, say aye.

(Chorus of ayes)

All opposed?

The ayes have it. It is unanimous.

Now let's go to the second issue on the timing of testing. Dr. Lumpkin, you have a quotation there that Dr. Barbo stated. Do you want to read that?

DR. LUMPKIN: I was writing this down very quickly as Dr. Barbo spoke. She said that the prescription would not be given to the patient until a report of a negative pregnancy test has been obtained or a patient has had normal menses. I hope I got that right, Dr. Barbo.

(Dr. Barbo nods in agreement)

DR. SCHROETER: Do I hear a second?

DR. DAVIDSON: Is this for the initial prescription?

DR. SCHROETER: Yes.

DR. BARBO: For the initial one I think they need both a negative pregnancy test and a period.

DR. NIEBYL: Because periods can be misinterpreted. Patients can have bleeding at the time of their expected periods.

DR. BARBO: Yes.

DR. SCHROETER: All right. Do I have a second?

DR. NIEBYL: But we are not there yet. We are not past the timing of the first prescription, are we?

DR. BARBO: I am talking about the first prescription.

DR. MCGUIRE: I have a question about mechanics. It sounds to me as if patients are going to receive their prescriptions for Accutane from the gynecologist, which is okay with me, but if I advise a patient that she is a suitable candidate for treatment and I give her a prescription with the admonition that she really should not have it filled until she sees her gynecologist, then she leaves the office and thinks, well, the pharmacy is on the way to the Safeway and so I will stop at the pharmacy and get the prescription, and as long as I have the prescription I might as well take it because I am going to see my gynecologist next week anyway --

DR. DAVIDSON: Two months.

DR. MCGUIRE: Right, if ever. So I think it is an

imperfect loop and I think we really have to consider the mechanics of it. I would be happy to give her the referral and give her the prescription, an unsigned prescription, and have the gynecologist sign it after she has the contraception consultation.

DR. NIEBYL: Just have her call you back and say that her pregnancy test is negative; make sure you get a report of the negative pregnancy test and then call it in. You are going to have to call it in every month anyhow.

DR. MCGUIRE: I can do that.

DR. HANEY: The gynecologist is not going to be willing to take the medical-legal liability of your prescription.

DR. NIEBYL: But he can fax you the negative pregnancy test.

DR. SHUPAK: I am a fairly pragmatic person. By interposing this obstruction, I think we are all going to be very unhappy with what is going to be going on in our offices. You see the patient; you go through the whole discussion and educational program; you get a consent form and so forth. To interpose yet another level here, like this, I think is unnecessary and complicated. It complicates the treatment of the patient. You just have to deal with them all over again on the phone or call the pharmacist and so forth. I do not see the necessity for it.

DR. SCHROETER: I am not sure that the motion really adds to it. All it says is that it should be done. Would you read it again, Dr. Lumpkin?

DR. DAVIDSON: A point of order, I had the impression that she was talking about subsequent periods and dosages, not the initiation --

DR. BARBO: No, I mean for both. I am concerned about the initial prescription when there have been a number of patients who were already pregnant and how you are going to catch those, as well as the ones who could get pregnant during the therapy.

MS. COSSMAN: As a consumer representative, I am having a real hard time understanding how possibly people can comply with this, as a patient. So I need to understand how someone walks through this and is able to not only see the dermatologist -- I mean, I feel real positively about a sensitive urine test. It increases access, number one, to something that is less expensive and, number two, you are dealing with a lot of teenagers who do not want anything that looks like an injection; they do not want anything that is invasive whatsoever. So urine testing I think is going to add to the opportunity for efficacy of a contraceptive program.

But I am having trouble understanding how a family dealing with a teenager that needs to go on therapy is going

to deal with gynecological issues, as well as dermatologic issues, and be able to follow a process of referral to ensure that you have the negative pregnancy test, that the prescription gets filled at the right time. Just explain this to me.

DR. NIEBYL: The dermatologist sends the pregnancy test to the lab, urine or blood.

MS. COSSMAN: Taken in your office?

DR. NIEBYL: Taken in your office, and sends it to any lab that does a pregnancy test, and simply gets the result before they call in the Accutane prescription.

MS. COSSMAN: Does it get called in or sent in?

DR. NIEBYL: It can be called in.

DR. MINUS: What you are doing is adding the burden on the dermatologist to draw the sample. They do not all practice like that.

DR. NIEBYL: If they do not, they should send the patient to a gynecologist because if it is a teenager who cannot figure this out, they are going to get pregnant. Send it to the lab; send them to the gynecologist.

