

1 effect for this drug.

2 DR. LAUGHLIN: Right.

3 DR. GULICK: Dr. Rodvold, a follow-up comment  
4 and then Dr. Seeff.

5 DR. RODVOLD: I've got a couple questions on  
6 the pharmacology as long as you're here. So, it's a good  
7 time.

8 DR. LAUGHLIN: Sure.

9 DR. RODVOLD: Is this linked to area under the  
10 curve or Cmax or anything? Can this be linked to  
11 concentration dependency? Does that lead you to  
12 concentration controlled trials?

13 DR. LAUGHLIN: Yes. The anemia is in fact the  
14 toxicity, and we've sort of modeled it in various different  
15 dose regimens. But the toxicity -- the two factors that  
16 control for the level of anemia are baseline hemoglobin and  
17 concentration of ribavirin.

18 Now, can you develop a concentration-based  
19 trial? I think not because the variability in that --  
20 there is clearly an association on a population basis. On  
21 an individual patient basis, that correlation is weak, and  
22 I'm not sure, because the toxicity is recognizable and  
23 manageable and reversible, that you would necessarily want  
24 to trade potential efficacy just to keep a hemoglobin where  
25 you want it.

1 DR. RODVOLD: But I'm wondering more in the  
2 sense of a trial fashion to find that dose versus putting  
3 people into all these different dosage regimens you're  
4 proposing that you try to get everyone to a set dose hunt,  
5 so to speak. So, the trial design would be to find the  
6 magical dose of the ribavirin, not necessarily to propose  
7 that to physicians in clinical practice.

8 DR. LAUGHLIN: Well, we have attempted to  
9 define that relationship both in terms of efficacy and  
10 safety. Again, I think the problem is it's a shallow  
11 relationship. It is clearly there for both efficacy and  
12 toxicity, perhaps more for toxicity. It's clearly there.  
13 But on an individual patient basis, I think the data just  
14 isn't strong enough to direct you toward a concentration  
15 based clinical trial.

16 DR. RODVOLD: My final question is, is there  
17 any data that you generate from a pharmacology point of  
18 view, particularly PK, maybe PD as well, where they  
19 absolutely studied people that were, say, less than 100  
20 percent ideal body weight, 100 to 150 percent body weight,  
21 and then a group that definitely was big, like 200 percent,  
22 an obesity group?

23 The reason I asked that was that in the  
24 clinical trials, you didn't have a lot of people in the  
25 extremes, particularly the upper extreme. So, I would

1 guess in this trial you'll run into the same problems.  
2 Would a trial that would sort some of that out to really  
3 look at weight as the key factor, control all the other  
4 variables out, and maybe throw gender in there as well  
5 because that keeps tripping occasionally as well. Have you  
6 ever done that?

7 DR. LAUGHLIN: We have not prospectively done  
8 that to look at light, middle, and heavy folks. What we  
9 have done -- and I'll need the backup slides. If I could  
10 have slide number 18.

11 We did go back and look at sort of the other  
12 side of this. We've been talking mostly this morning about  
13 weight-based dosing and efficacy. We looked at weight-  
14 based dosing on a milligram per kilogram basis and exposure  
15 as measured by AUC. Each one represents an individual from  
16 one of the earlier clin pharm studies. Again, if you sort  
17 of break it where we've been talking about all morning,  
18 there is a relationship that exists that appears to be  
19 linear, at least within fairly wide ranges.

20 DR. RODVOLD: My question, though, is actually  
21 to ask you to look at the data like as a percentage of  
22 ideal body weight on the bottom x. Then go get your PK  
23 parameters. We've done that with some of the chemotherapy  
24 agents where again you have the problem of intracellular  
25 concentrations and all these issues. What you find is that

1 actually there are relationships there that trip out  
2 clearance, for example, or half-life but not volume. And  
3 that starts to make you rethink about who should be getting  
4 the right doses because there is a PK parameter.

5 I understand this part, and I saw that in your  
6 insert, but I'm wondering, does one of the parameters come  
7 out -- is clearance different in people that are fatter or  
8 smaller? And is that what's driving this dose? So you can  
9 search for that. Maybe you've done that.

10 DR. LAUGHLIN: We can go back, if we have it.  
11 That's certainly something we could look at in the  
12 database.

13 DR. GULICK: I'm seeing lots of hands, although  
14 we really need to end. A follow-up question from Dr.  
15 Englund.

16 DR. ENGLUND: I have a follow-up  
17 pharmacokinetic question, and that is certainly in earlier  
18 studies in pediatrics we've studied ribavirin and have  
19 noted the presence of ribavirin triphosphate in the red  
20 cell fraction, which really is where we believe -- some  
21 people believe -- the toxicity derives from with very high  
22 intracellular RTP concentrations.

23 My concern for getting the pharmacokinetics is  
24 that we have a large population of, for example, HIV-  
25 positive patients that I want to be able to use a drug like

1 | yours on, and if we could get levels and get some  
2 | pharmacokinetics, we may be better able to translate it.

3 |           So, I have a question. Do you have plans to  
4 | study not just ribavirin levels, which are not that  
5 | difficult to do but perhaps not going to relate to your  
6 | toxicity as much as your RTP or perhaps other levels, which  
7 | I'm not so aware of?

8 |           DR. LAUGHLIN: If we could have slide number 8  
9 | please.

10 |           I think you raise very good points. However, I  
11 | think that we probably need to approach the different  
12 | toxicities differently.

13 |           I think in terms of red cell toxicity, we don't  
14 | know precisely what the mechanism is for that toxicity, but  
15 | certainly one of the defining characteristics of that is  
16 | for nucleated cells, this equilibrative transport system  
17 | will generate mono-, di-, and triphosphate that is  
18 | reversible. And it uses the same enzyme systems as  
19 | adenosine to generate ATP. In the red cell, by contrast  
20 | there's a massive accumulation of RTP, about a 60 to 1  
21 | ratio between intracellular red cell and plasma. And we  
22 | have looked at that.

23 |           If I could have the next slide. Perhaps one of  
24 | the speculations for the ribavirin-induced anemia is in  
25 | fact this competition for ATP generation where you

1 basically generate a nonfunctional energy store within red  
2 cells that can't be used, and that energy store is critical  
3 for the oxidation reduction of proteins, which when they  
4 get overexpressed on the red cell membrane, that's the  
5 signal to come out, for extrahepatic hemolysis.

6 In terms of use with other nucleoside  
7 analogues, I think that's a different issue than the red  
8 cell RTP but something that clearly needs to be looked at.  
9 And we've known the interaction between ddI certainly.

10 DR. RODVOLD: But I think you've got a great  
11 opportunity here.

12 DR. ENGLUND: I'm just saying I don't see any  
13 data.

14 DR. RODVOLD: It would be a shame if you passed  
15 this up on 4,000 patients that you're giving multiple  
16 different levels of this drug. This is the opportunity of  
17 a lifetime.

18 DR. LAUGHLIN: To measure what?

19 DR. RODVOLD: Well, to take a measure of not  
20 only whole but also one or all these functions. I mean,  
21 you'll never get a database this big again.

22 DR. GULICK: Dr. Siegel, a follow-up?

23 DR. SIEGEL: Yes. Well, just an addition to  
24 the answer to Dr. Hoofnagle's original question, which  
25 opened this field, which is why do a large clinical trial.

1 Can't you get the weight adjustments you need from PK?

2 I would say PK studies can be very important,  
3 can answer a lot of questions, but there are some important  
4 parts of the question they're not going to answer. So, you  
5 could, from a PK study, learn how to adjust the dosage so  
6 that large people have the same level as small people as a  
7 population, recognizing individual variations. Once you  
8 know that, you could decide, as Schering has proposed, to  
9 give small people 800 and move up to 1,400 in large people,  
10 or you could give large people 800 and adjust down for  
11 smaller people, or you could try to get the average, which  
12 this study did, by giving 800 to the average sized person  
13 and adjust up and down from there. So, you can adjust to  
14 achieve approximately similar exposures, but what the  
15 optimal exposure should be can only be done I think through  
16 a clinical trial.

17 So, what the nature of the trial that's  
18 underway will tell us is, at least in larger people, will a  
19 more intensive regimen actually provide, as hypothesized,  
20 better responses in a tolerable range. And you're not  
21 going to learn that from PK adjustments.

22 DR. HOOFNAGLE: But you could from PK  
23 adjustments learn whether this is the right scale. For  
24 instance, they're proposing to use 85 kilograms, whereas  
25 everyone up to here has used 75 kilograms. And actually if

1 | you use 75 kilograms and then your endpoints -- you're  
2 | dealing with very few people who are more than 250 pounds  
3 | and very few people anymore who are less than 120 or 110.  
4 | And no one would argue that with the small people that you  
5 | really should go down. The large people you're a little  
6 | bit concerned with, and at what cut point should you  
7 | increase the dose of ribavirin.

8 | DR. SIEGEL: Right.

9 | DR. HOOFNAGLE: 75 or 85 kilograms?

10 | DR. SIEGEL: You're right, and this scale was  
11 | chosen -- and I believe that's data driven, although I  
12 | don't have the PK data before me -- to weight-adjust on  
13 | milligrams per kilogram, so to keep in a range of  
14 | approximately 13 milligrams per kilogram, regardless of  
15 | your weight, with some variability because of the  
16 | discontinuity of the cut points.

17 | Some drugs, if you want to get similar exposure  
18 | are better adjusted by milligrams per meter squared and  
19 | some by powers in between a power of 2 as in surface area  
20 | or a power of 3 as in weight. Those decisions can and  
21 | often are made on the basis of PK data, and I believe in  
22 | this case were. I don't know if we have the people who  
23 | reviewed that here at this meeting.

24 | DR. HOOFNAGLE: Well, ribavirin is distributed  
25 | with water and comes out in the urine. So, it's not fat

1 mass. It's lean body mass that should be the determinant.

2 DR. RODVOLD: I think that's an important part.  
3 It would help you understand the mechanisms. That's what  
4 I'm after so that we can make sense of this. And the  
5 question the FDA presented about lean body weight, there's  
6 an adjusted lean body weight, there's a total body weight  
7 -- you can do some of that but you can't -- at the same  
8 time as I was mentioning and followed Dr. Englund's  
9 question, I think that in this big controlled trial you  
10 have the chance to do PK/PD. I think the sponsor is right.  
11 What do you actually measure is the question. But that  
12 will also be important there because now you can go  
13 linking, hopefully, those two in addition to this raw  
14 milligram per kilogram basis.

15 I get a little worried we're only looking at  
16 one finite thing here, and when you're going to put that  
17 many people into that much pharmacology potentially, to  
18 pull out, man, I think it's a once-in-a-lifetime chance.  
19 It will help in peds potentially too.

20 DR. GULICK: There's clearly enthusiasm around  
21 the table to further discuss the design of the  
22 postmarketing studies. Let me hold us back and try to  
23 finish off the questions here because we are running a bit  
24 behind schedule.

25 Dr. Seeff has been waiting very patiently.

1 DR. SEEFF: Well, I'd like to make comments as  
2 a practicing hepatologist. Perhaps what I'm going to say  
3 is not for now and it may be a discussion for later and  
4 you'll stop me because this may be really the issue that  
5 Mike Marco brought up a little earlier.

6 In looking at the data that we see in the  
7 Michael Manns paper, there's clearly evidence that the  
8 drugs that we used were significantly better than the  
9 combination of conventional interferon plus ribavirin, and  
10 the difference is 6 percent or 7 percent significant. But,  
11 of course, that's an overall number.

12 And the question is how do we apply that to the  
13 patients that we actually take care of. When I address the  
14 patient and I see the patient, I have to say, you have an X  
15 percent likelihood of responding.

16 If you look at the data, it's quite clear that  
17 there are only subgroups in which there is a significant  
18 response rate and other subgroups in which there is no  
19 difference between the two drugs. For example, two-thirds  
20 of the patients are genotype 1 and have high viral load and  
21 the response rate is the same between the pegylated  
22 interferon and the conventional interferon together with  
23 ribavirin. It's only in the low titer group where you  
24 actually see a significant difference in which nobody could  
25 argue that you should be using the pegylated interferon.

1                   Now, there may be a variety of reasons to  
2 choose one drug over the other, but I'm not sure that  
3 there's enough information here to say that one is  
4 significantly better than another in the high titer group.

5                   I'm intrigued with the difference between the  
6 U.S. and non-U.S. people, and I'm more interested in the  
7 fact not so much that there's a difference in the U.S.  
8 group -- and there is and clearly that's important and  
9 probably will work out to be perhaps weight-based -- but  
10 that there was no difference in the non-U.S. group,  
11 absolutely no difference. 57 versus 59 percent.

12                   And then from my point of view, in my own  
13 personal practice, I'm at the VA hospital in Washington,  
14 D.C. 85 percent of my patients are African Americans. 98  
15 percent of them are genotype 1, and when we measure their  
16 titers, about 75 percent, maybe 80 percent have got high  
17 titers above 2 million copies. I have to tell you that we  
18 have found that using the conventional interferon and  
19 ribavirin, that our response was less than 10 percent.

20                   So, now I am faced with the fact that we have  
21 data that's been reported that there's a much higher  
22 response rate overall. And obviously, this study can't  
23 answer it. I'm delighted to hear that Schering is going to  
24 do a study looking at African Americans, and of course, we  
25 are doing a study at NIDDK to look at the issue of lack of

1 response.

2 But my point is I guess to cite a figure as an  
3 overall figure that can be applied to patients that we're  
4 taking care of is probably not accurate and not correct and  
5 is not applicable in our discussion with patients. I  
6 cannot go to my African American patients and say, when we  
7 start you on this combination, this is what we can  
8 anticipate. We have to find that out.

