risk, an increased risk of malignancy in humans. Assuming we -- if the FDA decides to allow this to go on the market, I think the company will have great difficulty conducting any more clinical trials where there's a placebo arm, because why would somebody volunteer for a trial once the drug is available? They can compare different doses, and they can look at the question of different doses for the people with low body weight, and they can look at the three doses -- there are a lot of things they can do for people receiving drug, but their ability to do placebo controlled trials is going to be limited once this drug is on the market.

So that -- and assuming people agree with that, that means that we have -- I think it's incumbent upon us to consider carefully what designs or what requirements would be appropriate to make sure that we get the information on long-term safety. And I think the committee needs to consider carefully what the strengths and weaknesses

are of a voluntary registry, like PSOLAR, or disease-based registry, versus using the Scandinavian population, where I'm concerned that there's not going to be enough uptake of the drug there -- even though that is a complete enumeration of patients and their outcomes.

I just am concerned that there won't be enough uptake of the drug in those countries to allow each individual biologic agent to be studied in terms of safety.

And so I think that leaves us with a restrict distribution, mandatory registry-type thing, like we do for Accutane. Even though that may not be perfect, at least it should allow nearly complete enumeration. And for those sites in the United States that have SEER registries, even if the patients are lost to follow-up, and I don't myself know what proportion of the United States population is covered by a SEER registry, somebody might know that here -- 20 percent,

you're saying? Okay.

The power may be limited, but at least they could be followed up in those sites in terms of their malignancies.

I guess I just want to argue for the committee to consider carefully that we can talk about randomized control trials after it goes on the market, but I don't think that they'll ever be powered adequately, because it will be so difficult to recoup patients to them, so we have to consider carefully what the alternate designs are.

DR. LEVIN: Another concern which was mentioned by somebody else before is the formulary issue, and the fact that if this drug is an expensive new brand name product, which it's likely to be, it will not be in the formularies of large, electronic databases such as health plans at VA and other places where we have a lot of enthusiasm about our ability to data mine, at least to look for signals of

problems, so I think we're going to be absent that resource for quite a while, because I don't imagine health plans like Kaiser and the VA are going to be quick to jump on putting this into their formula.

DR. HECKBERT: I agree with that comment completely. I do a lot of work in those settings, and they do not rapidly take up new expensive therapies until they are proven.

REPORTER: Turn your mic on, please.

DR. KATZ: People are discussing the later part of eight. Should we vote on the first part if we recommend?

DR. BIGBY: That's my intention.

DR. CALLEGARI: Do you want me to return? I can address that. I can discuss it later or I can address it now.

DR. BIGBY: Later. So I think that we can put this to a vote. Do you recommend approval of ustekinumab for the treatment of adult patients with moderate to severe plaque psoriasis? Those voting yes, raise your

hand.

DR. CRAWFORD: (inaudible)

DR. BIGBY: No voters raise your hand. Abstainers? So this was a unanimous yes vote. And let's start with Rob Stern.

DR. STERN: Yes, and you can imagine -- in fact, the conditions I would require for, in fact, the drug to be marketed are very much as has just been suggested, because otherwise we'll be in the same situation we are with the other biologics of being five years from now, having no robust information on what are critical questions.

I'll make two other comments.

One, if this drug is in clinical practice as effective as it has been in the clinical trials, it's likely to dominate the marketplace because of ease of administration combined with high efficacy.

And the second is an anecdotal observation, but for the drugs that I've used in my life, those generally that are more

effective have more side effects. So I've seldom run across the drug that's better and safer for a given indication, and that makes me concerned as I was earlier about what's the minimal effective dose and what the long-term toxicity is going to be.

DR. BIGBY: Dr. Katz?

DR. KATZ: I vote yes. And it says if the answer is yes, to answer the others. Could I answer the others?

DR. BIGBY: No.

DR. KATZ: My answer is yes.

DR. BIGBY: Tor?

DR. SHWAYDER: Do you want yes or no? Or do you want a comment?

DR. BIGBY: I want your name.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BIGBY: A yes or no, and a comment.

DR. SHWAYDER: Tor Shwayder. Yes. And my comment is, just thinking in the back of my head when a "me too" drug comes along and I

presume there's other me too drugs that will, it force the company to do these comparative studies that you guys are talking about.

DR. RINGEL: Eileen Ringel. Yes. With the comments already stated.

DR. HECKBERT: Susan Heckbert. Yes.

DR. DRAKE: Lynn Drake. Yes. And I voted yes because -- a minute ago, I said I don't know about the risk-benefit. That's still absolutely true, but this drug has the potential to be so powerfully helpful to patients, that I think there's an ethical issue here of keeping it from them. If there's something we know is we know it can help them. We don't know if it's going to hurt them, and so I think the answer is to make sure there's proper follow-up studies so that we can identify any early markers. So I'm voting yes, because I think ethically, we have to make this available to our patients.

DR. CRAWFORD: Stephanie Crawford. Yes. And like panelists Katz and Levin, I can't wait until we get to 8B.

DR. LEVIN: Arthur Levin. Yes. And I just want to mention there's another ethical issue, because if this is not picked up by health plans, by Medicaid, et cetera, there's going to be an economic rationing issue here, which is we're going to have a wonderful product that's available for people who can pay for it out-of-pocket or who have health plans that are more generous in their drug coverage, and not available to the rest of the population.

DR. THIERS: Bruce Thiers. I voted yes. Dr. Stern really took the words right out of my mouth. It's the efficacy of this drug that scares me most in terms of potential long-term side effects. So there's going to have to be very close follow-up with patients who are using this drug.

DR. BIGBY: Michael Bigby. I voted yes, and my comment in this section is the same as in seven, and that is if you compare it to what else we have available, at least based on the information we have, the

risk-benefit looks good.

DR. MAJUMDER: Mary Majumder. Yes, and I'll keep it that brief so we can get on to discussion of all those conditions.

DR. BIGBY: So I think since no one voted no, we can skip down to Section B, unless the Agency objects.

Describe the recommended dosing regimen and the length of treatment. So, comments? But I mean, I think we've kind of discussed the former part of that. The length of treatment issue is I think a more open one.