DR. SCHROETER: The motion does not specify who will do it. It just says that it will be done, whether the dermatologist sends it to a lab, whether he wishes to do it himself and take that responsibility, or if he dose not want any of the responsibility he sends them to a gynecologist for

a second consultation. So it does not have to be done by the dermatologist and the statement does not imply that. Is that correct?

DR. BARBO: That is correct.

DR. SHUPAK: So when one gets the negative pregnancy test result, one calls the pharmacy and then one calls the patient because by now they have forgotten how they are supposed to take the drug. Right? So you are spending an hour on the phone in a second phase to this initial visit. I just think it is unworkable.

DR. NIEBYL: Pregnancy tests are available in a couple of hours.

DR. SHUPAK: What is wrong with telling the patient not to fill the prescription until you speak to the office?

DR. SCHLESSELMAN: I thought that this was a package insert rather than a detailed prescription for how you manage patients. It seems to me that we are getting into far, far too great a detail about this. The statement here says that effective contraception must be used at least one month before beginning Accutane therapy. Extraordinary statements are given in here about the importance of avoiding pregnancy and not prescribing to a woman who is pregnant. I do not think one needs to go through all these micro-steps.

DR. SCHROETER: That is left up to the physician and patient to work out. I do not think that you need to

consider that here.

DR. HANEY: We are considering those things here. That is what we are talking about. My suggestion is that you get a negative pregnancy test. The prescription should not be filled without a negative pregnancy test -- sensitive etc. -- and that the patient should be instructed not to take the drug until the second day of her next menstrual period. Women with birth control pills do that very well. They start those birth control pills on the second day of the next period without any problem.

DR. SCHROETER: That modifies it slightly. Have you got that, Dr. Lumpkin?

DR. LUMPKIN: Dr. Haney, tell me if I have this right. You were saying the prescription should not be filled until a report of a negative pregnancy test has been obtained, and the patient should be instructed not to initiate medication until the second day of her menses.

DR. HANEY: Correct.

DR. SCHROETER: Is that okay with you, Dr. Barbo?

DR. BARBO: Yes.

DR. SCHROETER: Do we have a second?

(Several members second the motion)

Further discussion?

DR. NIEBYL: I have a comment about within two weeks currently in the labeling. From the information

presented today, I think it should be within one week. Say, the patient came in the day before conception and had a negative pregnancy test, took the drug for two more weeks --

DR. DAVIDSON: They still have to wait until the menstrual period.

DR. HANEY: That is fine.

DR. MINUS: You are changing the word to "fill." So that means that you are putting the onus back on the patient to determine that. I think if you want to be sure, it would be better to say "given" than "fill." A lot of patients will go out and fill it anyway, no matter what is on the labeling and no matter what you tell them.

DR. SCHROETER: We have a motion on the floor. I do not have any suggestion for an amendment.

DR. MCGUIRE: Will you read it one more time?

DR. LUMPKIN: What I have right now is Dr. Haney's suggestion of the following, the prescription will not be filled until a report of a negative pregnancy test has been obtained and the patient will be instructed not to initiate therapy until the second day of her menses.

DR. MCGUIRE: How does the practicing dermatologist or the treating doctor control when the prescription is filled?

DR. NIEBYL: He does not give it.

DR. HANEY: You can do it different ways but I

think it is perfectly reasonable to call it in.

DR. MCGUIRE: That is the way I would do it but we have heard some resistance to that from Shupak and perhaps others. I am quite happy to call it in.

DR. SHUPAK: I like the motion the way it is presently worded because it allows the individual physician and the individual patient to get along in a proper way.

DR. SCHROETER: Let's call the question. All those in favor, say aye.

(Chorus of ayes)

All opposed?

One negative vote. That brings us to the changes that might be appropriate for indications of use. Do I hear any recommendations or motions to change the indications of use? Do you want me to read that again? Cystic acne -- by the way, according to our colleagues, that is not an appropriate word -- Accutane is indicated for the treatment of severe recalcitrant cystic acne and a single course of therapy has been shown ... I do not think the latter part of that needs to be changed. Do I hear any comment to change?

DR. DAVIDSON: From the discussions I have heard so far, it seems as if that labeling and definition is sufficient to cover what is practical now.

DR. MCGUIRE: Let me try one out on you, I am quite comfortable with this but we do see people who scar without

having what any of us would call significant cystic acne. I would like the word "scarring" in here because that certainly influences my level of care. Let's hear some discussion about that.

DR. SCHROETER: You are suggesting that in the indications and use we change "cystic" to "cystic-nodular and scarring acne" or "scarring acne?"