9 So, I think that we can say that there are  
10 subgroups in which there is clear-cut significance with  
11 respect to a treatment response and others in which we  
12 either don't know and we can't make a recommendation one  
13 way or another, or that we have to find out more  
14 information in the studies that are being done. So, that's  
15 just a comment and that may be one that should have come  
16 later.

17 What I'm also intrigued about is that the  
18 criteria used here to exclude patients was very carefully  
19 selected at 1,500 I guess for neutrophils and 1,000 for the  
20 platelets. Perhaps I shouldn't be saying this in front of  
21 the FDA, but I'm hearing that there's a tendency for people  
22 to be bringing patients into treatment with lower levels.  
23 Now, while I recognize that the more important concern is  
24 the anemia, I guess that we don't really know what would  
25 happen if we treat patients who have 1,000 instead of 1,500

1 or 750 instead of 1,000 using this particular combination.

2 So, I think that we have to be very cautious  
3 until the studies have been done to identify that, and I  
4 think we need to make sure that whatever recommendations  
5 are put in, that it makes clear that we have to stick with  
6 the numbers that were selected because we are concerned  
7 right now about the potential side effects, and this may  
8 become more evident if we start off with lower values.

9 So, that's just a comment rather than a series  
10 of questions.

11 DR. GULICK: Again, we really need to finish  
12 up, and if there are some burning questions -- Dr. Wood has  
13 a burning question.

14 DR. WOOD: And it's kind of a segue and a  
15 follow-up to the issue that Dr. Seeff raised regarding  
16 neutropenia. This is for the FDA.

17 While there clearly wasn't a direct correlation  
18 in terms of incidence of neutropenia at the time of the  
19 serious infectious adverse events, I'm curious as to  
20 whether or not the individuals in the PEG 1.5 arm had been  
21 dose-reduced for neutropenia. So, even though they did not  
22 have neutropenia at the time of their event, they had a  
23 history of requiring a dose reduction for neutropenia. Is  
24 there any information about that?

25 DR. MARZELLA: I don't have that information,

1 but I'll have to look at the data. Does Schering have that  
2 information?

3 DR. WOOD: That would be helpful just because  
4 there were 17 serious infectious events in the PEG group.  
5 We clearly know that the PEG 1.5 group had a higher  
6 sustained dose reduction for neutropenia. So, that's the  
7 reason for wanting that information.

8 DR. ALBRECHT: I was just speaking with Dr.  
9 Cohard, who is the director of my group, and we looked at  
10 this data. We can't exactly answer your question, but what  
11 we did is, as I said. None of the patients were below 750  
12 neutrophils during the course of the study. She remembers  
13 that 1 or 2 patients may have earlier had a dose  
14 modification for neutropenia, but there doesn't seem to a  
15 clear association with either dose modification at the time  
16 or around the time associated with those infections.

17 DR. GULICK: Dr. Marzella.

18 DR. MARZELLA: I just wanted to return to a  
19 comment that Dr. Hoofnagle asked about a relative  
20 comparison of treatment response of the  
21 interferon/ribavirin arm in later studies and also to some  
22 comments that the sponsor made about higher adverse event  
23 rates in the interferon/ribavirin arm in this study and  
24 whether or not those are due to different ascertainment  
25 methods for adverse events.

1 I think it's important to emphasize in this  
2 particular study, in contrast to all others, that the  
3 ribavirin was given with food, whereas in previous studies  
4 it was given without regard to food and that there's data  
5 that the sponsor has which indicates that the absorption of  
6 ribavirin increases dramatically, as much as 70 percent.  
7 So, it's another factor to be considered in that issue.

8 DR. GULICK: I'm going to take the chair's  
9 prerogative and ask the last question. That's strongly  
10 worded there.

11 (Laughter.)

12 DR. GULICK: Could you please compare the  
13 demographics in your pivotal phase III study with the  
14 demographics of hepatitis C infection today in the U.S. and  
15 address any differences?

16 DR. ALBRECHT: These are the demographics that  
17 were in the study. Now, as I commented earlier, these  
18 demographics are really pretty consistent with what we've  
19 seen in the previous study in 1998. The weights are not.  
20 The Americans have gotten heavier, and if you'd like, I'll  
21 be happy to show you the distribution on the weight in the  
22 Americans. We had a large number of patients over 100  
23 kilos.

24 Maybe, Dr. Hoofnagle, would you be willing to  
25 comment -- and we have this demographic slide, as well as

1 disease characteristics -- about what your opinion is and  
2 whether this is reflective of really what we see in the  
3 United States population?

4 DR. HOOFNAGLE: Well, the mean age is probably  
5 about correct. You did exclude children and the elderly,  
6 though. So, it's not completely it.

7 The gender is the approximate breakdown in  
8 gender distribution of hepatitis C in this country.

9 The race is not. Our estimates are that  
10 African Americans represent 22 percent of chronic hepatitis  
11 C in the United States. Hispanics you don't break out, but  
12 they're also over-represented as having this disease.

13 As far as weight, I have no information.

14 The other issues, though, are socioeconomic  
15 class. This is a disease that's much more common in the  
16 poor. It is, of course, a major risk factor today, as  
17 injection drug use, and I'm sure in this study, you  
18 probably excluded patients who were using drugs or had used  
19 drugs in the previous year. So, that is a major  
20 difference, and they represent, of course, the large  
21 reservoir and the difficult reservoir.

22 You also excluded HIV positive patients. This  
23 is an important disease in those patients.

24 So, no, it doesn't represent the demographics  
25 of this disease, but it certainly represents the

1 demographics of people enrolling in large clinical trials  
2 no matter what the disease is.

3           What we need to do now is go back and pick up  
4 these special groups and do special studies in them. They  
5 have special concerns. Like in HIV-positive patients, you  
6 have to be very careful with the ribavirin dose I think.  
7 With injection drug users, you have to use all kinds of  
8 other special monitors of compliance. Actually PEG-  
9 interferon will be a major advance for that group I think  
10 because of the ability to administer the drug actually.  
11 So, this isn't representative, but it's hard to say that  
12 they could have done differently.

13           But I think it's interesting. The patients are  
14 getting heavier and yet your response rates are getting  
15 better.

16           (Laughter.)

17           DR. HOOFNAGLE: This is the conundrum that  
18 occurs in all obesity studies. Americans are becoming more  
19 and more obese. Deaths from heart disease and cancer are  
20 decreasing. How do you explain this dichotomy? We haven't  
21 got an answer.

22           DR. ALBRECHT: And I know the chairman wants to  
23 stop. I have two brief comments. Dr. Hoofnagle touched on  
24 something very important.

25           In trying to have a more homogeneous group in

1 | these trials, we do exclude the HIV-positive patients and  
2 | current injection drug users. Schering is supporting  
3 | trials in these patient populations. In the HIV group in  
4 | particular, we're doing a study with the ANRS in France,  
5 | looking at PEG/ribavirin versus actually Intron/ribavirin.  
6 | We're also supporting studies in patients in methadone  
7 | clinics. Indeed, the once-a-week dosing allows the patient  
8 | to get their drug at the clinic in certain cases as opposed  
9 | to self-injecting, which is a problem with these patients.  
10 | So, we are supporting studies in these small populations.

11 |           Not everything is done by the Research  
12 | Institute, but we do have another group within our company  
13 | where we support these studies, many of which are under the  
14 | INDs or under the purview of the individual investigator.

15 |           DR. GULICK: Thank you.

16 |           We're going to take a 10-minute break, 11:25.  
17 | I recommend if you do eat something, that it be low fat.

18 |           (Laughter.)

19 |           (Recess.)

20 |           DR. GULICK: Could people please take their  
21 | seats? We're ready to go.

22 |           Welcome back. I'd like to open the open public  
23 | hearing portion of the meeting. There are three people  
24 | that have signed up and one group that asked that a letter  
25 | be read. First is Brian Klein from the Hepatitis C

1 Advocacy and Action Coalition. You can either use this  
2 mike or you can come to the podium, whichever you prefer.

3 Dr. Stanley, are you with us?

4 DR. STANLEY: I am here.

5 MR. KLEIN: Good morning. My name is Brian  
6 Klein and I'm a community patient advocate and a founding  
7 member of the Hepatitis C Action and Advocacy Coalition, or  
8 HAAC. HAAC is a grassroots, all-volunteer group of  
9 individuals committed to non-violent direct action for  
10 access to treatment, funding and resources for care,  
11 prevention efforts, and sound public policy in addressing  
12 the hepatitis C crisis. We accept no money from the  
13 pharmaceutical industry and that includes no industry  
14 funding for my appearance here today.

15 I am also a person living with co-infection of  
16 HIV and hepatitis C.

17 I thank the chairperson and the advisory  
18 committee for this opportunity to provide testimony to you  
19 today. There are written copies of my complete testimony,  
20 but I will try to abbreviate it a bit and try to keep it  
21 down to about 10 minutes. I know the panel wants to  
22 probably move on this morning.

23 I want to address three concerns related to  
24 Schering-Plough's PEG-Intron and PEG-Intron/Rebetol post-  
25 approval. These issues are concerns on the weight-based

1 dosing studies of Rebetol in use with PEG-Intron, current  
2 off-label promotion of weight-based dosing of Rebetol, and  
3 the Access Assurance PEG-Intron Registration Program.

4 Most of my comments on the concerns for the  
5 weight-based dosing studies will concur with much of what  
6 the FDA has said this morning. I was very relieved to hear  
7 that presentation and most of the comments this morning.

8 We support the current FDA labeling of PEG-  
9 Intron with a fixed 800 milligram per day dosing of  
10 Rebetol. That is what the true intent-to-treat analysis of  
11 the registration trials demonstrated as effective. The  
12 study showed equivalent, not superior virologic or  
13 histological efficacy to standard interferon/ribavirin  
14 treatment for the vast majority of patients, including  
15 genotype 2/3 patients and genotype 1/high viral load  
16 patients. These patients do no better on PEG-  
17 Intron/Rebetol therapy.

18 Anecdotally, we have been getting more reports  
19 than we received with standard interferon/ribavirin of  
20 patients who have to dose-reduce the PEG and/or the  
21 ribavirin due to respective adverse events. Also, in  
22 regards to the convenience issue, we've been getting  
23 reports of dosing errors due to the confusion over the  
24 reconstituting of the product since it comes in a powdered  
25 form. This is difficult for many patients as well.

1 Be that as it may, I do question whether this  
2 drug was even ready for approval when we are not sure of  
3 the dosing and it offers such disappointing results. But  
4 as was stated earlier, the genie is already out of the  
5 bottle. Therefore, weight-based dosing of Rebetol should  
6 definitely not be approved unless or until the prospective  
7 study demonstrating statistical significance of the  
8 efficacy and safety of such dosing is completed and clearly  
9 demonstrated.

10 I am very concerned that this haste by Schering  
11 to have weight-based dosing of Rebetol is an attempt to  
12 market higher doses and sales of ribavirin and bring back a  
13 bundled product. There are several pertinent points here.

14 One, we still don't clearly know the mechanism  
15 of action for ribavirin. No one is really sure that high  
16 intracellular levels are really needed for improved  
17 efficacy. It is unclear whether there is a strong dose-  
18 dependent efficacy effect with ribavirin, but we certainly  
19 know there is a dose-dependent toxicity effect.

20 I believe the situation is similar to that  
21 which we experienced with AZT, a nucleoside analogue, as is  
22 ribavirin. Only later it was seen that half the original  
23 dose of AZT would be as effective and far safer. As with  
24 other nucleoside analogues, we are seeing reports of  
25 mitochondrial toxicities with increasing ribavirin dose,

1 particularly in highly sensitive HIV/HCV co-infected  
2 patients. There are also reports of decreased bone mineral  
3 density after therapy containing ribavirin.

4 Next, it is well established that increased  
5 body weight, as has been talked about a number of times  
6 this morning, is an independent negative prognostic  
7 indicator for response to any HCV treatment to date. This  
8 effect is all that the retrospective analysis in the Manns  
9 data demonstrated.

10 As was also stated earlier, ribavirin is known  
11 to be as much as 70 percent more bioavailable when taken  
12 with a high fat meal. No mention or attempt was made to  
13 control that within this particular analysis.

14 The weight-based dosing conclusions hinge on  
15 really the results of 58 genotype 1 patients at that 10.6  
16 milligram per kilogram dose out of over 1,500 patients in  
17 the study. I have no idea what statistics would show that  
18 to be significant.

19 When looking at the lower dose of PEG in the  
20 study, the ribavirin milligram per kilogram dosing scheme  
21 seems to be a moving target, up to 13 to 15 milligrams per  
22 kilogram. What I really believe we're seeing here is an  
23 effect of the PEG-Intron dosing, not ribavirin. If one  
24 were to believe these efficacy numbers that are in table 4  
25 of the Manns study to be valid, it would mean concluding

1 that ribavirin had a larger effect on sustained response  
2 rates than the PEG-Intron dose itself.

3           Whenever patients have had to be dose-reduced  
4 on ribavirin for safety reasons, data from Schering and  
5 from Roche have demonstrated no significant loss of  
6 efficacy at the lower doses. One question that was asked  
7 earlier and was answered by Dr. Albrecht regarding the 80-  
8 80-80 studies that were done, at AASLD last month, Dr.  
9 Forensi did show that dose-reducing of ribavirin did not  
10 affect the efficacy. So, I think these kinds of things  
11 need to be looked at.

12           There are studies that compare various doses of  
13 ribavirin. Bonkovsky in the October 2001 Digestive  
14 Diseases and Sciences concluded that a lower 600 milligram  
15 dose was better tolerated and was equally effective in  
16 bringing about a sustained virologic response. Schering  
17 has conducted at least two major studies that have compared  
18 various doses of ribavirin with their interferon products.  
19 I have learned from investigators that one multicenter  
20 study used Intron A with doses of ribavirin varying from  
21 600 to 1,200 milligrams per day. The results of that study  
22 have never been made public.