DR. SHWAYDER: I just want to restate what I said before, that I'd prefer things be left in a suggestion rather than a mandatory, A, so the insurance companies don't restrict you; and B, so you have some variety when you have a heavy or a light person.

The second comment is, it will take Centocor about two New York seconds to get out the advertisements that four times a year

with a shot is cheaper than four times a week with UVB. And I know that at my hospital, when biologics came along, suddenly they started covering UV when they didn't before, because it was a lot cheaper than the biologics.

DR. KATZ: I hate to sound like a broken record, but the first part of B says, "Describe recommended dosage and regimen length of treatment."

We can't say length of treatment, but the dosing regimen, I would still object to here. With the lower-weight patients, they have a total of 13 patients that we're making a recommendation on dosing at the same dose as people who almost weigh twice as much, when we know it's a dose-dependent response. And the minimum effective dose would be important on those patients.

DR. STERN: I guess all Roberts are broken records. In addition to the minimum effective dose, I think we do need a study on

re-response in individuals who have discontinued therapy and whose psoriasis has come back because that will clearly affect strategy. I think as Robert has implied, generally we tend to reduce dose in people on maintenance and try to get them off. It's a little bit different consideration if this is a once in a lifetime drug. So since we have experience with efalizumab that suggests that, I think we should require the sponsor in reasonable time to do such a study in terms of effectiveness with second courses of therapies.

DR. LEVIN: Just a point of information from FDA. I mean, as I remember, most labeling does have a recommended dose and duration, and also reports on the evidence from the approval trials. It does both. So that would be -- despite the sentiments around the table that this is an individual patient-physician decision. The fact is that labeling requires some general parameters based on the approval trial evidence.

DR. GUZZO: I do have some data if you want me to --

DR. LEVIN: I'm aware of the data you have in terms of when you have in terms of when you re-treated people when they lost 50 percent of their PASI gain. I think often, we have patients who go a bit further than that and they're off treatment longer than I think was up to about -- not very many patients beyond 20 weeks off treatment in terms of reintroduction. And this is, you've got to remember, biologic affect for drugs where I came from is eight times the half-life and 24 weeks would be eight times the half-life of this drug before it's really gone from the system.

So in terms of my question, I don't think you have substantial data with people off for 24 weeks who have had substantial recurrences. And I think that's an important clinical issue in terms of rotational therapy, alternative therapies -- and not that I'd hold it up in terms of approval, but

I think it would be very useful to know that information in treating our patients for psoriasis.

DR. GUZZO: I just wanted to make you aware of the data we submitted.

DR. BIGBY: Hold on a second.

DR. WALKER: Just to speak to the labeling question. One of the goals of labeling is to provide information to inform physicians and their patients in making informed clinical decisions, and we do have one example, though, of a relatively restricted duration of use that I think may be useful to the committee, and I'll ask Mark to describe that.

DR. AVIGAN: I was going to say something along those lines, which is that often in the label for chronic ailment, there will be an instruction or there will be a description of the longevity of the clinical trial, with a stipulation that beyond a certain point, the risk is not known, or the long-term effect is not known.

And we have had occasions where there was a fact of risk over time that built up so that the short-term use was not a problem. But the indicated use was for a condition which was chronic. So even though the label was somewhat legalistic and said that it should be used for short-term use, in reality, this particular drug, it was one of the anti-inflammatories, was used in practice chronically, and the risk emerged, because in fact, there was a time-dependent factor.

DR. STERN: I would add, though, in our clinical practice, there's a once very popular treatment for psoriasis where there's clearly a dose-dependent effect, quite safe for up to 100 treatments, medium safe for up to 200 treatments, but after that, substantial carcinogenic risk, and that's obviously PUVA.

DR. DRAKE: Earlier on, I talked about first-in-class, and I want to clarify what I was saying a little bit. Having started with this process with the first biologic -- Rob and I

were both involved in this very early -- I think part of what you've heard is that any drug, and there are others that might suppress IL-12, might suppress other things. So there are others that have been proven over time to be fine; there are some that haven't been proven. And my sense is that, at least from my perspective, is I want to know the answers to these questions. We're six years out now and we still don't have much information.

I would really encourage the sponsor and the FDA to try to come up with some way to help gather that information, not just on this drug, but anything else that might suppress specific things that could potentially cause us problems on down the road. I don't have a magic answer, but if you have to convene a special group of experts to come up with design and protocols, and work with sponsors and experts, I would really encourage you to do that, because I think this whole issue of unanswered

questions you've seen bog us down big-time today. And I think this is a perfectly good drug. It's a wonderful example of something that potentially has powerful efficacy, but could have had a different outcome today had we not had these substantial questions. And it might have moved much quicker had we had these answers to these questions. So I just want to encourage you to try to do whatever you need to do to capture this information.

Thank you.

DR. BIGBY: I saw somebody else reaching -- Tor or Eileen? No? What was it that you were going to provide just now, the sponsor?

DR. GUZZO: Treatment data. Dr. Stern said he was aware of it.

DR. STERN: As I recall the data from last week, you reintroduce people when they lost 50 percent of their PASI, but there were relatively few people who were more than 20 or 24 weeks from when they'd stop drug, which is

still within eight half-lives of the drug.

So to me, there weren't sufficient numbers of a sufficient period to really talk about reintroduction of the molecule. And for clinical reasons, I would like to see a study that was designed to really look at effectiveness of the second course.

But you --

DR. GUZZO: Second course.

DR. STERN: You have the slide picked out?

DR. GUZZO: I also have additional data that hasn't been submitted to the Agency, but I don't know if --

DR. BIGBY: Show it.

DR. GUZZO: Slide up, please.

DR. CRAWFORD: I must ask, though, why do you have additional data that's not being presented to the Agency?

DR. GUZZO: These are ongoing studies, so data continually comes out with additional database locks.

So this is just additional data in larger numbers of patients and their re-treatment data. So here, we have 32 percent of patients responding four weeks after re-treatment, 71 percent eight weeks after re-treatment, and 85 percent 12 weeks after re-treatment. And the ends go up to 150 patients. And so this comes from --

DR. BIGBY: And the period of no treatment was how long?