DR. MCGUIRE: Well, I am not thrilled about nodular but I do not care about that. I think scarring is an important description.

DR. SCHROETER: All right. Dr. Shupak?

DR. SHUPAK: Doesn't that go back again to the original clinical trials and the indication for the drug? We have to stick with the terminology that the original pool is based on.

DR. SCHROETER: Dr. Lumpkin is going to speak to that.

DR. LUMPKIN: The only point I was making earlier is that, clearly, the indications and use section will have to be based on the data that are in the adequate and well-controlled trials. That means that if it is the opinion of the Committees that you would like to add the word "scarring" the people from Roche and we can go back and look at the trials and see if there are data there that would support that kind of a change.

DR. MINUS: When you use the word "scarring," as we have already seen, we have a problem with the definition as it is, recalcitrant cystic acne. If you survey dermatologists, to answer the question that you asked earlier, it would be no, they are not doing it because there are all kinds of ways of interpreting that definition. If you say "scarring" and ask people as well as physicians what they mean, you would get a variety of opinions and I think you are just adding more confusion by putting "scarring" in.

DR. SHUPAK: We were given a consensus statement. Could we not leave it just as it stands and perhaps add parenthetically as defined by this consensus statement?

DR. SCHROETER: Read the consensus statement.

DR. SHUPAK: Oh, this is several pages.

(Laughter)

DR. SCHROETER: I know, it is. Did you want to summarize it?

DR. SHUPAK: Well, you can read their own conclusions on page five.

DR. DAVIDSON: Do we have a motion on the floor?

DR. SCHROETER: No, there is no motion on the floor.

DR. LUMPKIN: Just as a way of trying to answer Dr. Shupak, I was not here when the original indication was worded. I know there are people in the Division who were there. I think as we have gone back and discussed it, the

whole point has been that the nomenclature of severe recalcitrant cystic acne was never intended to be a definitive statement. It was intended to be a descriptive statement. Because of the toxicity that is associated with this drug, the point that the Division was trying to get across to the practicing community was that you have to think about the patients for whom you are going to use this drug; that it should be limited to those who have severe recalcitrant cystic types of acne.

As we have said earlier, if the definition of severe has evolved in the past ten years, the question before us is does the labeling still allow you to practice medicine as you think it should be practiced in 1990 with the terminology of "severe" as it is interpreted in 1990? That is what we are trying to put before you.

I am not sure I have heard today that you feel that this is limiting your practice but, rather, there has been a redefinition of the word "severe."

DR. SCHROETER: The original document, as it was reviewed in labeling, did not include scarring but scarring was implied. I know because I sat on the Committee at that particular time. So there is no question that scarring is involved in the process as it was originally labeled by the Company. In your criteria that was part of it; it was implied. Dr. McGuire?

DR. MCGUIRE: The consensus committee did take that into account in this document -- and I am not going to read it all --

(Laughter)

-- but I will read half a sentence: No nodules are apparent but the presence of scarring and a moderately severe papular eruptions would designate this as a severe case. In other words, we will use scarring to bump people up into the severe category, and I think that is quite appropriate.

DR. SCHROETER: Is there a motion to change the labeling? Are you satisfied with it as it is?

DR. SCHLESSELMAN: I guess I have a problem with the indications which uses the term severe recalcitrant cystic acne, which, so far as I can tell, does not appear in the classification of acne that is given here. How is one going to use this classification scheme that has just been developed with this package insert?

I think that there needs to be a revision and that it needs to, in some way or another, correspond to the new classification that has come out. Exactly what the words ought to be, I cannot say.

DR. SHUPAK: How about this, Accutane is indicated for the treatment of severe recalcitrant nodular and inflammatory acne?

DR. SCHROETER: Do you want to propose that?

DR. SHUPAK: I am proposing that.

DR. SCHROETER: Would you repeat it once more, Dr. Shupak?

DR. SHUPAK: All I am doing is substituting the usage of this position paper --

DR. SCHROETER: I realize that.

DR. SHUPAK: -- to say that Accutane is indicated for the treatment of severe recalcitrant nodular and inflammatory acne.

DR. SCHROETER: Okay. Do I have a second?

DR. MCGUIRE: I think you do but let me see if I have it straight, the consensus committee classified mild, moderate and severe. I am quite happy to take their definition of severe. Forget about cystic and forget about nodular because that all falls under the consensus committee's definition of severe. About half of our patients do not understand recalcitrant. What we intend -- and I use these words with patients -- what we intend is that we treat patients who have not responded to conventional therapy or other therapy. So far as I am concerned, we are talking about severe acne as defined by the consensus committee, severe acne that has not responded to other therapy.

