negative.

Now, looking for results for looking for a latent infection with PERV, I first wanted to tell you that the results were not add up to 160 because with some patients we had to go back and retest them. So we actually have more than 160 results. So we had 153 patients whose total result was regular, 23 patients had evidence of pig cells circulating and in the 13 patients, only one patient who we were unable to actually isolate a peripheral blood mononuclear cells and were unable to go back to the patient.

Twelve patients were considered uninterpretable. Now out of those 12 uninterpretables, we were able to retest seven of them and four of them turned out to be negative and three of them remain uninterpretable because we had insufficient amount of DNA to complete the testing.

Now the most interesting thing are

of course the 23 patients with circulating pig cells. All 23 were patients who had had splenic cell perfusion and what one sees here is that probably in the first two months, almost 50 percent of them you could actually detect pig cells that were circulating. But more surprising is that at one year, two years, three years, four years, et cetera, up to eight and a half years after splenic perfusion, we were able to detect other incidents of pig cells circulating in these patients. Remember, each of these pig cells contains PERV DNA.

In terms of antibodies, 156 patients tested negative. There were four patients who were seroreactive. Two of these patients were seroreactive as tested at the CDC and fortunately these were patients who had received treatment with a HepatAssist, one with a HepatAssist device. Another one was an islet cell transplant from Stockholm. Fortunately, both of these patients, we are

able to have serum from before the procedures and both these patients tested positive at the time before the procedure so we know that this is cross reactivity or at least unrelated to the procedure.

Two of the patients were positive at Q-One Biotech. One became negative seven months later and, in these two patients, we tested them by RT-PCR on saliva. It allows you to the feline leukemia where viruses shed in the saliva.

We also were able to go back to the patients who were seroreactive and these were both Russian patients in St. Petersburg. We were fortunate these were one of the few that we were able to get because actually the two patients were people who worked in the hospital themselves. One was a surgeon and the other one was somebody who worked in the emergency room. So we were to go back and test their five close contacts and they were negative for PERV DNA on their peripheral

blood mononuclear cells. They were negative when we tested them on saliva and on the antibodies, they were negative as well.

Now, we were able to then do additional serological testing on the four seropositive patients. We sent these samples to Professor Denner at the Paul Ehrlich Institute. All four patients tested positive against the p27 (Gag) about Western Blot. All four were negative against the Recombinant p15E which is an envelop protein. Then they were all four, negative again, in the ELISAs using multiple peptides from the envelop proteins.

Now, of interest is when he did a testing using his Western Blot with the Gag antigen, that two to four percent of five hundred random tests and this includes blood donor patients and butchers, et cetera, show Gag reactivity. So that the conclusion is that the four patients were Gag positive, where we found Gag positivity are indeed due

to cross-reactivity.

So in conclusion, we have no evidence of active PERV infection in any patient, despite 36 who were pharmacologically immunosuppressed and presumed to be an increased risk of infection and despite prolonged exposure to pig cells for 43.7 patient years, there were no clinical or laboratory findings suggestive of a PERV infection. Thank you very much.

DR. COFFIN: For the sake of efficiency, I'd like to take questions to this, are directed at this speaker in this presentation now. I think it would be a little bit easier. Actually I had one question.

The antibody positive individuals were different from the individuals showing microchimerism?

DR. PARADIS: There was only one, oh, actually, there was only one patient that was a splenic perfusion patient and that

patient did not show microchimerism.

DR. COFFIN: Are there any other questions?

DR. HOLLINGER: Yes. What's your thoughts about why these cells are still around oh, eight years later and so on?

DR. PARADIS: That's a good question. Unfortunately, as you can see the level of microchimerism is extremely low and so that we weren't really able to tell what kind of origin the cells were. Our hypothesis is that seeing as these are all splenic perfusion cells that they probably find a nest somewhere in the body and what we catch are intermittent release into the circulation. Our guess here is that these could be perhaps dendrite cells that are, perhaps they don't express as much gall as the other cells. But just to say that this is not actually, since that we've also analyzed some xenotransplant in primates with porcine organs and we find extensive

microchimerism even in the long-term survivors.