DR. GUZZO: It's variable for each patient. But it can extend from -- this goes up to a 76-week database lock. So they stop treatment at week 40, and then the next database lock would be at week 76, so this is where this comes through. So these are patients who were re-treated through that week 76 database lock.

SPEAKER: Their last treatment was week 28 --

DR. GUZZO: Yes. But they have (inaudible) on board until week 40.

Your question?

DR. SHWAYDER: Is this a single shot?

DR. GUZZO: No. It's two doses. It replicates their initial treatment of zero and four. They receive zero and four again when they're reintroduced to treatment.

DR. SHWAYDER: So when it's labeled, it will be 0, 4, then 12, 12, 12, and then we don't know beyond that?

DR. GUZZO: The proposed labeling is 0, 4, with every 12-week therapy. This treatment was -- this was obviously done to address questions. We know that patients come off treatment. We know that they switch on to other treatments. We know that they go back to treatments. So patients were allowed to lose 50 percent of their PASI response and then be re-treated. And just to bring up the issue of antibodies which was discussed earlier, we actually measured antibodies in these patients. Ninety-seven percent of them were drug-free and the antibody rate was about 5 percent.

DR. SHWAYDER: I'm sorry. I need to

go to the dosing regimen again, because I'm still unclear. So what are you going to tell the FDA? Are you going to say, 0, 4, 12, 12, 12, until Christmas? Or are you going to say X amount of time off the drugs, start again 0, 4, 12, 12, 12?

DR. GUZZO: So the proposed labeling is for 0, 4, and then every 12-week treatment for chronic therapy. And of course, it is the physician's judgment how long a patient should stay on individual therapy.

DR. SHWAYDER: Because then -- yeah, again -- all right, here's my experience. So Protopic did a study, 0.03 versus 0.1. It was statistically moot below a certain age, so the company, they were no idiots -- took them a third amount of dose, a third amount of active drug, and therefore the insurance companies won't cover it -- 0.1 under a certain age, but my colleagues in England use only 0.1 because they don't think 0.03 works.

So I don't want this to happen with

this drug, where I know I have a subset of patients that's going to need it every four weeks, and yet I can have an insurance company telling me I can only give it every 12 or they're not going to hand it to me.

DR. STERN: But I think the other side of this is -- at least in the patients I manage with Enbrel, there's sort of the psoriasis paradigm which Dr. Katz has talked about, and there's the rheumatoid arthritis-rheumatologist paradigm where they keep people on -- then psoriatic arthritis -- they keep people on TNF-alpha inhibitors who have had no perceptible symptoms for months and months and months, and we generally -- at least I don't, when a patient's clear of psoriasis, I start backing off -- whether it's Enbrel, or UVB, or whatever, or methotrexate.

And this labeling would be more along the rheumatoid arthritis-rheumatologist approach to these chronic diseases than how we've treated cutaneous psoriasis.

The risk is bound to be in fact more than linear with time on.

If there is an increased risk of cancer, that risk at least is going to be more than linear with time on immunosuppression, which every immunosuppressive agent has shown to be the case where that affects cancer risks. So I think that recommendation is not how many of us practice for cutaneous psoriasis, and is clearly good for the company. And if you think about it, you know, if the perception is of safety, wouldn't you like to have one injection four times a year forever and keep your psoriasis away?

DR. BIGBY: I think to move on, this is not a vote-able question, so I think what we'll do is just go around and just make a comment about recommended dosing regimen and length of treatment, starting with Tor.

DR. SHWAYDER: I would say present --

DR. BIGBY: Name.

DR. SHWAYDER: Tor Shwayder. I would say present the data as given, as a recommendation, but not as a mandatory.

DR. RINGEL: I think all we can do is state what the company has done in the label, and there's no other information.

So that's all we can say.

Eileen Ringel.

DR. HECKBERT: Susan Heckbert. I agree with what the company's recommending as long as the label indicates that that's all the information, that the information presented is all the information we have.

DR. DRAKE: I'm thinking.

DR. CRAWFORD: The dosing regimen, my comments earlier about my desire for a mid-tier dose still stands. The length of treatment, I have no comment on. Crawford.

DR. LEVIN: Arthur Levin. Again, I think we follow what labeling has always been, which is the company submits a recommended dosing and duration and the evidence from the

approval trials is presented in the label. And clinicians have always been free to do with that what they want to do. Insurance companies are also free to do with that what they want to do, but we can't deal with our health care system reimbursement mess in this setting.

DR. THIERS: Bruce Thiers. I agree. We just present the company's data, and we might indicate that some patients may respond to different dosing and duration of treatment regimens.

DR. BIGBY: Michael Bigby. I actually have no objection to the dose availability or to the dosing regimen in terms of two doses, four weeks apart then every 12 weeks. I think we don't have sufficient data to talk about length of treatment. And I think that, at least in part, will sort out during practice. And I do think post-marketing surveillance will be very important, because I do think it's going to be used on a chronic basis.

DR. MAJUMDER: Mary Majumder. I agree with the prior statement.

DR. STERN: Nothing to add. Rob Stern. Nothing to add.

DR. KATZ: Robert Katz. Nothing to add. I've expressed my objection to the 13 patients at 50kg, which hasn't been addressed.

DR. BIGBY: Lynn?

DR. DRAKE: I agree with what's been said pretty much around the table. I think we should go with what the company has done, because anything else will hold up the approval process, and I don't think we ought to do that. I would encourage the sponsor to please look at minimal effective dose when they're planning their next round of studies. I think that would be very helpful.

DR. BIGBY: For the next question, with your permission, I think that we should just put this to a vote and then hear the comments. Does anybody object?

DR. LEVIN: Just a point of

clarification. If the drug becomes unstable, what does that mean to a patient? I mean, I have epi pens because I'm allergic to certain insect stings, and it tells me look at the clarity, but I'm never really sure what that means. I think it means it might not be effective. Is it the same thing here? So if it loses stability, I mean, if it gets this particulate or whatever, what does that really mean?