23           Another has been published by Paul Glue in  
24 Hepatology 2000 and was a phase II study for PEG-  
25 Intron/Rebetol combination approval. In that study, doses

1 from 600 to 1,200 milligrams per day were used. While  
2 safety data is presented in this study, efficacy of the  
3 various doses is omitted. When Dr. Glue presented this  
4 data at AASLD in 1999, he said they collapsed the data into  
5 one set because there was no statistical difference between  
6 the doses of ribavirin. In fact, it was this study that  
7 was initially used by Schering to design the phase III  
8 study using a fixed 800 milligram ribavirin dose. Now the  
9 company doesn't like the results of the trial, it starts to  
10 manipulate the data, making retrospective analyses.

11 I ask this committee to recommend that Schering  
12 be required to supply it and the agency with its entire  
13 ribavirin dose-ranging efficacy data with Intron A and PEG-  
14 Intron to consider while reviewing prospective weight-based  
15 dosing data.

16 It is my belief that while the company is  
17 conducting frivolous patent infringement lawsuits to delay  
18 a generic version of ribavirin from coming to market, this  
19 weight-based dosing marketing attempt is not only an effort  
20 to sell more Rebetol to patients, but also may be an excuse  
21 to bundle Rebetol with PEG-Intron in a new co-packaging  
22 scheme. Once again, this type of marketing strategy will  
23 restrict choices by medical providers and patients by tying  
24 the sale of one product to the sale of another. Three and  
25 a half years after the introduction of Rebetrone, the FDA

1 still does not have a comprehensive policy on bundling.  
2 And without one, we are going to see this anticompetitive,  
3 anti-patient market manipulation perpetrated on the public  
4 again in the name of safety for the patient, while safe and  
5 effective individualization of treatment is lost. Rebetol  
6 changes from being safe or unsafe for separate sale  
7 depending on market advantage to the company not on  
8 scientific grounds.

9 I ask the committee to recommend that the FDA  
10 develop a policy preventing the marketing of products in a  
11 bundled only form on safety and efficacy grounds as it  
12 purposely hinders and prevents individualization of  
13 treatment for the patient. Dosing and product choice  
14 should be up to the physician working with the patient, not  
15 the whim and revenue projections of the drug manufacturer.

16 My next issue is concerning the current off-  
17 label promotions of weight-based dosing of Rebetol. Sadly  
18 too few health care providers are reading the intent-to-  
19 treat analysis in the labeling of this treatment. Schering  
20 marketing efforts are currently doing everything to avoid  
21 showing that label and are instead working with national  
22 pharmacies and physicians to promote off-label weight-based  
23 dosing of Rebetol. Some physicians are paid by the company  
24 to promote the weight-based dosing as the new gold  
25 standard. There are already slide presentation programs

1 from the company promoting this weight-based dosing under  
2 the guise of certified medical education, CME. One such  
3 presentation is available for free to anyone with Internet  
4 access at [projectsinknowledge.com](http://projectsinknowledge.com).

5 Schering is working with national pharmacies to  
6 promote off-label dosing of Rebetol. These pharmacies  
7 include at least Caremark, CuraScript, CVS Procure,  
8 Priority, and Walgreen's. These pharmacies carry dosing  
9 tables and/or prescription forms with the weight-based  
10 formulas already written on them and marked as optimal or  
11 other such dosing labels. While the approved labeling for  
12 PEG-Intron/Rebetol combination shows data and guidelines  
13 for patients only up to 95 kilograms in weight, these  
14 dosing tables manage to go up to over 105 kilograms of  
15 weight and up to 1.4 grams per day of Rebetol. Only in the  
16 tiniest print is the approved dosing marked. These  
17 materials are purposely written to mislead the reader into  
18 believing weight-based dosing of Rebetol is preferred or  
19 optimal.

20 These pharmacies did not independently cook up  
21 this promotion. It is all coming from Schering for mutual  
22 benefit. Schering sales reps can go handing out the  
23 pharmacy marketing pieces pretending they are from an  
24 independent source having nothing to do with Schering.

25 The well-intended FDA disclaimer that

1 accompanies the Manns article in promotions is not enough.

2 At the AASLD meeting in November at the  
3 Schering exhibit booth, the only copies of labels on  
4 display were PEG-Intron monotherapy labeling and separate  
5 Rebetol labeling. This was purposeful evasion of having  
6 the full actual combination use label and data readily  
7 available.

8 While HAAC supports doctors using their  
9 expertise to prescribe off label in order to individualize  
10 patient treatment needs, we also support regulations that  
11 intend for pharmacies and drug manufacturers to not promote  
12 such off-label uses. And we believe the FDA needs to  
13 rigorously enforce these policies with Schering and all  
14 manufacturers and pharmacies. With all such product  
15 promotion activities, the entire pertinent labeling must  
16 accompany all marketing materials used by a company  
17 regardless of their source. We ask this committee to  
18 recommend that the FDA compel Schering to live up to the  
19 letter and intent of such marketing guidelines and stop  
20 this off-label promotion by them and their pharmacy  
21 surrogates.

22 The last issue I want to address many on the  
23 panel may not be familiar with. I hope some of you are.  
24 It's the Access Assurance Registration Program from  
25 Schering. This is one of the largest concerns of patients

1 because where do patients go to have their privacy rights  
2 protected here.

3 This program, instituted in late October,  
4 requires patients to register with the manufacturer.  
5 Patients will not receive medication if they do not  
6 register.

7 Patients register by divulging the following  
8 confidential information: name, address, phone number,  
9 best time to be contacted, gender, weight, date of birth,  
10 their doctor's name, referred to on forms as the  
11 investigator as if the patient were signing up for a  
12 clinical trial, health plan, and anticipated start and  
13 completion dates of therapy. Company representatives claim  
14 this has been tinkered with in recent weeks and pared down  
15 to main identifying information of name or name, address,  
16 phone number, and permission to be contacted or not. But  
17 whenever I call the number, as recently as yesterday, to  
18 check, the same full set of information continues to be  
19 required.

20 Once the company has all the information, only  
21 then is the patient given a unique identifier number to  
22 give to the pharmacist to use to get the prescription  
23 filled, which seems to take anywhere from two to five days.  
24 There is no guarantee from the company as to what will be  
25 done with this information.

1                   While Schering publicly states that a third  
2 party administrator McKesson is handling the information  
3 and this constitutes a firewall protection for the  
4 information, when patients call the access number, all they  
5 are told is that they are speaking to a Schering  
6 representative or a PEG-Intron representative, which makes  
7 it purposely sound that they are giving the information  
8 directly to the company or a representative working for the  
9 company. There is no mention or guarantee of any firewall  
10 to the patient calling.

11                   The FDA did not request, require, or approve  
12 this program for safety or for any other reasons, but when  
13 a patient calls the access line, they are told the FDA  
14 approved the program. Schering unilaterally initiated it.

15                   Now, Schering built great anticipation for the  
16 approval of this combination therapy. This resulted in  
17 patients and physicians deferring treatment and creating a  
18 backlog of patients until approval. There has been  
19 significant misinterpretation and mistrust of the program  
20 and significant anxiety that patients won't be able to get  
21 drug. The company initiated this plan without appropriate  
22 and timely education of any kind. In fact, Schering  
23 started it with no warning or consultation with the patient  
24 community, pharmacists, payers, health care providers, or  
25 the FDA.

1                   If Schering-Plough really could not meet  
2 production, launch should have been delayed until such  
3 issues were resolved. Standard interferon/ribavirin  
4 therapies work as well, so there was no patient crisis. I  
5 suspect if there were current competition in the  
6 marketplace, this program would instantly vanish. Yet,  
7 this program was only instituted after Rebetol was approved  
8 and made available to use with PEG-Intron. PEG-Intron  
9 itself has been on the market, sold with no such program  
10 since February 2001, plenty of time for the company to  
11 anticipate any potential increase in demand so many months  
12 later.

13                   Schering has never shown any public proof of  
14 the need for a registration program. It is outrageous that  
15 the burden of proof has to be on everyone else to prove  
16 that they do not. Even with a legitimate need, there are  
17 easily ways to have set up this program to maintain  
18 confidentiality. One simple example would be the use of  
19 bar coded or preprinted unique identifier number stickers  
20 for the physician to put on a prescription. That only  
21 takes one or two seconds. Then all confidential  
22 information stays with the doctor and pharmacist, as the  
23 intent of federal and state patient health information laws  
24 intend. This program was purposefully designed to skirt  
25 these laws by making the patient contact the company and

1 | its representatives directly.

2 |           Schering has managed to compromise with the  
3 | Veterans Administration and, I understand, at least one  
4 | prison system, that of the State of Pennsylvania that all  
5 | identifying information stays with the VA or respectively  
6 | that prison system. Suddenly when the threat of losing  
7 | this revenue stream became clear, Schering managed to find  
8 | a way. If Schering can do it for the VA and this prison  
9 | system, then the company is perfectly capable of doing it  
10 | for the rest of us.

11 |           A Schering representative has been quoted as  
12 | saying, "Well, you cannot expect us to make up drug that is  
13 | just going to sit on the shelf." So, I do not believe that  
14 | this registration program is to assure patients access to  
15 | drug in an environment of potential scarcity of the  
16 | product. Rather, I believe it was designed to assure the  
17 | company quick and free access to patient confidential  
18 | information in order to ensure itself that it does not  
19 | manufacture too much product. The safety concern of drug  
20 | access is of artificial creation by the company. It is  
21 | time for patient rights to come before marketing needs.

22 |           I ask the committee to recommend the following.  
23 | That the FDA put in place a more comprehensive oversight on  
24 | this Schering program and any other such program from other  
25 | drug manufacturers. FDA approval should be required before

1 initiating any such program. These kinds of programs  
2 should only be allowed when proof of clear safety need is  
3 demonstrated to the agency by the company and then done in  
4 such a way as to preserve that all patient identifying  
5 information remain with the primary health care provider as  
6 the law intends. Schering and any other drug manufacturer  
7 should and can easily comply with such a policy.

8 In closing, I want to say that the FDA is one  
9 of the only lines of protection patients have from these  
10 kinds of tactics from drug manufacturers. Schering-Plough  
11 has continued to show its disregard for patients and health  
12 care providers by engaging in these tactics and refusing to  
13 engage in any meaningful dialogue on them, using misleading  
14 information wherever it can. Community meetings and  
15 communications with this company continue to be the worst  
16 in the industry. Schering's community meetings are simply  
17 a window dressing exercise conducted in the hopes that  
18 patient advocates will simply rubber stamp what the company  
19 has already decided upon. Or as in the case of the Access  
20 Assurance Program, the company doesn't even bother to  
21 consult the community whose privacy rights it intends to  
22 violate. Most companies with HIV and hep C products that I  
23 work with make some level of attempt to balance patient  
24 needs with those of investors and profits and to seek  
25 substantive input from the community they wish to use their

1 | drugs. We don't always agree but there is some level of  
2 | meaningful dialogue and real work to compromise. This  
3 | company continues to not even care to try. In the absence  
4 | of competition in the marketplace, regulation by this  
5 | agency is the only way to protect patient rights and needs  
6 | in drug treatment. I hope this committee will consider the  
7 | requests I have made.

8 | I thank you for your time and attention today.

9 | DR. GULICK: Thank you.

10 | Our next person to speak at the public hearing  
11 | is Jules Levin from the National AIDS Treatment and  
12 | Advocacy Project, NATAP.

13 | MR. LEVIN: Hi, everybody. I'm pleased to be  
14 | here today, although it was tough for me to get here. Some  
15 | of you know me and some of you don't. I'm pleased to see  
16 | some of the press here today even though it's somewhat of a  
17 | relatively small audience.

18 | I think that it should be clear to everyone in  
19 | the room today why this hearing took place today, why this  
20 | public hearing took place today. The PEG-Intron and  
21 | ribavirin or PEG-Intron alone was approved in August. The  
22 | community, of which I'm one -- I'm a person that's had HIV  
23 | and hepatitis C for 18 years, and actually I've been on  
24 | pegylated interferon and ribavirin for 7 months now, which  
25 | is why I have this big tummy here. It's not from

1 lipodystrophy. I'm the only person who gains weight on  
2 interferon. Everyone else loses weight.

3 (Laughter.)

4 MR. LEVIN: Although I do have lipodystrophy.  
5 And these are issues that need to be addressed.

6 The drug was approved in August and the  
7 community, of which I'm a member, of infected people put  
8 together a consensus statement to ask the FDA to meet with  
9 us to talk about issues and concerns we have regarding  
10 treatment and drugs and various issues related to hepatitis  
11 C and co-infection. And the FDA responded, and we had a  
12 meeting with them during the summer. One of the requests  
13 we had was to have a public hearing like this regarding  
14 PEG-Intron and ribavirin.

15 I think that it's clear to me and I hope to  
16 everyone in the room that the FDA and one of our supporters  
17 -- I'm going to mention his name -- Richard Klein, who  
18 works in the FDA, deserves a lot of support, a lot of  
19 thanks and credit. The FDA gets credit for having this  
20 meeting here today. And I've been a critic of the FDA in  
21 the past, and there are times when I'm sure in the future  
22 I'll be criticizing them. But I think that the FDA gets  
23 credit for this.

24 And I think that one of the important things  
25 that we had here today -- because in my opinion this -- and

1 I'm going to talk policy here for a few minutes. This is a  
 2 very key meeting here today, to bring public scrutiny to  
 3 hepatitis C and to co-infection and to new drugs coming to  
 4 the market and to use for patients who have HCV and,  
 5 perhaps more importantly, co-infection. Without this  
 6 hearing, a lot of what you heard here today would not have  
 7 been brought to public scrutiny. Key HIV treaters and  
 8 researchers who are on this panel here today would not have  
 9 had the opportunity perhaps to ever hear some of the  
 10 issues.