DR. COFFIN: Do these patients raise extensive antibodies against the transplanted cells?

DR. PARADIS: None of them have really any antibodies.

DR. COFFIN: Against the cells. Any other questions of this speaker? Hal?

DR. VANDERPOOL: Very impressive study in terms of the variety of patients and their conditions and also we were privy to maybe very reassuring conclusions regarding worries we've had. Does anyone on the committee want to comment about what you see as the import of the study for our deliberations and worries in the past and on deliberations at the present?

MR. ALLAN: I think the data demonstrates that you've got, even in the patients who had evidence of PERV, the levels were extremely low and the numbers of cells

are very low and, in many cases, you show they disappeared. In some cases you actually had microchimerism in for several years.

Obviously the concern then is the fact that whatever virus is harbored by those pig cells is still there in the patient up to eight years later which, although the risk may be very small, the potential is that those viruses could express themselves at any given time during the post-transplant period. So, in some sense, the microchimerism is advantageous in some respects but it can also be a disadvantage in the fact that you'd be continually exposed to an infectious agent.

DR. PARADIS: If I may point out that once the patient will be transplanted, they will have a whole organ that will have cells that contain PERV and that they will be also hopefully keeping these organs for a long time.

So I think that actually these patients with microchimerism are reassuring,

telling us that even though you have cells circulating in your body for several years, that this has not caused any clinical symptoms nor any signs of infection.

DR. ALLAN: I don't know if this is the appropriate forum for this but I still have questions regarding the types of assays that are used to detect PERV and the validity of some of those assays. I'm not sure that this is the form for that. We may, whether we should discuss that now or not.

There's several different assays that are being used and for the molecular assays at least in two different laboratories, the algorithms are such that if you get a positive, you rescreen it. If you get a negative, it's a negative.

I've always fundamentally had a problem with that. Usually when you do a study what you generally do is you have some other asset to validate your results. I know that there is statistical reasons to believe

that you can actually get away with it by doing it once or twice or three times but it still can present problems in terms of interpretation. The reason I bring that up is because when you're dealing in the situation where you're looking, where you may be looking for only one cell in a million, that changes your ability to detect something.

So you may get a negative one time, you may get a positive another time. It doesn't mean that the fact that you get a negative the second time means that the sample was negative. Even statistically, if you got less than ten copies present in that sample, then the statistics about the false negative rate are not based on one to five copies or whatever it is.

So, I think you really have to go back and really look at how you're validating these studies in terms of your algorithms. Having said that, still in most situations,

what you're really looking for is whether the viruses is being expressed, whether the patient has actually gotten infected. If that patient's infected, they should have much higher levels. So I'm just talking about in terms of validation of the assay. I think the data's still good.

DR. ONIONS: The algorithms been referred to as one that has been developed by, by a doctor and colleagues at GTI and I don't want to get in a debate about defending that algorithm because I think it's probably not the right audience and it's certainly too late in the day. But, I think, just as a general statement, since I wasn't involved in that bit of the study I can sort of, to some extent, look at it more objectively.

I honestly believe that what's been happening here is really pushing these tests, using the kinds of technology that are the best technologies available. Pushing these sensitivities to the limits.

When you start doing this, this does get you into, in other words, if you use a less sensitive test and all these problems disappear, but the reason that this kind of analysis has to be done is that you're using the most sensitive assay systems available and however you look at the results of this, it is clear and regardless of what conclusion that you draw from it, it is clear there has been no, in my view, there's been no established infection of human cells at least on a scale, of the scale that is detectable by the best techniques that we have available at the moment. That's, I think, a reasonable statement to make about these results.

DR. COFFIN: Might it not be reasonable in a case where you had a positive Env instead of doing one replicate reproduction to do ten replicate reproductions or something like that to try to address more specifically the exact statistical issue that Jon just raised. I

don't think it would solve all the problems but I think it would perhaps tell you whether you were seeing a real but very, give you a feeling toward a real but very low positive or a negative and false positive.