DR. LEVIN: One of the concerns that was expressed about self-administration was could patients recognize when the drug was appropriate for administration by anybody or not. And there was some issue about -- I don't know whether it was stability or particulate matter or something like that. I want to clarify that issue.

DR. CALLEGARI: It should be no different than any of the other drugs that come as liquid in vial. Certainly, the biologics have been that way. To clarify the point, the

drug is not shipped at all in advance. The drug only goes to the patient at a specific time and at a specific place after the physician has sent the prescription to the managing pharmacy to get the drug shipped. If the patient isn't there, the drug isn't left. If the patient isn't contacted, the drug isn't shipped.

DR. BIGBY: But the question was, if the contents of the vial are cloudy or do not meet the prerequisite for appearing to be active and they inject it, what is the consequence? Does it just not work? Will they die of anaphylaxis?

DR. CALLEGARI: I don't know if there's any human data on that. Certainly not from our clinical trials. We know that we will instruct patients that if it's cloudy, not to inject; we will replace it. But I don't think anyone's studied -- yeah, as long as it's within the shelf life. I don't think anybody's studied that.

DR. BIGBY: Why don't we do this in

this way: should the product be labeled for self-administration? Those voting yes on this, raise your hand. Those voting no, raise your hand. And abstentions?

I think we can start with Robert and just go clockwise.

DR. KATZ: Robert Katz. I don't see the problem here. Enbrel is self-administration. It's sub-cu, and it's not a problem.

DR. BIGBY: It's a preloaded syringe.

DR. KATZ: But before it was preloaded -- I had great difficulty doing it myself, but patients seemed to manage doing it. The prefilled syringes are great, but it is more cumbersome doing it this way.

DR. STERN: My issue with this is if we have any prayer of having a complete follow-up, we're going to have to tie in some way the administration of the drug to the medical establishment. And in my experience,

all the patients I've ever given home UVB only come to see me when there's a problem. And if one of our strategies is more information, having patients doing it on their own just will make a difficult process impossible.

DR. BIGBY: I forgot to give the summary for self-administration. There were four yeses, seven noes and no abstentions.

DR. MAJUMDER: I just don't think there's a one size fits all, and if it's prescriber only, then you can't say, well, this is a very sophisticated patient, we have a great relationship, so I'm going to give them the convenience of self-administration, because you only have prescriber -- whereas if you approve it for self-administration, that's not mandatory. If there are issues, you could still bring particular patients into the office.

DR. BIGBY: I must say that I think -- you know, when you start talking about having patients check the vial for cloudiness, it just makes me a little

nervous, so it is such an efficacious-appearing drug and the duration of therapies have to be long enough that -- I mean, I think at least some monitoring of how it's given and what the effects are would be useful.

DR. THIERS: Bruce Thiers. I think for a drug like this that's going to be quite expensive, having a patient come in every three months for follow-up just to make sure they're responding is worthwhile, and also obviously to make sure they're not having any untoward side effects. So I think a visit to the doctor every three months at the time of the visit is not asking too much, and I think the fact that the injection would be given then would give them more incentive just to show up for their visit.

And in contrast to what was said at the open public hearing, dermatologists don't make any money treating psoriasis. It was mentioned that we need to have the patient come in so we could bill the patient.

Personally, from a financial standpoint, I'd rather have somebody come in and freeze a wart. Treating psoriasis is very rewarding because we have a lot to offer patients, but economically, it doesn't do much for us.

The only problem with having it administered in the physician's office is that it makes it logistically difficult. The drug would have to be shipped to the physician. Otherwise, if it's shipped to the patient, the patient would get this container on dry ice, presumably, and have to rush to the doctor's office to get it injected, so it would have to be shipped directly to the physician's office.

DR. LEVIN: I voted yes although I certainly share the concern about data collection, but I think there are probably ways around that. I like the notion of patient empowerment, and the logistic issue is certainly an important one. If we think it's so important to get this drug out to people, then we have to

make it pragmatically possible for people to use it.

DR. CRAWFORD: Stephanie Crawford. I voted for prescriber, or at least office-based administration. These initial years, we need more monitoring for this very promising new product because it's been well-stated -- there's the opinion that there's currently a lack of sufficient long-term data, especially on safety.

Secondly, the sponsors did talk about there would be training on self-administration. That's only part of it. Again, I have far less concern about that, but there was no description that I heard about what that training process would be if there were self-administration.

Thirdly, and I absolutely take seriously the comments that were made in the open hearing -- I'm hoping that if there's office-based administration, it would be both in monitoring efficacy, in this case effectiveness, as well as any safety concerns

that would go on, because we all know -- we might not remember if we took one pill in the morning, much less the exact time -- and the way we administered a subcutaneous dose during certain 12-week intervals.

DR. DRAKE: I voted for office-based delivery because --

DR. BIGBY: Name.

DR. DRAKE: Oh, sorry. Lynn Drake. I voted for office-based administration because I agree with the comments from my like-minded colleagues.

DR. HECKBERT: Susan Heckbert, and I voted for prescriber administration for exactly the same reasons that Robert Stern gave.

DR. RINGEL: I'm Eileen Ringel, and I voted for patient self-administration because I think doing it any other way is going to be a logistical nightmare. I was trying to think my way through this. If the patient has delivery of medication and needs to keep it at 2 to 8 degrees and I'm on vacation, I'm trying to

figure out exactly how this is going to work if he gets the medication before coming to the office.

If I have to purchase this medication, it's going to be extremely expensive, and I as a private practice physician have no intention of putting up that kind of money and potentially losing it if my patient doesn't feel like coming in. We've been through that with Amevive. It hasn't worked well.

I think the control should simply be the physician who refuses to prescribe the medication unless that patient comes in with a visit. And if you want to be really Draconian, you can have the physician sign a form that says, yes, I saw this patient, and he brings that little form to the pharmacy or whatever -- or sends it to the pharmacy when they pick it up. I don't know that that's necessary, but few physicians want to perjure themselves, and I think that would be a

control on the physicians.

I'm not saying you need to do that, but it would be an option. I also think that that way would also encourage them to participate in any registry that we might come up with.