11 Co-infection and HIV treaters becomes a crucial  
 12 part of where we go from here, due to the fact that overall  
 13 30 percent of everybody with HIV has HCV. Perhaps more  
 14 importantly is 80 or 90 percent -- or it's estimated 60 to  
 15 90 percent of everybody who got HIV through IV drug use  
 16 also has HCV. That's the population that is mostly what  
 17 we're talking about here. We're talking about former and  
 18 current IV drug users. We're talking about African  
 19 Americans. We're talking about people who are poorly  
 20 educated and, as one of the persons on the panel mentioned,  
 21 of low income. That is most of the group we're talking  
 22 about here, and I suppose we're also talking about, as was  
 23 brought out here, a high viral load and genotype 1  
 24 patients.

25 And that would not have been emphasized as much

1 | publicly in front of all of us if we didn't have this  
2 | hearing. So, I think that it's really important that we  
3 | have this hearing here today.

4 |           One of the reasons that we requested this  
5 | hearing is because we're entering into a new era now.  
6 | We're entering into an era where there's a lot of HCV  
7 | research going on. A lot of the drug companies are going  
8 | to be doing a lot of research in hepatitis C and hopefully  
9 | a lot of new drugs will be coming to market. The major  
10 | companies are all showing attention. All the major HIV  
11 | drug companies are showing major attention to hepatitis C  
12 | research.

13 |           And this meeting here today sets a precedent.  
14 | We need hearings. We need discussion. We need to  
15 | scrutinize publicly the data and where we need to go from  
16 | here.

17 |           Thanks to a lot of HIV advocates and activists  
18 | over the years, going back many years, 10 years, 15 years,  
19 | the FDA has been sensitized to the consumers and the  
20 | community in having public hearings and to addressing our  
21 | needs and issues related to HIV. We need to do this now in  
22 | hepatitis C. HIV advocates and activists are bringing this  
23 | now to the co-infection era and to HCV.

24 |           And we need to continue this so when Pegasis  
25 | hopefully gets approved, the Roche product, next year we

1 have the same hearing, and when other HCV drugs come before  
2 the FDA, we have hearings because look at, in my opinion,  
3 the important tone and questions that came out of this and  
4 the important information that was discussed here today.

5 I want to talk just a little bit about co-  
6 infection. I'm co-infected. There's a key group of people  
7 who are co-infected. There are about 900,000 people in the  
8 United States with HIV. A third approximately have HCV.  
9 The key figure is perhaps, like I said, 60 to 90 percent of  
10 people who got HIV through IV drug use has HCV as well.  
11 And that's the population that we're mostly dealing with  
12 here. This is going to be a population that may be much  
13 more difficult to treat and certainly to educate.

14 That's what my organization does is treatment  
15 education for HIV and for co-infection in affected  
16 communities and people who work as professionals in the  
17 field. And I can tell you that they are not well informed  
18 about the issues about treatment. It is difficult to  
19 educate these individuals. There are a lot of issues  
20 surrounding this. And co-infected people -- we don't know  
21 how they're going to respond to the treatment. There are a  
22 lot of variables here.

23 And this needs to be addressed this afternoon  
24 by you guys when you have your private meeting with  
25 Schering and by the FDA, and in the future hopefully public

1 | hearings that we'll have not just with the FDA but the NIH,  
2 | to talk about these issues and get them out on the table.  
3 | How can we treat and handle co-infected patients better who  
4 | are suffering with HCV than we are up to now? This is  
5 | going to take a lot of public policy, a lot of public  
6 | discussion.

7 |           Before I forget, let me mention that I'm  
8 | certainly glad that Dr. Sun is on the panel and someone  
9 | from industry is on the panel because in my opinion every  
10 | HIV drug company has a stake in this and needs to be more  
11 | interested in this discussion because it's their clients,  
12 | it's their patients that are suffering with HCV and have  
13 | co-infection. They have a stake in this. The HIV drug  
14 | companies need to take more interest in this and to do  
15 | more. And I'm not talking about one company. I'm talking  
16 | about all of them. In my opinion, the HIV drug companies  
17 | have neglected this subject and not because I haven't tried  
18 | and others haven't tried to bring it to their attention.

19 |           So, what is needed here? Well, we need more  
20 | and better studies in co-infected patients. I know that  
21 | Schering has a study. I know that Roche has a study. In  
22 | my opinion, one study doesn't answer the questions. As you  
23 | can see here that was discussed today, there are a lot of  
24 | questions that are not addressed by the big studies, the  
25 | one big study that the companies do. We need a lot of

1 studies to look at all the variables because I'm telling  
2 you now that the HIV activist community is going to bring  
3 this to public attention. And that's what this hearing  
4 hopefully starts us doing, to bring this to more public  
5 scrutiny and attention. In my opinion, in the HIV  
6 community the studies are better, they're more scrutinized,  
7 and they certainly deal with all the minor issues a little  
8 better.

9           So, there are some things that we need to look  
10 at I think that are very important for us who are co-  
11 infected. One was mentioned, the food effect with  
12 ribavirin. I think that the product label mentions that a  
13 high fat meal increases ribavirin blood levels or  
14 intracellular levels significantly. And that's key when we  
15 talk about the food effect and timing of dosing for  
16 patients who are co-infected who are on all sorts of other  
17 drugs. Eating food, can't eat food. I mean, it's a  
18 problem for people who are infected with HIV, and now we're  
19 adding something else onto the regimen. That needs to be  
20 talked about. And this was mentioned before by some other  
21 people, I think by Brian or some other people.

22           The issues of diabetes, the issues of  
23 lipodystrophy, the issues of bone mineral density, these  
24 are all issues that HIV patients suffer with. This is  
25 going to be somewhat increased, the problem, with

1 | interferon and ribavirin. We need to sort this out a  
2 | little bit more in studies and look at this.

3 |           There haven't been enough studies. One study  
4 | of retrovirus showed that patients who had co-infection had  
5 | more of an incidence of lipodystrophy, body changes.  
6 | Certainly bone mineral density has become a major issue.  
7 | It's been an issue ongoing in interferon and ribavirin for  
8 | years and in hepatitis C, but it needs much more study and  
9 | to be looked at much more carefully to understand it  
10 | better. It's never really been done that much before, and  
11 | hopefully now we can start to look at this stuff.

12 |           And what about diabetes? Diabetes is  
13 | associated with HCV. It appears to be associated with HCV  
14 | treatment. It certainly is associated with HIV treatment.  
15 | This needs to be better understood. Are co-infected  
16 | patients who go on interferon or ribavirin going to have  
17 | more problems with lipodystrophy and diabetes and bone  
18 | mineral density? And how can we understand this better and  
19 | deal with this all?

20 |           I think lastly what I want to mention is -- and  
21 | this is one of the issues that we brought up in our  
22 | consensus statement in the meeting during the summer with  
23 | the FDA, which the FDA nicely agreed to have with us. I  
24 | think it was a key moment and this is a key moment today.  
25 | The issue of fast track approval for hepatitis C drugs.

1 | You know, we've had this in HIV for years, fast track  
2 | consideration, fast track approval, close attention paid to  
3 | study design and outcomes and so forth. We need to have  
4 | this in HCV now. We need to discuss more openly, the FDA  
5 | needs to consider more carefully where we're going with  
6 | policy with drug development, how the studies should be  
7 | designed, what kind of outcomes should we be looking for in  
8 | these studies, and what about fast track approval for  
9 | hepatitis C drugs?

10 |           I'm certainly not going to recommend policy on  
11 | all this stuff today, but these are issues that need to be  
12 | considered very carefully because there are certainly some  
13 | patients who are going to need fast track access to certain  
14 | hepatitis C drugs if we make progress in research. And I  
15 | think we will. Those things really need to be carefully  
16 | considered by this panel, by all of us in the community, by  
17 | the FDA, and all interested parties, including the drug  
18 | companies.

19 |           So, just last, I hope that this meeting today  
20 | will be the beginning of better cooperation between the  
21 | industry in hepatitis C, the industry in HIV, the public  
22 | interested parties, the FDA, the HIV researchers. I'm very  
23 | pleased that we have the ACTG represented here today. The  
24 | ACTG has a liver disease focus group where they're doing a  
25 | bunch of hepatitis C studies. It's a good place to do a

1 hepatitis C study. So, I hope that this all will foster  
2 better cooperation and collaboration in trying to  
3 understand and to do better studies, do better research,  
4 respect community issues and concerns, and certainly to pay  
5 the most attention we can to co-infection issues.

6 Thank you.

7 DR. GULICK: Thank you.

8 Our next speaker is Dr. Kathleen Schwarz, who  
9 is the Chief of Pediatric GI and Nutrition at Johns  
10 Hopkins.

11 DR. SCHWARZ: Mr. Chairman and other members of  
12 the committee, I really appreciate the opportunity to  
13 provide some pediatric perspectives this morning. My name  
14 is Kathy Schwarz. I'm Chief of the Division of Pediatric  
15 Gastroenterology and Nutrition at Johns Hopkins.

16 I'm also a member of an informal international  
17 group of pediatric hepatologists who care for large numbers  
18 of children with hepatitis C. Both we hepatologists and  
19 also the very concerned families who have children with  
20 hepatitis C have been anxiously awaiting a statement from  
21 the FDA following the pediatric presentation on April 23rd  
22 requesting a pediatric mandate for interferon, pegylated  
23 interferon, and ribavirin trials.

24 What I would like to do today is to go over the  
25 rationale why we as a group believe that it is

1 | inappropriate to extrapolate from adult efficacy and safety  
2 | data and that we need properly done, randomized, controlled  
3 | pediatric pegylated interferon and ribavirin trials and we  
4 | need the mandate from the FDA to do these trials.

5 |           My clinical research has been supported by both  
6 | Schering-Plough and by Roche Pharmaceuticals, both of which  
7 | manufacture pegylated interferon products.

8 |           So, what I'd like to do very briefly is to  
9 | share with you the magnitude of the problem of hepatitis C  
10 | infection in children and then to go over these five  
11 | points, natural history, safety, pharmacokinetics,  
12 | efficacy, and some public health considerations as to why  
13 | children with hepatitis C should be regarded differently  
14 | than adults with hepatitis C.

15 |           Hepatitis C is a big problem in pediatrics.  
16 | Dr. Miriam Alter did a very nice epidemiology study of  
17 | unselected 6- to 14-year-olds showing that the prevalence  
18 | rate was .2 to .4 percent. However, more data is needed.  
19 | There is only one study of prevalence in a high risk group.  
20 | This was 5 percent of adolescents in an Oregon shelter.

21 |           We have a study, which has been funded by NIDA,  
22 | in which we have the privilege of doing epidemiology of  
23 | hepatitis C in homeless children in Baltimore. Although  
24 | our study has been underway only a couple of months, we are  
25 | very alarmed by our findings. These are very preliminary.

1 About 35 percent of the mothers in the homeless shelters  
2 and 7 percent of the children 2 to 18 years of age that we  
3 have surveyed are hepatitis C positive. There are about a  
4 million homeless children in the United States ages 2 to  
5 18. If our figures are anywhere close to the mark, this  
6 may mean that there are 50,000 to 70,000 high risk children  
7 with hepatitis C.

8 Furthermore, we have extrapolated from the  
9 prevalence data that Dr. Alter supplied and what we have,  
10 the 1990 Census data of children in various age groups, and  
11 have estimated that in addition to these high risk  
12 children, there are probably about 150,000 children in the  
13 U.S. now with hepatitis C.

14 And then Dr. Eve Roberts from Toronto Sick  
15 Children just published an article in Hepatology last month  
16 making some projections about the new patients with  
17 hepatitis C who will be born each year using world  
18 prevalence rates, 35 percent of women in the child-bearing  
19 age, annual fertility rate of 2 percent, maternal/fetal  
20 transmission rate of about 4 percent. So, we anticipate  
21 that somewhere in the neighborhood of 10,000 to 60,000  
22 newborns will be born every year in the world with  
23 hepatitis C.

24 We do not have elegant natural history data in  
25 unselected populations of children with hepatitis C

1 comparable to the wonderful studies that Dr. Seeff has done  
2 in adults. However, there are a few clues. There is the  
3 New England Journal paper by Vogt, et al. in a 20-year  
4 follow-up of newborns operated on for cyanotic congenital  
5 heart disease and transfused with contaminated blood.  
6 There was a 55 percent persistence of hepatitis C RNA.

7 On the other hand, there is another study by  
8 Toyo, et al. in infants who had maternal/fetal acquisition  
9 of hepatitis C showing a 90 percent chronicity rate.

10 In most published series -- and admittedly  
11 these are university selected patients, so they would tend  
12 to be more severely ill -- those children who have  
13 undergone liver biopsy have mild to moderate hepatic  
14 fibrosis, and then a few do have cirrhosis, up to 8 percent  
15 in a paper from Harvard from Dr. Maureen Jonas.

16 Dr. Guido, et al. showed that as hepatitis C  
17 progresses in a child, the fibrosis scores increase. We  
18 are very concerned about this data because we believe that  
19 there is little rationale for just waiting until a  
20 hepatitis C positive child becomes an adult before  
21 treatment is considered.

22 Then finally, although it is rare to have a  
23 child with such aggressive hepatitis C disease that he or  
24 she requires transplantation, it does occur. Every  
25 university center, including ours, sees children who have

1 aggressive end-stage liver disease from hepatitis C.

2 In the 1998 SPLIT database, which is a  
3 pediatric liver transplant database -- this was 1998 data,  
4 and at that time SPLIT only represented a fraction of the  
5 transplant centers in the United States. There were 10  
6 children who had either undergone liver transplantation or  
7 who were awaiting a transplant for hepatitis C cirrhosis.  
8 However, given the long life of a child, the cost burden of  
9 just one child to have a liver transplant for a preventable  
10 disease or a treatable disease is unacceptably high.

11 And then finally, there's very interesting data  
12 to suggest that in general children have lower viral loads  
13 than adults. Now, this is important, as you know, because  
14 lower viral loads are one of those factors that predict a  
15 good response to therapy.