DR. CHAPMAN: My colleague Waleed Heneine asked me if he needed to come to this meeting. I said no, I didn't think so. Now, I'm regretting that he isn't here. Not being the best person from the CDC Group involved to speak to this, still, let me try to address for the people for whom this is outside their expertise.

I think the concepts, I think what you're saying is correct, Jon, in that you're inserting into the discussion the recognition that there's still a lot of uncertainty here. That no matter how much work we've done at CDC or they've done at GTI trying to validate the assays, there's still a limit to how validated they are and how much confidence you can have in the negative results.

Having said that, let me say that one reason, there's several reasons as an agency, we felt that it was important to do the confirmatory testing that Novartis asked us to for this study. One was because we wanted access to the assessments and we wanted to know what those results said in our hands.

As an agency involved in developing policy. The second is that we thought whatever the results of the study, it needed to be a study in which there was public confidence and, for that reason, there was value to having a laboratory that was taxpayer-funded and that had absolutely no vested interest in the outcome other than having the most valid possible interpretation of the outcome publicly involved.

But the third reason is trying to do the best job we could have addressed in exactly what you're asking which is the usual way one would proceed is, you take an

investigational assay and you test specimens and then you compare that to the results you get when you use the gold standard assay. There is no gold standard assay here. If there was one, I suppose it was ours because we had already published one small series with. But we've got two investigational assays and part of the reason of doing independent testing was given the circumstances and the limitations of reality and available specimens which is the absence of any known positive infected people against which to test as positive controls, we felt the best information could be gained by doing this kind of head-to-head comparison.

I think a lot was gained that's reflected in the paper but I know there was also a lot and one reason it took so long to get this out is that every stage there was the additional R&D done in multiple labs on the basis of trying to make the comparisons.

The point you raise which is if

you've got uncertainty about a result, rather then doing a second test and taking the results of those, why not do ten additional tests, is, again, in ideal circumstances that would be terrific.

But one of the problems here is that we ran into limitations with having enough DNA on the patient to actually complete ones that have testing at GTI and ones that have testing at CDC. So, again, these are important points about the importance of people continuing to not only develop their assays, to test them against other assays to make those results public and to constantly exercise caution about the degree to which they get dogmatic about belief in their results versus reality.

But I also agree with David Onions said at least for our folks and the folks we're collaborating with, this is the best we could do at the current state of knowledge.

DR. COFFIN: You can apparently get

back to at least some of these patients. I don't know if there's, so if there's only more, maybe at least in some cases more samples could be, could be obtained. I don't know.

DR. CHAPMAN: Unfortunately, the ones we can get back to are not the ones which there was concern about what the results meant.

DR. COFFIN: They're not the ones you want. They're not the ones you're interested in, yes.

DR. MICKELSON: I just had a quick question about the number, the 23 that appeared to be microchimeric. Did that correlate with any difference in their particular clinical course or were they, did they have more fevers of unknown origin or is this just a fact? You've pushed the limit of detection. You've got a result here and it doesn't correlate with anything except your tests.

DR. PARADIS: Sorry. Actually none of the patients from Russia reported any clinical symptoms whatsoever. Of course there's a regional difference in how you report severe adverse events and Russians tend to be more stoic I guess.

DR. MICKELSON: Nicely put.

DR. PARADIS: But, none of them reported having any unusual symptoms. The age of the patients did not seem to have any relevance. Unfortunately, we didn't expect microchimerism and when we planned the study in our case report forms, we did not ask what the reason was for each individual patient, for them to undergo their splenic perfusion. So that all we did was go back to the investigator and ask overall what they were. So I really cannot give you any kind of correlation and anyways it would be retrospective and I don't think you could make any sort of conclusion.

DR. MICKELSON: No. I was just

wondering whether there might be precipitating factors. If you're saying there's a sort of a --

DR. PARADIS: My suspicion is that if we followed all 100 patients, prospectively, with multiple samplings, that we would have had a lot more than 23 patients who are microchimeric.