DR. SHWAYDER: Tor Shwayder. I vote it to be given in the doctor's office for several reasons. Basically, there are a lot of stupid people out there, and they're going to blow it -- and my apologies to the people who are in the audience, but I've had young lady who I gave explicit instruction in how to use her cyclosporine and came back and she was taking three times the amount that I told her to take. So slips do happen.

Secondly, you need the quality control of the vial. Thirdly, you need the follow-up for the malignancy. Fourthly, it's not just going to be dermatologists using this stuff -- and I've had the following thing sent to me by family doctors labeled as

psoriasis: Pityriasis rubra pilaris, psoriasis like anoytes (?), eczema, mycosis fungoides, et cetera. So I already know there's going to be somebody who's going to be prescribing this and I'm going to see them on follow-up and I'll say, mein gut, this wasn't psoriasis to begin with, what are you using?

DR. THIERS: Michael, can I ask a question, please? Maybe Susan could answer this question. If a drug is office-administered, does that by definition mean that the physician has to buy it? I mean, can't the patient purchase it, have it shipped to the doctor's office?

DR. WALKER: I don't think it necessarily means the physician has to buy it. There are a lot of complications surrounding some of those delivery systems, but to answer your question, I don't believe the physician has to buy it.

DR. LEVIN: Maybe the pharmacist

amongst us can answer the question, what does state law require? If a prescription is written to an individual, that that either be picked up by that individual or it be mailed to the home address of record of that individual? Is that what state law requires?

DR. CRAWFORD: I'm sorry, I can't answer. Each state might have different laws.

DR. LEVIN: What would Illinois require?

DR. CRAWFORD: I don't know. I told you, the state of North Carolina thinks I'm a pharmacist.

DR. BIGBY: Very briefly.

Go ahead.

MR. BOSCIA: Hello, I'm Jerry Boscia from Centocor. Just a point of clarification. The specialty pharmacy will inspect the vials. Then they will draw up the ustekinumab into the syringe, and it will be the syringe that is delivered to the patient and then the patient administers it. Just that clarification.

DR. BIGBY: But like an hour ago, you said it goes in a vial.

MR. BOSCIA: That's the first time I've been up to the microphone.

DR. BIGBY: No, no, I mean, what came from there before.

DR. GUZZO: (inaudible)

REPORTER: You need to go to the microphone.

DR. BIGBY: So with that confusing end to this discussion -- I mean, that was not what was presented to us. What we heard was that the patient was going to get a vial that they had to take it out of and inject. So I don't know where you -- I mean, I think you're going to have to work this out with the Agency in a meeting, but I mean, given what we were presented with, this is how we voted, and I'm not sure what -- I mean, how you want to proceed.

But we are over time, so I think we need to discuss the last issue and that is

three, are the applicants risk assessment proposals sufficient to characterize the long-term safety of ustekinumab?

DR. KATZ: That's better than Bruce would have done.

DR. THIERS: Much better.

DR. BIGBY: Open for discussion.

DR. CRAWFORD: Thank you. Stephanie Crawford. First, I'm a little confused now. Certainly, the expanded proposed risk management program was moving more into the right direction, but based on that last comment, I'm very concerned. It seems to be a moving target. So part of this is, I want to state I am concerned about -- it's such an important aspect of our consideration of this drug, I'm concerned about the last-minute provision of this expanded risk management plan, and the lack of sufficient details provided to the Agency in advance.

I ask that the sponsor's slide 155 be displayed, because it's a point of clarification as we're looking at these last

sets of questions under 8(b)(3).

I want to ask the Agency, should we address the questions as asked, or based on what we saw this morning for the risk management plan or the addition we just heard two minutes ago that was a change from what was stated before?

Also, if it is proposed that there be specialty pharmacies involved, I don't really see in slide 155 what is the role of those specialty pharmacies in terms of collecting data on safety, and to some extent, efficacy.

DR. WALKER: I think one of the best ways to provide us information in answering this question is to give us an understanding of the degree of rigor committee members feel is necessary in order for us to obtain safety data on this product.

So we're really looking for -- you know, different plans have different degrees of rigor, and as we look at the types of

plans that are possible, I think I've heard today a variety of advice, so we're really -- we're looking for information about what you really feel is an appropriate level of rigor for post-marketing surveillance for this product.

DR. LEVIN: A point of clarification. Would you equate restricted distribution with specialty pharmacy, that the sponsor is talking about? Is that --

DR. WALKER: No. I mean, it can be a component, but that alone is not.

DR. AVIGAN: Just to clarify that point. The restricted distribution idea as a concept is that you give the prescription with the proviso that there's a gate-keeping step of some kind, some measure, some interaction, some test. The fact that you have a specialty pharmacy can be a device that's useful for marketing, or it can be used as a gate-keeping step. But they're not necessarily linked.

DR. BIGBY: Just a point of

clarification. Is there any other drug currently marketed where this method of distribution exists where the pharmacy draws a single dose up in the vial and sends it to the patient on ice?

DR. DRAKE: What's it called, Avastin? It's the drug for building up your bone marrow when you're a kidney patient. The specialty pharmacies send it out in a pre-drawn vial. It's on ice. It shows up at your house. It's not Epo -- what's the next -- it's called Aranesp. Aranesp is handled that way.

DR. CALLEGARI: Excuse me, just to clarify, and I apologize to my colleague for the confusion. The drug is shipped in a vial, liquid in vial, with a syringe to the patient. And so it is not in a prefilled syringe, it is shipped in a vial.

DR. BIGBY: Did the other gentleman just say that it was shipped in a syringe?

DR. CALLEGARI: He did, and that's why I'm apologizing for the error.

DR. BIGBY: Okay.

DR. STERN: Is this your final answer?

DR. CALLEGARI: Yes. And I can't call for a lifeline and I'm sort of stuck here.

DR. BIGBY: So I think in that regard, the vote that we had is a legitimate vote then.

DR. BEITZ: Yes. Could I just clarify from Centocor that when you are shipping these vials to patients, this assumes that you have a knowledge of who these patients are, so that is in essence a registry, and patients have to be on this list so that you know who to ship to.