16 This is our own data which we have published  
17 showing hepatitis C viral load in different pediatric  
18 cohorts, and those who acquired hepatitis C by a blood  
19 transfusion, those who acquired hepatitis C by a  
20 maternal/fetal transfusion had viral loads of below a  
21 million per ml. This is good news. The hemophiliacs had  
22 very high viral loads, but very little liver injury,  
23 suggesting that they are a population that needs to be  
24 treated differently.

25 Then there are safety issues, different in

1 adults and children we believe.

2 Dr. Deidre Kelly of Birmingham presented data  
3 from an uncontrolled study of interferon and ribavirin of  
4 61 children treated with this regime and varying doses of  
5 ribavirin. She presented this data in the liver meetings  
6 this year in Dallas and did show that during the therapy  
7 there was weight loss and there was a reduction in linear  
8 growth velocity. Now, after cessation of therapy, these  
9 problems resolved, but it does call to mind that these are  
10 important pediatric issues. So, we need to know how to  
11 give these drugs to children. What about the effects of  
12 the treatment regimens on reproductive capacity and on  
13 puberty?

14 One of the important issues that shows how  
15 children differ from adults in this arena is that they do  
16 appear to respond better just to interferon monotherapy,  
17 and if they respond better to interferon monotherapy, they  
18 may very well respond better to pegylated interferon  
19 therapy. The reason that this is so important is if it's  
20 not necessary to give a teratogenic drug to children with  
21 chronic hepatitis C, then we shouldn't be doing it, and  
22 until we have the support to do the appropriate prospective  
23 randomized, controlled trials, we're not going to be able  
24 to answer this very important question.

25 Now, it's also interesting to note the

1 toxicity. Hemolysis, of course, is a known toxicity of  
2 ribavirin. In the data supplied by Dr. Kelly in the liver  
3 meetings this fall on the interferon/ribavirin therapy,  
4 there was actually less hemolysis from ribavirin in  
5 children compared to published data in adults. So, this is  
6 good news.

7 Our group has reviewed all of the reports in  
8 the English literature of interferon monotherapy of  
9 children with hepatitis C that had what we thought were  
10 valid virologic endpoints. This summary will be published  
11 in the Journal of Pediatric Gastroenterology and Nutrition  
12 in the spring and addresses results in about 300 children.  
13 It's very interesting in that both the end-of-treatment  
14 results and the sustained response results in the group of  
15 children were two and a half to threefold better than the  
16 comparable published results for adults treated with  
17 interferon monotherapy.

18 Finally, what about the public health  
19 considerations? Well, the American Academy of Pediatrics  
20 in 1998 recommended the screening of high risk infants,  
21 infants born to high risk mothers, for hepatitis C. So, by  
22 the mandate of the American Academy of Pediatrics we are  
23 going to be identifying a large number of children and we  
24 need to know how to treat them.

25 So, there's a large number of children

1 available for study and treatment. Our preliminary  
2 uncontrolled data suggest that the children may actually  
3 respond better to treatment than adults, and this is not  
4 surprising because they have lower viral loads, they have  
5 less fibrosis, they've had the disease less, they weigh  
6 less. So, if we're able to eradicate this large reservoir  
7 of hepatitis C, then the hepatitis C burden is going to  
8 decrease.

9           Finally, if we have properly done randomized  
10 controlled trials, supported by the FDA, then this is a way  
11 to address the increase in proportion of new hepatitis C  
12 patients who are going to be continuing to occur because of  
13 maternal/fetal transmission because right now we don't have  
14 any way that we know to prevent maternal/fetal  
15 transmission.

16           And finally, because we would be treating  
17 children, because we hopefully would be eradicating  
18 hepatitis C in a proportion of children, there is a better  
19 cost/benefit ratio per year of life saved.

20           For a parent to have a child with hepatitis C  
21 is emotionally devastating both for the family and for the  
22 child. So, this is an emotionally charged issue both for  
23 the physicians who care for these children and for the  
24 parents of the children. As of last night, there were over  
25 110,000 Internet sites where hepatitis C in children was

1 mentioned or addressed.

2           And these parents are pressuring us, a group of  
3 pediatric hepatologists and pediatricians, to come up with  
4 appropriate treatment. There is a very active support  
5 group, Parents of Kids with Infectious Diseases, which  
6 publishes support materials for families of children with  
7 hepatitis C. And scheduled for release in January 2002,  
8 supported by the Centers for Disease Control, is a  
9 pediatric handbook which addresses all of the viral  
10 hepatitis problems in children. It contains the statement,  
11 currently there is no FDA approved drug to treat children  
12 with hepatitis C. Most physicians use experimental drugs  
13 that have been used in adults to treat liver damage in  
14 children. That's the best we can come up with.

15           So, as I said, we as a group are very concerned  
16 that we need a mandate from the FDA to inspire the  
17 pharmaceutical companies to do the appropriate prospective  
18 randomized, controlled trials in children with hepatitis C.

19           I have given you the letter. I just excerpt a  
20 couple of quotes from it. We're concerned that since the  
21 approval and release of one form of pegylated interferon  
22 and ribavirin, that there will be indiscriminate and  
23 unregulated use of these agents in children without  
24 adequate scrutiny by the FDA, and given the differences in  
25 published trials between adults and children, we do not

1 believe that simple extrapolation of adult efficacy data to  
2 children is appropriate.

3 Finally, we believe that properly done,  
4 prospective, randomized, controlled trials would be most  
5 consistent with the intent of the pediatric rule. Such  
6 trials would optimize drug development and safe and  
7 appropriate use in children.

8 We would very much appreciate your directive to  
9 the pharmaceutical companies to comply with the pediatric  
10 program requirements. Thank you very much.

11 DR. GULICK: Thank you.

12 Lastly we have a letter from Glenn Eichhorn  
13 who's a Pharm.D. and Marshall Flam who's an M.D. from the  
14 Hematology-Oncology Medical Group of Fresno, Incorporated.  
15 It's a short letter, but they've asked us to read it at the  
16 open public hearing.

17 DR. TURNER: Thank you. All of the committee  
18 members should have a copy of this letter in your folders.

19 It says, Antiviral Drug Advisory Committee:  
20 This concerns a newly established drug distribution policy  
21 by Schering-Plough for PEG-Intron.

22 On Monday, November 5, 2001, we attempted to  
23 place our weekly order of PEG-Intron as we had for the last  
24 year. At this point was referred to the "PEG-Intron Access  
25 Assurance Program" (1-888-437-2608). The staff at this

1 program required we have each of our patients call and  
2 register with the program to be assigned a patient ID, and  
3 this program claimed the Access staff asked the following:  
4 patient name, patient address and home phone number,  
5 physician name, stated the Access staff would only contact  
6 the patient to inquire as to the reason for stopping  
7 therapy with PEG-Intron.

8           Upon securing a patient ID number, we were  
9 informed that the patient needed to obtain an authorization  
10 number. This number could only be released to a retail  
11 pharmacy with a NCPDP number and that our clinic could no  
12 longer purchase PEG-Intron. The issues that concern us  
13 surrounding this policy are:

14           Number 1, lack of adequate notification of  
15 medical providers, threatening to interrupt patient  
16 therapy.

17           Number 2, violation of patient/physician  
18 confidentiality.

19           Number 3, intrusion by Schering-Plough into  
20 patient disease management by controlling access to drug  
21 therapy.

22           Number 4, redirecting therapy provided from  
23 major medical to retail pharmacy. This will subject  
24 patients to higher insurance deductibles, transporting this  
25 refrigerated medication for physician office injection or

1 potentially self-administering an incorrect dose without  
2 home health care support.

3 Number 5, no clear rationale for instituting  
4 this Access Assurance Program.

5 We are concerned that Schering-Plough, by  
6 claiming a product shortage, may gain a monopoly of the  
7 interferon alfa market for the treatment of hepatitis C  
8 patients. The FDA can assist in resolving this potential  
9 shortage of PEG-interferon by giving fast track approval to  
10 Roche's PEG-interferon, Pegasis. This move will relieve  
11 any potential shortage and may provide a cost-competitive  
12 market for the hepatitis patients.

13 Additionally, we support the request to  
14 unbundle ribavirin with Intron (Rebetron). We have been  
15 disappointed with the bundled product Rebetron because it  
16 does not allow for dose-adjustment for either the  
17 interferon or ribavirin. Bundled products only benefit the  
18 manufacturer, not the patient or clinician. We would  
19 appreciate the FDA not allowing the bundling of products in  
20 the future.

21 We thank you for your time and efforts  
22 concerning this matter.

23 Sincerely, Glenn Eichhorn, Pharm.D., and  
24 Marshall Flam, M.D.

25 DR. GULICK: Thank you.

1                   If there are no further comments for the open  
2 public part of the meeting, then we'll go ahead and close  
3 that and turn to the discussion by the committee.

4                   I think it's important just to remind us why  
5 we're here and what the purpose of the meeting is. There  
6 will not be a formal vote taken today, and we've been asked  
7 by the agency really to focus on two very specific  
8 questions. During the question period, we've actually  
9 begun to consider both of these questions, and although our  
10 time is relatively short, I think we could turn to both the  
11 questions, get input from the committee, and try to come up  
12 with some consensus.

13                   Dr. Weiss or Dr. Siegel, anything to add to  
14 that?

15                   DR. WEISS: No.

16                   DR. GULICK: Okay.

17                   I thought it would be helpful actually to  
18 address the first question. If we could actually display  
19 the designs of the postmarketing studies proposed by  
20 Schering, and then I'll go ahead and read the first  
21 question. And I should say they're summarized in Dr.  
22 Marzella's presentation on page 11, and we'll try to get  
23 the slides up there too for the committee's benefit.

24                   So, the purpose of the meeting today was to  
25 update us on the approval of PEG-Intron in combination with

1 ribavirin. Question number 1 to consider as a committee  
2 is, please comment on the nature and design of the  
3 postmarketing studies outlined in the August 7, 2001  
4 approval letter. Let's go ahead and look at the design of  
5 those studies again to refresh people's memories.

6 So, Dr. Marzella actually summarizes it nicely  
7 on page 11 of his handout, slide number 2, that the  
8 postmarketing studies were to look at the safety and  
9 efficacy of PEG-interferon and ribavirin as a weight-based  
10 regimen and the safety and efficacy of shorter durations of  
11 PEG-interferon and ribavirin in patients with a high  
12 likelihood of response, specifically genotypes 2 and 3 or  
13 genotype 1 with a low viral load.

14 Why don't we read them together as we get this  
15 up there? So, this is the third slide on page 11. This is  
16 the initial large postmarketing trial proposed. The  
17 optimization of the ribavirin dose and treatment duration.  
18 So, both of those combined essentially into one study.  
19 Multicenter, randomized, open-label trial in 4,000  
20 treatment-naive patients with chronic hepatitis C. Arm A  
21 is fixed dose ribavirin, PEG at 1.5 mgs per kg, plus  
22 ribavirin at the standard dose of 800 milligrams for either  
23 24 or 48 weeks of duration. Arm B is the weight-adjusted  
24 ribavirin arm, again using PEG 1.5 in combination with  
25 ribavirin at 13 mgs per kg plus or minus 2 for 24 or 48

1 weeks, and then the doses as outlined on the slide.

2 So, let's open for comments about that study.

3 Dr. Wong.

4 DR. WONG: I guess I'd just ask. It's hard to  
5 comment because, I mean, what's the hypothesis here? Is  
6 this a superiority or a noninferiority trial? Why 4,000  
7 subjects? I mean, I think we have to be told a little more  
8 before we can comment.

9 DR. GULICK: Could the sponsor address those  
10 particular issues? So, I guess what's the primary  
11 objective of the study and then what's the power  
12 calculation in terms of supporting that objective. And how  
13 does that relate to the sample size of 4,000?

14 DR. KOURY: Well, it's certainly a superiority  
15 trial because we've controlled the dose of PEG to be 1.5 in  
16 both groups and then we're testing two different dosing  
17 strategies with ribavirin.

18 With that sample size, it's powered to detect a  
19 5 percent difference in response rates, and perhaps just as  
20 important is to try to get additional information in  
21 important patient subgroups. A subpart of that study will  
22 be to test the duration effect in the genotype 2's and 3's  
23 with the better prognostic factors, and we're also hoping  
24 to get a substantial number of African American patients in  
25 order to be able to assess the response rates there. So,

1 | it's a large study powered to detect differences in the  
2 | ribavirin dosing strategy and to obtain important  
3 | information in patient subgroups.

4 | DR. DeGRUTTOLA: What's the endpoint?

5 | DR. KOURY: The endpoint is the standard  
6 | endpoint of sustained response 24 weeks following the end  
7 | of treatment.

8 | DR. DeGRUTTOLA: So, the endpoint is measured  
9 | at different times depending on whether patients are  
10 | randomized to 24 or 48 weeks of therapy?

11 | DR. KOURY: Right.

12 | DR. HOOFNAGLE: I'm sorry. I don't know what  
13 | you mean. You mean 72 weeks for the 1 year and 48 weeks  
14 | for the 24-week patients?

15 | DR. KOURY: It's 24 weeks following the end of  
16 | treatment. So, that's correct.

17 | DR. HOOFNAGLE: And you're not going to ask for  
18 | liver biopsies at follow-up?

19 | DR. KOURY: No.

20 | DR. HOOFNAGLE: So this is factorial design I  
21 | take it.

22 | DR. KOURY: It's partially factorial. In the  
23 | genotype 1's there's only treatment for 48 weeks, but  
24 | within the 2's and 3's there's the cross with the  
25 | durations.