DR. MICKELSON: Yes.

DR. COFFIN: Arifa?

DR. KHAN: I just wanted to ask you, the patients in which you have the persistence of the pig cells, have you attempted any stimulation or induction studies to see if you can induce the retrovirus on this may potentially address some potential risk concerns?

DR. PARADIS: I have to admit that we had a lot of difficulty going back to obtain samples again from Russia. We were just able to get them again to retest them for microchimerism but we were unable to do

any more than that. I'm sorry.

DR. LERCHE: Did you indicate that one particular type of exposure was more associated with microchimerism than some of the others?

DR. PARADIS: Yes. It was all in the splenic profusion patients.

DR. LERCHE: Only. All 23 were?

DR. PARADIS: All 23 were splenic profusions.

DR. VANDERPOOL: I don't want to put you on the spot but I guess I am. Carolyn, do you have any comments about the importance of this study to you? You're well-known as a researcher.

DR. WILSON: I think that this is a very important study and it's very valuable data and we're very encouraged by the results from this study but I think that, at least at the FDA, we still feel that it's an issue that requires continued data.

The type of exposure that these

patients, that they had, is not necessarily going to be the same as what's currently being tested and planning for being tested in clinical trials. So, we feel that it is important to continue accruing this type of data in current and future clinical trials.

DR. COFFIN: I'd like to move on then to hear from David Onions.

DR. ONIONS: I wonder if somebody could be kind enough, is this on?

DR. COFFIN: He certainly needs no introduction at this point.

DR. ONIONS: That's fine. I'd just like to give you a very brief outline of what I deemed here an experiment. But that's perhaps an exaggeration.

It's a very preliminary observation that derives out of a study to develop antibodies to one of the subgroups of PERV, that's PERV-B. This virus had been prepared in human 293 cells and we have perhaps a sequence of this particular virus. A

standard viruses preparation was prepared so this does not contain cells. We're looking at a virus preparation that was then inoculated subcutaneously into guinea pigs and because this was an antibody-raising experiment, the virus was given twice, 28 days apart. The analysis I'm going to show was taken 14 days after the second inoculation.

So this was really an antibody-raising study. But we did actually analyze these animals to look to see whether there was actually evidence of infection in these guinea pigs and we looked for the presence of viraemia using a para-toxical ingredient we call F-PERT which I'll comment on in a moment.

We looked for latent infection or the presence of proviruses, proviral DNA within cells and we looked for the expression of those proviruses by RT-PCR. We looked for antibody by a number of criteria both Western

Blots and the ELISAs using Hovius, recombinant p30 and recombinant envelop protein.

First of all we just screened by a non-quantitative PCR just as a quick look see, was there anything there. To perhaps a little bit surprising, perhaps all of these animals came up positive by a standard PCR with the signals being most intense in lymphoid tissue. I'll come on and show you some quantitative data in a moment.

Although this was not a cell preparation we did want to exclude that these animals had not just passively taken up contaminating DNA in the viral preparation. So we checked for the 293 DNA. That's the DNA of the cell line from which the virus was prepared and in none of these animals did we detect such DNA. Similarly, we obviously looked at non-infected controls. These were actually litimate (?) controls and there was no cross-reactive retrovirus in these guinea

pigs. There was a guinea pig retrovirus, the L2 virus. But there was no cross-reactive virus in these animals.

What was more, I think, interesting is when we did quantitative PCR, I won't go through the testing detail because, if you know it you know and if you don't you probably don't want to know it. But simply, it uses a PCR technique and it uses a fluorescent labeled probe. The point being that it allows you in real time to detect the quantity of the target that you're looking at. In other words, it gives you a quantitative PCR result. That's all you need to know really.