DR. CALLEGARI: That is correct. Every prescription that the physician writes, as it's sent to the specialty pharmacy provider, needs to identify the person, the place, and ultimately the specialty provider -- in this circumstance -- I mean, that's what happens. Both Embrel and Humira use specialty provider distribution networks as well, so it's not such a unique thing. Virtually -- that's how they

get distributed. They use that distribution network through more retail pharmacies. We actually, to sort of limit the likelihood of mis-prescriptions, we really move toward centralizing that through a centralized SVP, which would account for -- and this includes 8 to 10 large pharmacy plans across the United States. The whole United States is bracketed with that program, and so it allows direct tracking, but it also allows the intervention.

I mean, I know there's been a tremendous concern about in office -- you know, the need for in-office injection, the question about self-administration, but what this allows is regular personal contact with the patient prior to each injection. It also prompts patients to schedule follow-up visits with their dermatologists, reminders for the next dose, and with each delivery, patient education tools can be delivered with each delivery.

DR. CRAWFORD: Thank you. I heard

prior to each delivery -- what about any reactions immediately afterwards or any problems in utilizing?

DR. CALLEGARI: There's a number of ways. Certainly they will be captured through our AERS system. They will come in as MedWatch. There's an 800 number both at Centocor as well as at the SVP that will track those, but the other thing I didn't mention is that before the drug is shipped, there will be a reminder sent to the dermatologist that their patient is scheduled to receive ustekinumab.

DR. BIGBY: Hold on a second. What was the question that you asked for the slide?

DR. CRAWFORD: 155. And as that's coming up, Mr. Chair, my specific question is, why are you not proposing to utilize the specialty pharmacies for more active surveillance, including asking through surveying after they receive it what was the condition of the product, describe it to us, how did you use

it.

DR. CALLEGARI: Those actually -- and we certainly can do those. We've thought through that. One of the challenges with that is the circumstance when we say if the specialty pharmacy has a checklist and says, I'm sorry, you've failed the checklist. You have a fever. You have a fever and illness, and we're concerned about sending the medication to you. One of the challenges is, it's difficult to verify then -- when we say we're not sending it to you until you see your physician, it becomes very difficult in that scenario to verify. We certainly can capture that data. And it's one of the proposals on the table. We're still in negotiation with the SP providers in terms of that, so you can get a lot of information from that, and all of that goes into the MedWatch -- actually it goes into our database, our adverse events database.

DR. DRAKE: I'm still confused, and that's probably because I'm so confused, but I

thought that they were not going to be able to get the medicine from the pharmacy unless a physician had seen them and written a prescription each time. I assumed the physician was going to have to write it each time. If they don't have to write it each time before the drug is shipped, then you're clearly not going to get any follow-up. They'll never show up at the doctor's office if they're going to get it automatically every three months. To me, that's a -- and maybe I misunderstood. So could you help me? What's correct?

DR. CALLEGARI: Either is potentially correct. You can gate a single prescription. Right now, the physician makes that decision in terms of how many renewals or --

DR. BIGBY: I think we should go back to discussing the questions and -- did you get your question answered about the slide?

DR. CRAWFORD: Partially, but I won't belabor it. Thank you.

DR. BIGBY: Okay. Fine.
DR. JONES: (inaudible)
REPORTER: Can you --
DR. BIGBY: Does anybody else at the panel have comment?
DR. STERN: I have one important -- one what I think is an important issue on all of this is that at least in my slightly more than 30 years of experience in terms of long-term toxicity, the most interesting patients are the patients who are no longer on treatment. And any of the information you get through something that is related to the dispensing of a prescription, particularly for serious, long-term toxicities as opposed to acute events, is likely to have lots of lost and missing information. So that's among the reasons why I find the strategies that you seem to have developed to be less than robust.
DR. CALLEGARI: Can I address that?
DR. BIGBY: No. Eileen?
DR. RINGEL: I'm sorry, I think Lynn's

comment is very, very important. If people are planning to allow their patients to fill prescriptions that are renewable, I think that's a big mistake for two reasons.

The first is the one that Lynn just mentioned, because there's going to be no way for us to collect the data that we all feel is so important. And the second issue is that as convenient as this drug is every three months, and patients will say, great, I have only one shot every three months, well, try turning around and saying you are going to be immunosuppressed for three months and there is nothing you can do about it. So when you get your cellulitis or you get a malignancy or whatever, you are stuck with that drug on board for three months or more.

And I see the other end of things. I'm married to a critical care doctor, and you know, in the diabetic patient who gets a cellulitis, who gets septic, and is on the blower, and you can't do anything about that

immunosuppressive drug -- it's a real problem. And I think we need to keep that in mind.

It's like prednisone. I don't like giving prednisone.

DR. THIERS: Bruce Thiers. But even if the drug is not renewable, you know what's going to happen. Patients are going to call the doctor, hey, it's time for my other shot. How you doing? I'm doing okay. Okay, I'll call it in for you.

DR. RINGEL: That's why I said --

DR. THIERS: That's why you need, I think -- you know, I know it's not optimal, but to get follow-up, you've got to have the patient come to the office.

DR. RINGEL: I think they can also -- if you could -- as I said, it sounds draconian, I don't think it's that bad, you could simply have the doctor write -- there should be a form that says, I saw this patient on such-and-such a date. He signs it. Doctors

are not willing to perjure themselves.

DR. BIGBY: The comment I would make about this is that that kind of restriction doesn't exist for any of the other currently available biologicals, many of which have been demonstrated to have an increased risk of infection and of malignancy.

DR. STERN: My response to that is that as a result of our laxity in all of our past approvals, we are operating with not a much better understanding of benefit and risk for those in long-term use of this chronic disease that the average person suffers from for 35 or 40 years than we did five years ago when we had initial approval, so maybe we should try to do it better this time.

DR. AVIGAN: I just want as a point of information, there's one exception, and that's the drug natalizumab, which is used to treat chronic relapsing multiple sclerosis, and now Crohn's. And there, there's actually a very

stringent risk management program which includes mandatory registry and re-prescription based upon a checklist, so that -- with the PML and other issues as well -- so that is an exception.