1 DR. HOOFNAGLE: So, you're not going to do a 24  
2 weeks in the low level genotype 1 patients. Is that  
3 correct?

4 DR. KOURY: That's correct.

5 DR. HOOFNAGLE: Just in 2's and 3's.

6 DR. KOURY: Yes, and part of that is because I  
7 think this is an investigator-sponsored study and there had  
8 to be agreement with the investigators. And there was not  
9 an agreement to look at the genotype 1/low viral load in  
10 that way for duration. But it will be assessed in another  
11 study that's being carried out in Europe.

12 DR. WONG: Can I just ask? Can you explain in  
13 a little bit more detail what the design of this study is?  
14 I'm afraid that this one slide, just showing what the two  
15 arms are, doesn't do it for me. I mean, what are the  
16 target groups? What are the inclusion and exclusion  
17 criteria? What are the hypotheses? What is the procedure  
18 going to be? It's very hard to talk about it without  
19 seeing a little bit more. In fact, quite a bit more, not a  
20 little bit more.

21 DR. ALBRECHT: We need slide 52.

22 This is a Schering-sponsored study under the  
23 direction of Dr. Ira Jacobson at Cornell University. The  
24 enrollment for the study was opened in January of '01 and  
25 as of December '01, we have 4,000 patients screened into

1 the study. There are 26 regional PIs who oversee a region  
2 of sites that are participating, and there are a total of  
3 225 sites.

4 As we mentioned, the study design, when it was  
5 initiated, was 1.5 micrograms per kilogram PEG-Intron once  
6 weekly plus either of the fixed dose of 800 milligrams per  
7 kilogram or an arm looking at 13 plus or minus 2 milligrams  
8 per kilogram of body weight administered once weekly. It  
9 was set up for 12 months of therapy.

10 The primary endpoint, as indicated, was  
11 sustained virologic response 6 months following the end of  
12 treatment, which is standard for all chronic hepatitis C  
13 studies.

14 As you have seen here, this is the dosing  
15 regimens we're using. It's not showing the 800 milligram  
16 regimen that's in there, but this is the distribution of  
17 the patients.

18 Now, after we had our discussions with the  
19 agency, there was a desire to include into this study --  
20 may I have slide 56 please -- genotype 2 and 3 patients  
21 with a shorter duration of therapy looking at this. We  
22 amended the protocol, or Dr. Jacobson amended the protocol  
23 later this year, and all subsequent patients with genotype  
24 2/3 are going to be randomized to either 6 or 12 months.  
25 We have assured that we will enroll at least 1,000 patients

1 into this cohort to look at the randomization. So, in a  
2 sense, this is a study that has been amended to look at the  
3 additional 6 versus 12 months' duration.

4 DR. WONG: How about African American subjects?  
5 Are HIV co-infected people eligible?

6 DR. ALBRECHT: The African American subjects,  
7 based on what we know about the database, right now for  
8 demographics will run about 10 percent of the trial. Most  
9 African Americans are HCV-1, so we can expect about 300  
10 patients in this study. There will be very few type 2 and  
11 3.

12 HIV co-infected patients are not eligible for  
13 the trial. These are simply hepatitis C patients that have  
14 as their primary disease HCV with compensated liver  
15 disease. We have no decompensated patients in this study.

16 The same criteria that I described for our  
17 trials apply. Females, 12 grams of hemoglobin; males, 13  
18 grams. WBC, 3,000; neutrophils, 1,500; contraception, all  
19 the standard criteria that you'll see both in the  
20 Intron/Rebetol trials and in this recent PEG-Intron trial.

21 DR. GULICK: Dr. Englund.

22 DR. ENGLUND: Are there any ribavirin drug  
23 levels going to be performed on this?

24 DR. ALBRECHT: No. This is a clinical trial to  
25 determine, as the primary endpoint, sustained virologic

1 response rate 24 weeks following the end of treatment.

2 DR. GULICK: Dr. Hoofnagle.

3 DR. HOOFNAGLE: So, you're treating patients  
4 with genotypes 2 and 3 with 1.5 micrograms per kilogram per  
5 week of PEG-interferon.

6 DR. ALBRECHT: That's correct.

7 DR. HOOFNAGLE: And you've already shown .5  
8 milligram per kilogram per week is equivalent. So, it  
9 seems to me the patients with genotypes 2 and 3 have gotten  
10 that bad vote twice, first on the original trial and this  
11 one as far as being given a lot of interferon, more than  
12 they need. In the previous trial, you were treating people  
13 for a year with your regular product you call Rebetrone I  
14 guess, when you've already shown that 6 months was as good  
15 as a year.

16 DR. ALBRECHT: I don't know if the committee  
17 has time to see this, but we have done regression analysis  
18 looking at genotype 2/3 for both the .5 PEG and the 1.5  
19 PEG. And all of the curves are shifted up simply because  
20 of the fact they respond better. If you look, there is  
21 still the differential between the .5 and the 1.5. I think  
22 this is probably a different question. I really think  
23 based on those regressions that we don't know whether .5  
24 would be the appropriate dose for the genotype 2/3's.

25 I do agree with you. I think the 6 months in

1 the 2's and 3's is probably going to be equally effective.  
2 However, it's just like the relapsed patients. We didn't  
3 do a study in relapsed patients. We're not licensed to  
4 treat relapsed patients because we haven't prospectively  
5 assessed it. So, now we are prospectively assessing the  
6 2/3's and I think it's probably a good guess that those  
7 2/3's will do well with 6 months. But I don't think we  
8 know yet and we will know when this trial is completed.

9 DR. GULICK: Dr. Schapiro.

10 DR. SCHAPIRO: I'm also actually very concerned  
11 about the PEG doses. This is a very large, long study, and  
12 it's assuming again the 1.5 dose. I think that dose has  
13 been shown to be the most toxic. It's been shown not to be  
14 superior to the 1.0 and to now proceed with this huge  
15 trial, assuming that dose, and then in a second phase to  
16 look, I think that's probably not a good approach. Based  
17 on this strategy, it will be years until we actually work  
18 out the PEG dose.

19 DR. SIEGEL: Let me comment on where we are  
20 historically.

21 It's, of course, as your comment reflects, a  
22 complex system where you're trying to optimize dose of two  
23 different agents, and there's a real potential and an  
24 expectation of synergistic toxicity, as well as the hope  
25 for synergistic effects, so that more of one may allow

1 | toleration of less than another.

2 |           So, when the question was asked earlier, a few  
3 | hours ago, are we comfortable that at the end of this we'll  
4 | know the optimum regimen, I had a little more doubts in my  
5 | mind than the answer you got because there are a lot of  
6 | different regimens and dosing levels you could be testing  
7 | and you could test different ones in different populations  
8 | and they interact with duration and with drugs and  
9 | whatever. And optimally a very large trial in which both  
10 | are married together in a factorial type design would  
11 | probably be more informative.

12 |           There's an historical perspective here which is  
13 | that at the time the application came in and the results  
14 | for this trial became known and then PEG-interferon got on  
15 | the market, there was a great deal of interest from a  
16 | number of investigators in studying or in using -- in some  
17 | cases studying, but in many cases using -- this combination  
18 | therapy. And we received many applications for its use.  
19 | Now I'm talking about a year ago now. Every week we'd get  
20 | in recommendations for hundreds or sometimes thousands of  
21 | patients with very little in the way of hypothesis testing.

22 |           So, we talked to Schering about the fact if  
23 | you're going to support these studies, then there are so  
24 | many unanswered questions, you should start using them to  
25 | address many of the questions that are outstanding. And

1 | they were quite agreeable to that.

2 |           But the result is that there are timing issues.  
3 | This study, for example, was done at a time before we had  
4 | even substantially progressed in the review in looking at  
5 | what the dosing issues were and what the subgroup issues  
6 | were and whatever. And in interest in not letting take  
7 | forever, it's hoped that the ribavirin trial will be able  
8 | to utilize some of the data from this trial, at least the  
9 | 24-week virologic data from this trial in optimizing.

10 |           That's how we got where we are. I'm not sure  
11 | necessarily that we shouldn't be doing something else, but  
12 | just as an explanation.

13 |           DR. SCHAPIRO: Just from what we've seen this  
14 | morning where it actually did not pan out that the 1.5 was  
15 | superior to the 1.0, we did not see any data to say that  
16 | 1.5, by the endpoints that were defined, was better. So,  
17 | this a dose which is not more efficacious.

18 |           We have seen data that there's more toxicity.  
19 | This is not trivial toxicity. This is very significant  
20 | toxicity. So, if we have a dose which is not more  
21 | effective and has serious toxicity, to now start a trial  
22 | knowing that with this many patients, I mean I'm compelled  
23 | to think with this patient number, maybe a factorial design  
24 | looking at both of the parameters would be more  
25 | appropriate, especially with the time line. I think some

1 of the input -- we had all these patients who were waiting  
2 for treatment. They're all going to get this dose now.  
3 That's the question.

4 We focused on ribavirin this morning  
5 appropriately, but we didn't really spend enough time  
6 looking at the PEG, and that had probably a greater deal of  
7 toxicity. We're used to seeing the numbers, but this is  
8 very toxic.

9 DR. SIEGEL: The plan, of course, is to study  
10 the PEG 1.5 versus 1. This trial got started because it's  
11 what this group of investigators was interested in. But it  
12 compares the regimen that was applied for by Schering to  
13 the regimen that they had actually studied, which was a  
14 logical comparison to do. It's enrolled. It might be  
15 possible to add on PK. I'm not sure if that is or isn't.  
16 There's advice we could take.

17 But there are other questions. The data from  
18 this will be used to determine whether the PEG-interferon  
19 dose should be studied in a dose response -- or at least  
20 the preliminary data should be studied with the higher  
21 ribavirin or the unadjusted ribavirin, although arguably  
22 you could say, because of interactions, the higher  
23 ribavirin may not be tolerated well in the study, but with  
24 the lower interferon, it might be tolerated and it might  
25 not get studied.

1 DR. SCHAPIRO: Right. It almost looks like  
2 we're zipping over some of the key issues because we  
3 already got this far. We didn't even see the non-  
4 pegylated, the Intron A, used at different exposures and  
5 seen how that would compare. It seems that we're at a  
6 certain point, so we're moving forward, but this is still  
7 very toxic and in many patients not efficacious, and we're  
8 sort of jumping forward without knowing maybe you can use  
9 less of the interferon. It's a little concerning since I  
10 think we're getting to that answer very late in the game.

11 DR. GULICK: Mr. Marco.

12 MR. MARCO: I think I share Dr. Schapiro's  
13 frustration.

14 I find it sort of interesting that this is the  
15 Antiviral Drug Advisory Committee under CDER but that we're  
16 sort of a little angry at CBER who, it appears, rushed to  
17 approve this combination therapy at a dose that we're  
18 really not sure should be the dose. And it looks like the  
19 sponsor has come in, at least on both of their pivotal  
20 studies, giving us dose-ranging phase III studies and not  
21 telling us exactly what dose should be used. So, it looks  
22 like many things here were rushed.

23 So, I really think that we need to find out  
24 which dose of interferon should be used before we really  
25 jump the gun in looking at the doses of ribavirin, and if

1 | it can be done in a factorial design, I think that would  
2 | great.

3 | I also think that in the year 2001, excluding  
4 | co-infected patients, is just wrong. We've seen data from  
5 | so many studies that have looked at regular  
6 | interferon/ribavirin and even pegylated  
7 | interferon/ribavirin in co-infected patients, and there  
8 | truly is no major difference in response rates and little  
9 | difference in safety.

10 | DR. GULICK: Dr. Wood.

11 | DR. WOOD: I was curious if Schering  
12 | representatives might be able to add to the logistic  
13 | regression analysis that we have presented in our handouts.  
14 | It initially had just the 1.5 and then the Intron A, and  
15 | then in the Lancet article, there's the higher dose of 1.5  
16 | and then the lower dose. What I'd be really interested in  
17 | seeing is to see if you could add to that analysis the 1.5  
18 | who got dose modification and to see how that fell out and  
19 | then the 0.5 who got a dose modification to see what the  
20 | difference would be between those lines. That might help  
21 | give us information to weigh the risk/benefits regarding  
22 | toxicity, as well as antiviral response, which is one of  
23 | the primary measurements that we'd like to see. I don't  
24 | know how hard that would be to do.

25 | DR. GULICK: Other comments from people? Dr.

1 Hoofnagle.

2 DR. HOOFNAGLE: The stop rules that you showed  
3 us were very interesting. Are patients going to be stopped  
4 if they're PCR positive at 24 weeks in this trial?

5 DR. ALBRECHT: No, not according to the  
6 protocol.

7 MR. MARCO: I just have a technical question.  
8 I'm used to when the Antiviral Drug Division often gives  
9 HIV drugs accelerated approval, they ask for postmarketing  
10 studies, and that's understandable. Why are we doing  
11 postmarketing studies when this has been granted full  
12 approval? What if the sponsor decides not to do it?

13 DR. SIEGEL: First, I do want to comment  
14 quickly while I have the microphone on your earlier comment  
15 and just make it clear to the members of this committee  
16 that you are an advisory committee to the FDA. You are  
17 managed by the Center for Drugs, but we look to you for  
18 advice as well and very much appreciate your advice. So,  
19 don't feel odd about giving advice regarding biologics.  
20 That is well within your purview and role.

21 Of course, here we're talking about a  
22 combination therapy that involves a drug and a biologic,  
23 and as I'm sure you all recognize, there are many members  
24 of the division at the Center for Drugs that has  
25 responsibility for ribavirin that are here. And we have

1 worked in close coordination on these therapies. So, let  
2 me make that clear.

3 We not uncommonly ask for postmarketing  
4 commitments for outstanding questions even when there's not  
5 accelerated approval. I have to say that we have somewhat  
6 less leverage in those cases. We can't make them happen.  
7 We can't threaten to withdraw their drug, but we work with  
8 companies and most companies, including this one, are  
9 willing to work with us and commit to do studies that they  
10 recognize as important.