For the afficionados, this just shows these particular results. The black dots show proviruses that are spiked into DNA to quantitate the system and you can see that it's linear, it actually gives a coalition coefficient of .97. You can then look in the test samples which are read and look for the

number of proviruses that you find in your test sample and then those number proviruses have been normalized to a million cell equivalents of DNA. So what I'm about to show are the number of proviruses detected in an equivalent of a million cells. This is from the spleen only.

So these are five of the eight guinea pigs that we analyzed in detail or are analyzing in detail, perhaps more accurate. As you can see, the counts very from around about 3000 proviruses per million cells right up to 70,000 parvovirusues per million cells.

Now we only put in 10^6 billionths and those were actually assayed by electro-microscopy so the effect of the type was probably lower than that. I think with this kind of count here it almost certainly means that there is evidence that those viruses must have undergone at least one round of replication to get those number of proviruses in those cells. So it's not just

a single one round hit.

We then went on to look and see whether there was expression of these proviruses and this was done by RT-PCR. You can do it two ways. One is to look for the splice message which is the envelop message which is present at a lower level in these cells probably by the globular down, the full length message which we also detect and this was to use in this probe here, this PCR action, this pole region.

The net results of that are that only one of the eight guinea pigs had detectable expression at the RNA level at this single time point. Remember, we've only looked at one time point. But, we're pretty convinced this is message because the signal was negative without reverse transcriptase indicating it wasn't due to contaminating DNA. However, we did not detect the lower abundant spliced Env message. So we've got one out of eight of guinea pigs that evidence

of expression at the time, the single time point of sampler.

We then asked the question, are these animals biorhythmic and to do that we use a PERT assay. Again, this actually was been mentioned before and plus it is relevant just to quickly touch on this because it is one of these new generation retroviral assays that's useful.

It utilizes an RNA from a plant, usually a plant virus. If you've got a virus that has reversed transcriptase and will cover that RNA into a DNA copy, and you can then amplify that residual DNA using a PCR approach, and in the old days we use to just block this out. But now combining it with the type main technology we just say a moment ago, you can actually get a quantitative result because you can actually quantitate the amount of this PCR product.

This just, the next slide just shows that this is a sensitive system. This

just shows the curves coming off the machine using a 10^6 billions or 10^2 billions and you can see even the at 10^2 billions, we're actually having a signal that we know through assay validations a valid signal. So we have a system that has a detection level of 10^2 billions in the assay but we limit the quantification, quantitation is not an English word, quantification to 10^3 billions.

In none of these eight guinea pigs was there evidence of viraemia. So we have animals that have proviruses, one of the animals his level of RNA expression but we did not detect the level of sensitivity to the assay, free virus in the plasma.

I want to go through all the antibody results just to explain that we use these multiple criteria. We use recombinant p30. We validated this assay quite extensively. We've also validated the product that shows the mass spec analysis. This is recombinant p30 here. These are

secondary fragments, they're not contaminates. They're just miss, different mass spots, mass charge fragments. This is very low molecular weight contamination. So it's a pretty clean product.

But I'll just show you the results. One result from one animal with, in fact, whole virus antigen just to convince you. This just shows the curve of dilation. You won't be able to read it. I'm sorry. But that says 1 in 12,800. So the chances of antibodies going up very high in these animals, in the case of this particular animal out to a tie to 12,800. So all eight guinea pigs had antibodies to both Env and Gag proteins by these multiple assay systems.

Well, the important thing is what, how do you interpret these words, what's happening and the answers we don't know because we've only looked at a single time point. But, this is a speculative interpretation based on other model systems

like cat virus and feline leukemia virus in cats, given eight leukemia virus in Gibbons and you have to accept this as just hypothesis and could be altered.

But we know that in most patients that frequently what you see after infection is a plasma viraemia. In the majority of animals, you actually get recovery from infection. So the majority of animals you eventually see a succession of viraemia and this usually is coincident with a development of antibody. That's not to say that antibody is the only clearance mechanism. It is not. T-cell immunity is absolutely critical but it's usually coincident. These two events are coincident.