DR. LEVIN: Mark, you could do both, though, right? I mean, you could still have this distribution system, but no something, no drug requirement at the distribution end, so you could have a checklist, a visit, checklist, and then the pharmacy couldn't proceed unless something came out of the doctor's office.

DR. BIGBY: So I'm going to set a new target end time for 5:30 and we're going to meet it. With that in mind, I would like to propose a vote on the issue iii here. Are the applicant's risk assessment proposals sufficient to characterize long-term safety of ustekinumab? Those voting yes, please raise your hand. That's zero. Those voting no, raise your hand. And abstentions. And I think we need to go on the record. Tor?

DR. SHWAYDER: I voted no.

DR. RINGEL: Eileen Ringel, I voted no.

DR. HECKBERT: Susan Heckbert. No.

DR. DRAKE: Lynn Drake. No.

DR. CRAWFORD: Stephanie Crawford. No.

DR. LEVIN: Arthur Levin. No.

DR. THIERS: Bruce Thiers. No.

DR. BIGBY: Michael Bigby. No.

DR. MAJUMDER: Mary Majumder. No.

DR. STERN: Rob Stern. No.

DR. KATZ: Robert Katz. No.

DR. BIGBY: This was a unanimous no. And also I think we can vote on this one, too. And the way I would phrase this is, is increasing the sample size of PSOLAR an adequate response to the aforementioned no? And those voting yes, raise your hand. Those voting no, raise your hand. And abstentions? Again, this was a unanimous no.

I'll go on the record, Michael Bigby. I don't think that PSOLAR -- I voted no. I don't think PSOLAR is going to be able

to answer this question in our lifetime.

DR. MAJUMDER: Mary Majumder. I voted no.

DR. STERN: Rob Stern. No.

DR. KATZ: Robert Katz. No.

DR. SHWAYDER: Tor Shwayder. No.

DR. RINGEL: Eileen Ringel. No.

DR. HECKBERT: Susan Heckbert. No.

DR. DRAKE: Lynn Drake. No.

DR. CRAWFORD: Stephanie Crawford. No.

DR. LEVIN: Arthur Levin. No.

DR. THIERS: Bruce Thiers. No.

DR. BIGBY: The next one is a little bit difficult for me because I'm not sure what this means, since it's not really a specific proposal. I mean, I don't know what you want us to do with this one.

DR. WALKER: It would be helpful to discuss each of these in terms of its appropriateness, or sort of the best way forward to get adequate post-marketing data.

DR. STRAHLMAN: I guess my understanding is that for B, C, and D, I think FDA is asking us, as was mentioned earlier, to consider certain parameters and the level of rigor and what questions would be answered by each of these types of studies, and I just wanted to offer a couple of comments in that context which I hope would help frame the conversation.

The first one is that the target population for this drug is not millions and millions, it's tens of thousands. That should be a context for risk, and has been mentioned earlier -- because the drug is very specific in -- it's a very specific antibody, we have the biological redundancy of the immune system to counterweight some of the comments that I have heard about malignancy.

And I just wanted to put that out there for the record, because I'm not denying the risk, but I just want to give a context here because there are other products on the

market, and because of the -- you know, the good news is the drug has a dramatic effect. The bad news is the drug has a dramatic effect. So it's going to be used a lot and that's why this has to be taken seriously, but I just offer that perspective in framing the question.

The second point I'd like the committee to consider for B, C, and D is which questions will be answered by what types of studies. There are advantages and disadvantages to voluntary versus mandatory registries. We've heard that often. But even mandatory registries are limited in the ability to detect low signal-to-noise ratios for rare events in what will be a population of tens of thousands, not millions.

Then the last question I wanted to -- last issue I'd like the committee to consider is what my colleague mentioned something about access, and is this going to be the type of drug where only people who can

pay can use it? I don't know the answer to this question, but depending upon how restrictive we are with regard to mandatory requirements, et cetera, I don't know if that will fuel the ammunition of insurance companies to cover and not cover it. This is just something I don't know, but I'd like us to consider that as a committee. It's a very fine line to walk. This is a strikingly effective drug, but it will be strikingly used, and it's a big responsibility and I just hope these comments might be useful as we consider B, C, and D.

DR. BIGBY: Other comments from the committee?

DR. KATZ: Yes. Are we going to do each one of these -- the epidemiologic study, I would assume -- Susan; correct me if I'm wrong -- is just hope that somebody will do a study and find out who's having problems. Mandatory registry -- are we going to discuss that now? Or can I? Or do you want me to wait?

DR. BIGBY: No, you can discuss it now, because -- I get the sense that what you want to know is how rigorous a study should we be demanding of them to be willing to perform to collect the available data?

DR. KATZ: And with a mandatory --

DR. AVIGAN: I was going to say just as a framework, here, the challenge is to cap risk -- that is, we have a concern about risk. So we want to do a study that is reassuring in a way that the absence of a signal will be informative. So that's one way of thinking about mixing and matching these various approaches, and they're not necessarily mutually exclusive.

DR. KATZ: With a mandatory registry, at least somebody will know everybody who's on that drug, I assume, and they can -- we've got to have the panel first before industry comments on it. At least somebody will be able to go back and see, and even after -- with Rob's concern -- even after people come off the drug,

what you're interested in knowing is well, what happens to them? Especially with this, if somebody's immunosuppressed, they're off the drug -- that doesn't mean that immune surveillance is automatically normal. At least somebody can go back, the company or whoever, and check on all the patients who've been on the drug.

And the mandatory registry would not be as cumbersome as Accutane, because it doesn't involve getting the drug within six days of a menstrual period and things of that sort. So I would strongly recommend that as being the ultimate vigor (?) for this for this very effective medication.

DR. HECKBERT: Since there seemed to be a little confusion about the epidemiologic study -- I think I know what the sponsor has in mind there using the Scandinavian countries. Those data are collected anyway. There's no extra work. Obviously there are costs involved in analyzing the data, but the data are there.