DR. SCHROETER: The recalcitrant statement is one indicating that previous conventional therapy has been trie and has failed.

DR. MCGUIRE: I know that.

DR. SCHROETER: But this is not for patient consumption; this is for professional consumption. So it probably should remain in there but I will listen to the wisdom of the Committees. You had left it in, is that correct, Dr. Shupak?

DR. SHUPAK: Yes.

DR. SCHROETER: Do I have a second to Dr. Shupak's motion?

DR. MCGUIRE: We are using severe in the sense of the consensus committee?

DR. SHUPAK: I used the two words, "inflammatory" and "nodular" and they used "numerous or extensive papules and pustules and many nodules."

DR. NIEBYL: We can always say severe acne as defined by ... and include the definition.

DR. SCHROETER: Then you would still have to state it in there somehow. I still do not have a second.

DR. MCGUIRE: Well, are we going to lean on this consensus committee? Is this going to be valuable for us?

DR. SCHROETER: That is a question you have to answer.

DR. MCGUIRE: My answer is yes. I think we should use this.

DR. SCHROETER: All right.

DR. MCGUIRE: And I think we should use severe in the sense that they intended it because this is our best working group to define this mess, and this is the best they could come up with.

DR. SCHROETER: All right. If you will add "severe" to your terminology, then will I have a second?

(The motion was duly seconded)

I have a second. Any further discussion regarding the change in indications?

DR. FLEISS: One of the possible criteria for severity, according to the new set, is merely the presence of sinus tracks. Would that be sufficient to qualify a patient for this drug?

DR. BARBO: Yes.

DR. SCHROETER: Do I have any further discussion? If not, Dr. Shupak, would you restate it for the FDA so they can write it down so they have no question regarding the labeling?

DR. SHUPAK: Accutane is indicated for the treatment of severe recalcitrant nodular and inflammatory acne.

DR. SCHROETER: As defined by?

DR. SHUPAK: No, unless you have to reference it.

DR. SCHROETER: And we will reference it. That would be the appropriate thing to do. All right? Everybody have the wording in mind? All in favor, say aye.

(Chorus of ayes)

All opposed?

(The motion carries unanimously)

As you will recall, in your letter stating the schedule, we were scheduled through the evening hours, and dinner would be ordered. We are going to address the second question. I perceive that we probably will not need dinner and I would like to have discussion of that.

DR. DAVIDSON: Let's proceed and move along.

DR. SCHROETER: I see nodding of heads here. Let's move to the second question that has been designed for us: Do the Committees believe that the distribution of the drug should be restricted? If so, how? I think we should have general discussion first and then try to formulate an answer. Comments?

DR. FLEISS: No, I have seen no evidence that in any essential, sizeable way it has made a difference to practice or the consequences whether it is dermatologists or anyone else.

DR. SHUPAK: You cannot practice medicine by committee. So I would say no, no restrictions.

DR. SCHROETER: All right. Ms. Cossman?

MS. COSSMAN: In looking at the materials, it is very clear that to restrict access of this drug any further would increase restricted access to people who do need it.

So I do not sup[port any further restricted access to the drug.

DR. SCHROETER: Any other comments? Do I hear consent?

DR. DAVIDSON: Consent; consent.

DR. SCHROETER: Then I will state it in a positive sense: The Committee does not see any need to restrict this drug in light of present data provided to it at this time.

DR. DAVIDSON: So moved.

(The motion was duly seconded)

DR. SCHROETER: All those in favor of the motion as stated?

(Chorus of ayes)

All opposed? I hear no dissent.

At this particular time, are there any other comments by the Committees? Yes?

MS. COSSMAN: I guess I would just like to say thank you again for the opportunity for urine testing to be supported, and I thank all of the folks on the Committee. I guess it will support the Company as well since it increases access to a tool that may, indeed, hopefully, affect the outcomes of pregnancies.

DR. SCHROETER: As Chairman of the Dermatology Advisory Committee, I want to thank all the presenters for the concise and well thought out presentations, which have

made our decisions easier to make, and have been given without emotion and given with fact that has been sufficient to make very concise answers to the FDA. The preparation by the FDA has been excellent. The material was sent in reasonable time, and this is an advancement far superior to what we have had in the past. We appreciate that very much.

(Whereupon, at 3:35 p.m., the Committees adjourned)

C-E-R-T-I-F-I-C-A-T-E

I, Darinka Gavrisheff , the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

s/ Darinka Gavrisheff