11 Similarly, here we're not only at the time of  
12 approval but we're several months past approval, but our  
13 anticipation is that if there is -- and indeed there is --  
14 important advice from this committee as to what other  
15 questions need to be studied, we will be discussing those  
16 with Schering. We don't have the leverage to say you have  
17 to do this or we'll withdraw you from the market as a  
18 condition of approval. We couldn't have said that even if  
19 we hadn't approved it yet. But we do work in a cooperative  
20 fashion to try to implement the advice and get the  
21 appropriate information.

22 DR. GULICK: Thanks.

23 Could I ask the sponsor to present the design  
24 in the detail that you just did for the second large study  
25 that you propose postmarketing? And then maybe we can talk

1 as a group about that one next.

2 DR. ALBRECHT: The second large study, we will  
3 select the dose as to whether it's to be weight-based 800  
4 to 1,400 based on the interim 24-week data as currently  
5 planned from the first study. We'll select a ribavirin  
6 dosing regimen. It is planned to use 1.5 with whichever  
7 regimen of ribavirin we select versus 1.0 of PEG with the  
8 selected ribavirin.

9 It will be randomized 1 to 1 in HCV-1 patients.  
10 The treatment duration will be 48 weeks. We will use the  
11 standard endpoint for determining response. It will be 6  
12 months post treatment.

13 There are currently scheduled to be  
14 approximately 1,500 patients. The sample size is 1,500,  
15 750 per group.

16 The inclusion criteria will be those studies  
17 that were used actually in the publication that you saw on  
18 PEG/ribavirin. We feel that HIV patients, for example, and  
19 some of the other subgroups need to be studied separately  
20 and those are separate studies. These will be treatment-  
21 naive patients with chronic hepatitis C with compensated  
22 liver disease, meeting the criteria that I previously  
23 described for our studies.

24 So, that study will be implemented once we pick  
25 out the regimen of ribavirin to be administered.

1 DR. SCHAPIRO: That's only genotype 1?

2 DR. ALBRECHT: Only genotype 1.

3 DR. WONG: Why does the other study require  
4 4,000 but this only 1,500? It seems to me that in basic  
5 design they're equivalent?

6 DR. KOURY: Yes. That's a logical question.

7 In this particular study, the way we set it up  
8 was not totally a conventional comparison of two treatment  
9 groups. In this case what we do is we set up a decision  
10 rule saying that in order to claim that the 1.5 had an  
11 advantage over the 1.0, we had to have an observed  
12 difference of at least 4.25 percent. So, that puts the  
13 burden back on the 1.5 in order to kind of stay in  
14 contention instead of the 1.0. So, it's a little  
15 unconventional, but we mapped out the statistical  
16 properties of a decision rule like that and showed that we  
17 thought the risks for the sponsor were worth taking and it  
18 protected very well against falsely claiming that the 1.5  
19 was better than the 1.0.

20 So, it's a little unconventional. It's made  
21 the keep the sample size within a reasonable framework, and  
22 effectively what it does, it says that if 1.5 is not  
23 performing reasonably better than the 1.0, we will agree  
24 that the 1.0 is the dose to go with. So, it's not that a  
25 simple lack of statistical difference will result in saying

1 that 1.5 is okay. We sort of characterized it in a  
2 slightly different way saying that we have to have enough  
3 evidence from the study to really continue the  
4 recommendation of the 1.5 dose.

5 DR. WONG: So, what you're saying is that an  
6 absolute difference of less than 4.5 percent is not  
7 interesting to know, would not be a sufficient  
8 demonstration to --

9 DR. KOURY: We're agreeing that that's a  
10 reasonable cutoff.

11 DR. WONG: I don't know. I mean, an absolute  
12 difference of 4 percent. I guess I'd say that that's not a  
13 trivial difference.

14 DR. KOURY: That's a nontrivial difference.

15 Well, we agree that that's a possible  
16 interpretation, but the only way to get the study more  
17 sensitive is to now start substantially increasing the  
18 sample size and this is what at the time we agreed was a  
19 reasonable way to go.

20 DR. GULICK: Dr. DeGruttola?

21 DR. DeGRUTTOLA: Can I ask you a question? I  
22 still am a little confused about the 4.5 percent. Are you  
23 saying that the study is designed to exclude a 4.5 percent  
24 difference, in other words, to demonstrate that the 1.5 is  
25 not only better than the other arm, but is better by 4.5

1 | percent, so that the lower bound of the confidence interval  
2 | will exclude 4.5 percent? Or are you saying that you have  
3 | power to detect --

4 | DR. KOURY: No, no. It's not power. We  
5 | actually have to observe a 4.25 percent difference which  
6 | turns out corresponds to a one-sided .05 percent confidence  
7 | interval or a hypothesis test.

8 | DR. DeGRUTTOLA: So, what you're saying is you  
9 | have to see a point estimate that's at least --

10 | DR. KOURY: 4.25.

11 | DR. DeGRUTTOLA: -- 4.5 percent.

12 | DR. KOURY: Yes.

13 | DR. DeGRUTTOLA: So, with a requirement that  
14 | the point estimate be 4.5 percent, what effect are you  
15 | actually powered to detect?

16 | DR. KOURY: Probably about 8 percent.

17 | DR. DeGRUTTOLA: Okay. So, that explains the  
18 | difference. It's powered to detect a smaller effect.

19 | DR. KOURY: Yes.

20 | DR. DeGRUTTOLA: I have one further question on  
21 | the other study. Sorry to go back to that. But in your  
22 | factorial design, when you do your analysis of the main  
23 | effects, will you combine over the levels of the other  
24 | factors?

25 | DR. KOURY: That's what we intend to do. So,

1 we intend to keep the precision as high as possible in  
2 answering the main point of the study which was the  
3 ribavirin dose. And I guess we'd have to look to see if  
4 there was substantial interaction. Then maybe we'd have to  
5 reconsider that. But in the absence of that, we would  
6 intend to combine over the durations to test the main  
7 effect of the ribavirin dose and to keep that as precise as  
8 possible.

9 DR. DeGRUTTOLA: And it sounds like you would  
10 have good power for that question.

11 DR. KOURY: That's right. So, there you do  
12 have the traditional power at a more modest difference of 5  
13 percent.

14 DR. GULICK: Dr. Kumar and then Dr. Schapiro.

15 DR. KUMAR: In the design of the study, my  
16 question is why are only genotype 1 patients being included  
17 and not genotype 2 and 3? Because here, at last, you have  
18 a dose comparing the 1.5 versus 1, and we know, at least  
19 from everything that we have heard, that genotypes 2 and 3  
20 in people with lower viral load probably will respond to  
21 the 1 microgram per kilogram dose and have much less  
22 toxicity. So, since we did not have the benefit in the  
23 earlier study and it's up and running to change the design,  
24 can we add the genotypes 2 and 3 to this thing, at least  
25 then to say, at least for those genotypes, a lower dose

1 | would be adequate?

2 | DR. HOOFNAGLE: They've already shown the lower  
3 | dose is the same as the higher dose in genotypes 2 and 3.

4 | DR. KUMAR: Right, but I think, if I remember,  
5 | you had just said in some of the models that you're not  
6 | sure that the lower dose is adequate for genotypes 2 and 3.  
7 | Or maybe I misunderstood what you said.

8 | DR. ALBRECHT: The reason we're using HCV-1 in  
9 | the 1 versus 1.5 is that's going to give us the most  
10 | opportunity to see the point difference we actually  
11 | described because that's where we think we will see a  
12 | difference.

13 | I think that there are two interpretations of  
14 | that PEG 1.0 versus 1.5 data. If you look at the PEG 1.5  
15 | throughout therapy, we have higher initial response. If  
16 | you go and look at the relapse rates between Intron A and  
17 | Rebetol and the 1.5 PEG, when we adjust for the dose of  
18 | ribavirin, what we see are very similar relapse rates. It  
19 | is my interpretation of the data, which you may not agree  
20 | with, that when we use 1.5 in the HCV-1's compared to 1.0,  
21 | we will see a differential. And I think if we want to see  
22 | a differential in those two doses, this is where we will  
23 | see it. That's why the agreement was made that we will  
24 | look at HCV-1. We're not going to find out until we run  
25 | the study, but that's the reason for looking at the HCV-

1 | 1's.

2 |           Whether the HCV-2/3's respond to a lower dose,  
3 | as I mentioned, the regression suggests that there is a  
4 | difference between the .5 and 1.5. Again, that is, if you  
5 | will, secondary analysis, so we can't prove it. I think  
6 | probably more importantly with the 2/3's will be the  
7 | duration of therapy.

8 |           DR. GULICK: Dr. Schapiro.

9 |           DR. SCHAPIRO: I think the process of  
10 | generating a hypothesis and then a protocol and then  
11 | proving it -- I think we should stay along those lines.  
12 | The study did not show that 1.5 was superior to 1.0, and  
13 | we've seen data here. I think it's been mentioned that  
14 | actually the lower dose PEG showed good results with 2 and  
15 | 3, and that's the one hypothesis which is not being studied  
16 | in these studies. So, basically the approved dose now for  
17 | 2 and 3 is the same dose, 1.5, and none of these  
18 | postmarketing studies are addressing the possibility that a  
19 | less toxic dose would be as effective and less toxic.

20 |           DR. SIEGEL: I'm not sure I understand that, or  
21 | if I understand it, that I agree with the premise. The 1  
22 | will be compared to the 1.5 in all genotypes.

23 |           DR. SCHAPIRO: No.

24 |           DR. KUMAR: No.

25 |           DR. SCHAPIRO: It will not. That's my point.

1 DR. HOOFNAGLE: This study that you propose  
2 will be actually larger numbers than you have in the  
3 current study with genotype 1 treated with these two  
4 regimens. It will be almost twice as large.

5 DR. KOURY: [Off microphone.]

6 DR. HOOFNAGLE: Well, what you're saying is 8  
7 percent difference is the difference between Rebetrone, is  
8 it called, and the PEG-interferon in the current study. It  
9 was 41 percent versus 33 percent in genotype 1. So, that's  
10 what you'll be studying. Again, you have twice the number  
11 of patients.

12 DR. GULICK: Dr. Seeff.

13 DR. SEEFF: If I read this correctly, are you  
14 intending to study 100 African Americans? Is that right?  
15 Would that be sufficient to show any difference that you're  
16 looking for?

17 DR. GULICK: Dr. Seeff, we didn't catch the  
18 whole question.

19 DR. SEEFF: I'm again going back to the issue  
20 of the African American. The total number that they look  
21 to be studying is 100, and I wondered whether this was  
22 enough to be able to show a difference or no difference.

23 DR. ALBRECHT: There aren't going to be any  
24 statistically significant differences in that 100 patients.  
25 What we were asked to do and what we agreed to do was study

1 | 100 patients to characterize these patients. And I think  
2 | it's important to note that in the large study, we think  
3 | there will be about 300 African Americans. Now, we have  
4 | about a 10 percent incidence in the big study which we  
5 | currently know about because we're screening. And so I  
6 | think 300 is a fair estimate. We add that to the  
7 | additional 100 that we're going to do. We're right at 400  
8 | African American patients.

9 | But to do a study to really compare differences  
10 | in the African Americans would be a huge number. So, we  
11 | will look at African Americans in the large study as a  
12 | subgroup and try to understand more about these patients.  
13 | But again, I don't think that we're going to ever be able  
14 | to do a study of the size we need in African Americans.

15 | DR. GULICK: Dr. Mathews.

16 | DR. MATHEWS: Was the issue of dosing of the  
17 | ribavirin on an ideal body weight versus given body weight  
18 | resolved in this first study? Is the dosing going to be on  
19 | total body weight?

20 | DR. ALBRECHT: We're dosing on total body  
21 | weight.

22 | DR. MATHEWS: I think this may be appropriate  
23 | to go back to the discussion that Dr. Rodvold had raised  
24 | because I thought those were very important points. If the  
25 | pharmacokinetics would suggest it should be based on ideal

1 | body weight, why proceed dosing it this way?

2 |           And secondly, also based on that previous  
3 | discussion, it's not clear to me that this dosing algorithm  
4 | based on total body weight, whether it's known that that is  
5 | actually going to provide comparable drug exposure across  
6 | the weight categories.

7 |           DR. ALBRECHT: Do you want to comment, Dr.  
8 | Laughlin?

9 |           DR. LAUGHLIN: I think Dr. McHutchinson has  
10 | made the suggestion that we will, in fact, go back and look  
11 | at some of the earlier data on an ideal body weight basis  
12 | as a first step in that, and I think that can be done  
13 | relatively quickly. In terms of modifying this present  
14 | study, I would guess that would be a difficult thing to do  
15 | at this stage.

16 |           Dr. McHutchinson?

17 |           DR. MCHUTCHINSON: Anecdotal, but we have  
18 | looked at about 200 patients from our own center, not  
19 | necessarily in these trials, looking at this issue, ideal  
20 | body weight, lean body mass index, body mass index, et  
21 | cetera. We haven't found anything. We may not have looked  
22 | at enough patients. But so far we haven't been able to  
23 | find any other than body weight. So, anything better than  
24 | body weight. That what we've done so far. That was  
25 | published in abstract form. It hasn't been submitted for

1 publication. That's the only data I have.

2 DR. GULICK: Dr. Englund?

3 DR. ENGLUND: Well, my concern is the problem  
4 with much of the dosing with ribavirin is the diet  
5 dependence on the levels. It really would be helpful to  
6 have a known meal and a known blood value. And one could  
7 do population pharmacokinetics with as little as two blood  
8 draws on one patient at a supervised setting, and it could  
9 be a subset of the patients. And I would just say that I  
10 would feel that would be potentially valuable information.

11 DR. LAUGHLIN: I guess the one caveat to all of  
12 that is it is very difficult to -- I don't think any of us  
13 in this room maintain the same diet day after day for an  
14 entire year, and this is a year of treatment and then 6  
15 months of follow-up. It's very difficult to quantitate and  
16 correlate the Christmas season with other times of the  
17 year, and those are very difficult things to control.