So the study would be compare psoriasis patients who don't use this particular biologic agent, who use a different biologic agent, and who use this agent, and compare for end points that are well-captured in automated data like cancer. You wouldn't be able to look at subtle questions such as restarting the drug after a year off. Those kinds of things, you wouldn't be able to look at, but some of the major endpoints that are well-captured by diagnosis codes like cancer, you would be able to look at.

I think my concern with the epidemiologic study, which I assume we should recommend because it's not very expensive, it's easy to do, the data are already being collected -- I think my major concern with it is that this drug will not be used by enough people in the Scandinavian countries to study it independently of any other biologic drug.

DR. STERN: Michael. I agree with

Susan that it shouldn't really be which ones -- it shouldn't be which ones don't we do. It should be what are the requirements, starting with the most rigorous ones. And that's clearly the issue. The other issues about some of the studies you've suggested are both generalizability, and as you've suggested, power.

But I think there are few key endpoints that there are ways of answering, much as Susan has suggested earlier, which involve registration of patients and a variety of mechanisms of follow-up for key endpoints, particularly cancer and death. And as you've suggested, in certain areas, we can get cancer. In the U.S., with about an 18-month delay, we can get death if we have that basic information. And if there is some monitoring, as there will be, of exposure, we'll have that exposure.

Now, there will be confounding because of other exposures and other

background, and you can decide how far to go, but the point is that without registering patients, restricting distribution, you'll never get a robust answer to the key question of cancer and death.

And the other part I would say, which will probably be very unpopular, is that I can't believe that this will be an inexpensive agent. If they're going to sell it for less than $2,500 an injection, I would be surprised and amazed. People who use this drug are using a fair amount of social resources directly or indirectly. And when people do that, I believe they have an obligation, if there's no additional danger to them, to help us learn from their experience.

So I don't see it as a burden on individuals who are using a real resource of society. We could not afford to put a million people on this drug and not bankrupt the health care system -- for them to, as

part of their consent process, to agree to share certain aspects, certain very discreet aspects of their long-term experience with respect to cancer, death, and perhaps a few other endpoints of interest.

DR. BIGBY: I think from this point on, we'll go on the record and this is like your final comment about this issue.

DR. MAJUMDER: This is Mary Majumder, and I was just going to say what I heard from the patients is that this is a genetic disease. It doesn't just affect them, it affects their family. So they have a real stake not only personally, but for their families, in finding out what exactly the risk might be from this kind of drug.

So I don't necessarily see it as a conflict between individual sort of self-interest and the public interest. I think there's probably a fair amount of support for getting the information, and the question is just how best to do that.

DR. BIGBY: Michael Bigby. I think that the five-year extension of the pivotal trials that are currently ongoing should provide useful information. Ultimately, the number of patients enrolled in these trials is not going to be sufficient to answer the question about malignancies. It might pick up a signal for infection. I think -- as I said before, I don't think PSOLAR is the solution to this issue. I think the epidemiologic studies using extant databases should be performed. However, their power, I think, is questionable.

I really don't want to burden them with mandatory registration, just because it's sort of so different than a current playing field. And I don't really have a suggested solution to the Agency for the problem of how it is that we're going to collect this data.

You know, spontaneous reporting, unless there is a fairly big signal, I think

spontaneous reporting we've all found underwhelming.

DR. THIERS: Bruce Thiers. I think when we think about mandatory registry, we think about I Pledge, but it doesn't have to be that way. If anybody here has ever prescribed thalidomide, it's really a piece of cake. So a mandatory registry could be made informative and easy to use, and could be the easiest solution of any of the other choices listed.

DR. LEVIN: And I'll second that. Arthur Levin will second that.

DR. CRAWFORD: Stephanie Crawford. My recommendation is there should be some type of commitment to negotiate a post-marketing surveillance study of some type, be it epidemiological or else-wise. I think strongly that the use of the registries can be enhanced. These registries should -- I really can't comment right now as to whether I think mandatory versus voluntary is preferable. But regardless, any registries used should pull in

data from a variety of sources, should plan for more active surveillance.

I'm a bit concerned from some of the comments I made before just to call to say it's coming and you need to get another dose. At a certain point, if it's an office-based administration, that more active surveillance should be worked out in consideration of how it would work for physicians. If it's self-administration, there needs to be a better delineation of how the safety and the efficacy will be monitored in the long-term.

DR. DRAKE: Do you really want a comment?

DR. BIGBY: I do.

DR. DRAKE: Well, this is Lynn Drake. I think I'm fresh out of comments, except I would tell you that I really don't like anything mandatory, but Bruce just made a persuasive argument as to why this should be. I think we have to figure out some way to monitor, because

it's been such a problem.

DR. HECKBERT: Susan Heckbert. I think the five-year extension at the pivotal trials is critical and should be done. I'm not sure that the PSOLAR approach is going to give us much, but there may be some limited questions that might be addressable there. The epidemiologic study should be done, because as was indicated earlier, it's already -- the data are already being collected.

I am in favor of mandatory registry and restricted distribution. I'm not sure what the disease-based registry refers to, but if it's a voluntary registry, I don't think it has much to add.

DR. RINGEL: I'm Eileen Ringel. I do feel this drug is different from other biologicals. It's extremely effective. It's going to be used a lot. It has an extraordinarily long half-life, which really is very different. There are animal signals for cancer which is different from other drugs. I

think that the only way we are going to get around problems of bias in recruitment and the problem of the denominator, which we always have when we're looking at AERS data and what not, is to have a mandatory registry which can be very simple, a la what Bruce recommended.

DR. SHWAYDER: Tor Shwayder. I agree with a mandatory registry. They have to put some sort of caveat on long-term surveillance off drug, what Dr. Stern was talking about earlier. I don't know how you would institute that. It might not be practical, but that would be the data you really would want to know, and certainly the five-year extension would be an easy first step, and that would be wonderful data to have as well.

DR. BIGBY: I am going to end the meeting.

I apologize to my committee for running over, but I think that the issues are sufficiently important to have warranted it, and I hope what we did is helpful to the

Agency.

DR. WALKER: I'd like to thank the committee very much for their comments today. It's been extremely helpful. Thank you.

(Whereupon, at approximately 5:36 p.m., the MEETING was adjourned.)

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