18 DR. ENGLUND: But, for example, RTP which  
19 accumulates over a month really could be perhaps a mean  
20 index as a better marker for overall body mass.

21 DR. LAUGHLIN: You mean specifically within red  
22 blood cells.

23 DR. ENGLUND: Yes, specifically looking.

24 DR. LAUGHLIN: Because it only accumulates to  
25 that extent in red blood cells. In nucleated cells --

1 DR. ENGLUND: That's right, and it's tricky and  
2 I can talk with you about it later. It's tricky to do but  
3 it can be done. I just offer that as a subset of patients  
4 that would potentially give you some data on which to  
5 proceed in future studies.

6 DR. RODVOLD: Yes. I would encourage that.  
7 Again, I come back to it because you're going to have a  
8 dose range in patients. This is a nice setting to start  
9 getting pharmacology, and you're drawing plenty of blood in  
10 this trial. Whether or not you can knock off a tube or two  
11 along the way and freeze down and do a POP analysis of  
12 this, I'd really look at that or look at the tail at the  
13 end of therapy when you're stopping up.

14 And you've already done some elegant PK work  
15 that you've published that you've already got a start, plus  
16 you have your own models already in place so that you don't  
17 have to do an elaborate study here other than a population  
18 type of analysis and link it to PK, both the toxicity and  
19 efficacy issues, because I think the dose ranging is where  
20 everyone is frustrated and so are you and so are we. And I  
21 think you just have a chance here to capture some things.  
22 Please, please consider doing that.

23 DR. GULICK: Dr. Weiss, these were really the  
24 two studies you wanted us to consider as a committee. Is  
25 that right?

1 DR. WEISS: That is correct. Those were the  
2 two main studies.

3 DR. SIEGEL: We've heard a number of ideas  
4 about other issues that might require other studies.

5 DR. GULICK: And that's where I want to turn  
6 next, but I just kind of want to sum up what we said as a  
7 group.

8 I think as a committee we thought it was  
9 valuable -- and it was echoed in the community comments --  
10 to really take a close look at the data with pegylated  
11 interferon and ribavirin. To have access to all the  
12 studies to be able to discuss this as a group was something  
13 that I think was valuable for the committee to do.

14 I think we appreciate in the design of  
15 postmarketing studies -- and John summarized it best --  
16 that there were hypotheses that came out of the previous  
17 study, and what you've done is to take these and propose  
18 prospective studies to carefully test those hypotheses.  
19 And as an approach, again I think that the committee is  
20 enthusiastic about that approach.

21 One difficulty I think we've had today is to be  
22 asked to comment on a study that's already designed and  
23 enrolling patients. Our input into such a study is  
24 relatively limited. Nevertheless, we --

25 DR. SIEGEL: I would simply note, though, that

1 I think your comments in that regard are very useful  
2 because they help define not only what those studies will  
3 and won't tell us, but also your thoughts as to how  
4 important the questions are that won't get answered. I  
5 suspect that Schering, as well as the FDA, will find that  
6 very useful, not perhaps necessarily in changing that  
7 study, but in figuring out, not just for this drug perhaps  
8 but other drugs as well, what are the critical questions.

9 DR. GULICK: And that's exactly what I was  
10 going to say next. So, thank you.

11 (Laughter.)

12 DR. SIEGEL: I'm sorry. I'll just express our  
13 appreciation.

14 DR. GULICK: It's a love fest here.

15 (Laughter.)

16 DR. GULICK: I'll be brief, but clearly the  
17 committee thought that the important questions were to nail  
18 down this ribavirin dose strategy. Should it be one-dose-  
19 fits-all or weight-based?

20 At the same time, we agreed that the interferon  
21 dose clearly needs to be detected, and then one of the  
22 major concerns that we had as a committee was can you  
23 really separate out those two questions. They might have  
24 different answers and different interactions. That's  
25 something to think about for future studies.

1 I think we were also pleased to see that the  
2 duration question was being addressed in the genotype 2/3,  
3 and that adequate consideration was being given to  
4 subgroups of patients, particularly African Americans and  
5 contrasting genotypes 1 and 2/3 in their responses.

6 A number of concerns were voiced around the  
7 table. Again, I think the most important is, can you  
8 really dose-adjust ribavirin first and then go on to look  
9 at the interferon dose question, or do those need to be  
10 carefully asked at the same time, perhaps in a factorial  
11 analysis?

12 A number of comments about subgroups came up,  
13 whether we already know some of the answers for the  
14 genotype 2/3 group in terms of duration and dose of  
15 interferon. Do we already know enough from the published  
16 studies to date?

17 Some concerns about special groups, like the  
18 HIV population, intravenous drug users. Not mentioned was  
19 the Latino population and might there be different  
20 responses in those groups.

21 And then a sincere plea to consider this as an  
22 opportunity to assess population pharmacokinetics and the  
23 importance of that and, along with that, the idea of body  
24 weight dosing.

25 So, that's a brief summary. I think we have

1 | limited time, but we want to turn now to the second  
2 | question that's been posed to the committee. Please  
3 | comment on other issues regarding PEG-interferon and  
4 | ribavirin that could be evaluated in further studies. Some  
5 | have already been mentioned.

6 |           Dr. Hoofnagle.

7 |           DR. HOOFNAGLE: Well, I'd like to ask the  
8 | sponsor what they're doing in pediatric studies. This is  
9 | very critical actually, and they're really good patients to  
10 | treat too. So, the results are usually much clearer.

11 |           DR. ALBRECHT: I think Dr. Schwarz mentioned  
12 | the program that's ongoing. We have a program in  
13 | Intron/Rebetol that has been ongoing. In that program, we  
14 | conducted pharmacokinetics with Intron A and ribavirin. We  
15 | selected a dose of 15 milligrams per kilogram in that study  
16 | to be used in combination with Intron A 3 million units per  
17 | meter squared. We have enrolled in an open-label efficacy  
18 | trial about 120 pediatric patients. Those patients have  
19 | completed study. They are completing follow-up as we  
20 | speak, and we will be providing to the FDA in April the  
21 | final dossier on that product.

22 |           I would mention that the first study we did we  
23 | did with ribavirin capsules. We had 50 milligram capsules  
24 | that we made as an interim thing to use with the pediatric  
25 | patients. The FDA asked us to try very hard to develop a

1 formulation, and this is actually the slide that shows  
2 this.

3 In part 1 of the PK study, we used children 5  
4 to 16 years of age. We looked at 8, 12, and 15 milligrams  
5 per kilogram of ribavirin. We selected the dose based on  
6 the hemoglobin and the antiviral effect in treatment at 12  
7 weeks.

8 In part 2 of the study, we treated 35 more  
9 children.

10 In the next study, which is an open-label -- I  
11 think it should be on the next slide probably -- we treated  
12 younger children. As I said, the FDA asked us to try to  
13 develop a pediatric formulation, a liquid formulation that  
14 the smaller children could take and that we could more  
15 closely regulate the amount of drug they were getting. We  
16 did this. We have a liquid formulation. And it was  
17 actually used in this study, and we treated 70 children  
18 with the formulation. Now, we did treat the older children  
19 with 200 milligram capsules, but a good proportion of these  
20 kids were treated with a liquid formulation.

21 At the moment, we have actually all of the  
22 follow-up data, and as I said, FDA will receive the entire  
23 dossier on these two studies in April. That's where we  
24 stand with the data right now, and it is just now being  
25 finalized. I can tell you I think Dr. Schwarz spoke a

1 little bit about what was presented at AASLD. Children  
2 have the same side effects as adults. You have to be  
3 careful with adolescents in psychiatric side effects  
4 because they are more prone. They actually tolerate it  
5 from a hemoglobin point a little better. They don't have  
6 as much hemolysis, and they actually have a little less  
7 neutropenia. So, all in all, from a response perspective,  
8 they look quite similar to the adult patients with  
9 Intron/Rebetol.

10 I will tell you these patients really had no  
11 fibrosis. So, these were patients that basically had  
12 inflammation. We did require that the patients have an  
13 elevated ALT in the first study, and in the second study,  
14 because many of these children have normal ALTs, we did  
15 allow those kids in as long as they have a liver biopsy  
16 that showed there was inflammation. We did not biopsy the  
17 children post treatment. We did biopsy them pre treatment  
18 to make sure they actually had inflammatory activity in the  
19 liver. So, that's being submitted in April.

20 DR. GULICK: We're actually going to need to  
21 wrap up the discussion. Let me just mention that we've  
22 talked about different groups over the course of the day  
23 that the committee was interested in seeing, pediatrics  
24 clearly just addressed, the HIV/hep C co-infected person,  
25 the methadone or intravenous drug using population, Latinos

1 and African Americans. Hemophiliacs came up on one slide  
2 as having perhaps a different response rate, and then we've  
3 talked a lot about genotype 1 versus 2/3.

4 Dr. Mathews.

5 DR. MATHEWS: We didn't talk about patients  
6 with end-stage renal disease, which is an important group  
7 because of the prevalence of infection and dialysis issues.

8 Then the other issue I wanted to bring up was  
9 an issue of toxicity management because in the trials that  
10 we reviewed, patients were discontinued for hematologic  
11 toxicity, and I know in clinical practice many people are  
12 using cytokine support, and we didn't see any data on the  
13 use of erythropoietin and white cell support factors.

14 DR. GULICK: Were there other specific groups  
15 that people wanted to mention? Dr. Englund?

16 DR. ENGLUND: I don't want to mention, but I  
17 just want to more strongly recommend. I didn't hear  
18 anything about PEG-Intron for the pediatric patients.  
19 We've got to have it. We have to have that available to  
20 our patients. And for my HIV patients at home, I have to  
21 say that our patients want it. They really want it. So,  
22 we have to really strongly as a committee say that we need  
23 it.

24 DR. SIEGEL: May I ask a question about that in  
25 terms of as we discuss this with the company? We're often,

1 as we've seen in the dose situation, faced with the issues  
2 of starting trials before we know the results of other  
3 trials to get the answers sooner or waiting for results so  
4 we can design the trials better or address the right  
5 issues.

6           Given the program in place with Intron A and  
7 the expectation that over the next several months  
8 substantially more will be known about risks and benefits  
9 with an Intron A/ribavirin approach in children, would you  
10 suggest that the company consider and we speak with them  
11 about starting a pediatric trial now with the pegylated or  
12 wait till there's some of those data to look at to  
13 determine what are critical questions, whether they're  
14 genotype related or age related or certain toxicity  
15 concerns or whatever?

16           DR. ENGLUND: I think no matter what, you're  
17 going to not necessarily want to use ribavirin in teenage  
18 girls. No matter what. I mean, I bet. So, you should be  
19 trying pegylated --

20           DR. SIEGEL: Oh, you're talking about PEG-  
21 interferon monotherapy.

22           DR. ENGLUND: I want PEG-interferon  
23 monotherapy. Maybe there's data but I haven't heard it.  
24 So, I think there's room to go with PEG monotherapy first  
25 and then, sure, let the adults get the ribavirin doses

1 down, and then we can translate that. But we don't even  
2 have PEG data, unless I'm mistaken, in kids.

3 DR. GULICK: So, besides the subgroups and the  
4 pharmacokinetic analyses that have been suggested, as well  
5 as the other questions posed by the first two studies, are  
6 there other areas? Let me stick with committee members  
7 right now, Jules, and if there's time, we'll come back in  
8 just a minute. But are there other areas that people would  
9 like to suggest?

10 DR. STANLEY: Trip, this is Sharilyn.

11 DR. GULICK: Oh, great.

12 DR. STANLEY: I've been listening and I just  
13 didn't make comments because most of my concerns were  
14 articulated by somebody.

15 But I would like to raise the issue that one of  
16 the public raised which is the whole issue of the marketing  
17 strategies and campaign. Again, I know that we as a  
18 committee don't have a lot to say on that, but I can tell  
19 you that in my view Schering has pushed the envelope of  
20 ethical marketing in a lot of areas. I've seen it here in  
21 Texas. So, I just would urge the FDA, whatever pull they  
22 have over that, to look at those issues.

23 DR. GULICK: Thanks.

24 Any last comments from committee members? Dr.  
25 Hoofnagle?

1 DR. HOOFNAGLE: Well, I'm not sure what you  
2 meant about monotherapy with PEG-interferon, but one of the  
3 frustrations was that once we had interferon/ribavirin  
4 combinations which were so much better -- that really was  
5 the breakthrough adding ribavirin -- then to have go back  
6 to monotherapy studies was really painful. And I would  
7 think in the children studies that you don't have to go  
8 back to PEG monotherapy studies unless there are specific  
9 contraindications. Certainly that may be the case in renal  
10 failure patients, in some HIV-positive patients. But the  
11 next study in children really should be PEG-interferon plus  
12 ribavirin and not PEG-interferon monotherapy. Please.

13 DR. GULICK: Any last comments? Jules, did you  
14 have a suggestion about an issue that hasn't been raised?

15 MR. LEVIN: Yes. We still don't really know  
16 the effect of HART on liver disease progression in co-  
17 infected people. We know hepatotoxicity can occur with  
18 elevated ALTs. We don't know the clinical significance of  
19 that. That's a question that remains unanswered.

20 Lastly, I think it would be very helpful for  
21 the FDA to consider approving Pegasis or reviewing it and,  
22 if appropriate, approving it as quickly as possible. I  
23 think it would be good to have a competitive marketplace.

24 DR. GULICK: Thank you.

25 Would anyone like to have the last word?

1 Besides me?

2 (Laughter.)

3 DR. GULICK: Okay. Then we'll close this  
4 section. Thanks to the sponsor, to the agency, to the  
5 audience, and to the committee members.

6 (Whereupon, at 1:19 p.m., the committee was  
7 recessed, to reconvene in closed session at 1:45 p.m., this  
8 same day.)

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