You do get a latent infection. So you do protect proviruses by PCR, either in peripheral blood or in spleen tissue and bone marrow. This latent state can last for years but without any disease development. Eventually we see to appear clonal

distinction. That's what we see in cats.

Now I don't know what's going on in guinea pigs what I might suggest is that probably what we're looking at is this sort of pattern of infection. We're looking at the transition from where there's been active replication to this sort of stage where we've got latent infection in the presence of antibody.

What is usually more serious in these infections and they are different to each other. One is usually the serious consequence is when these animals don't go into recovery phase and they develop a persistent plasma viraemia, often with infection of many tissues, epithelioma surfaces. Generally these animals don't develop antibody.

So in conclusion, what I think we're seeing certainly cross-species infection where we're seeing this cross-species infection falling into this

latent impossibly recovery pattern. That's the thing that we're seeing.

What might we use the model for? Well, we've already discussed, we don't have any evidence about what in this expression may or may not do. I think this may provide a tool to actually look and see what kinds of expression and where it's modified the pattern of infection. It may also provide other tools to look at other aspects of intervention in these kinds of retrovirus infections. Thank you.

DR. COFFIN: Very interesting. This is open for discussion and I would like to ask a question. What would you expect the outcome to be if you took these guinea pigs and infected them with a known pathogenic C-Type retrovirus like melomaniac leukemia virus or FELV? Do you think you'd see anything much different from what you did see?

DR. ONIONS: The answer, I'm not

sure. I think, I'm not entirely surprised that you're able to get virus into guinea pigs *en vivo*. I'm not entirely surprised by that.

I think I'm a little bit surprised by the fact that all of them were positive and all of them were positive at relatively high levels which implies replication. The answer is: I don't know. People have put, for instance, feline leukemia virus into it, but that's a bad example, because it doesn't replicate in rodent cells very efficiently.

DR. COFFIN: Right.

DR. ONIONS: I don't know, anthrotrophic FELV might be interesting. I don't know. But given for instance the data from Phil and others, then, maybe, when you introduce these viruses by these other roots, intraperitoneal or subcutaneously, you bypass because of barriers. If you don't have a compliment system that's going to clear, then maybe it's not unexpected that we will see

infection.

I believe that when we first discussed this issue at the first committee meeting, we did actually, on the sort of story scale, actually come to the conclusion that it was not unlikely that in a xenotransplant, that some human cells are likely to be infected.

DR. COFFIN: But, I mean, were these viruses, if you, these are immunocompetent animals that you infected.

DR. ONIONS: Yes.

DR. COFFIN: You did not obviously infect newborns for this experiment. I assume you are planning to do that at some, at some time soon if you haven't already.

DR. ONIONS: We've obviously doing a time core study at the moment. We are, obviously, a very interesting response study in suppression. We have to do through this regulatory hurdle in the U.K. to get permission to do that experiment because it

requires home office permission. But, yes, that will be done eventually.

DR. COFFIN: Because many of these retroviruses are, of course, pathogenic.

DR. ONIONS: Sure.

DR. COFFIN: Most pathogenic are only pathogenic in newborn animals.

DR. ONIONS: Yes. That's correct.

DR. COFFIN: Are there other questions or comments? That's very interesting. Is there any general discussion of these issues that anybody would like to raise even going back to the first talk? Oh, we're getting quiet.

DR. NOGUCHI: I just wanted to say one comment here. I think that it's very, this data is very encouraging because it's a possibility for actually having a model.

Whether we might be able to model some of the potential outcomes that we need to look for. Once you get something infected that's fine if the antibody stays up but if

you later immunosuppress, could you get something coming out later? So, I think from our point of view, it's always very encouraging when we can have actual models to work with.

DR. COFFIN: Actually, given that perspective, have you looked in circulating blood? Circulating them for sites?

DR. ONIONS: No, sorry. We haven't looked at circulating lymphocytes. We looked at plasma but we didn't look at circulating lymphocytes. But we will do that.

DR. COFFIN: Because that would carry us right back to the previous topic, of course.

DR. ONIONS: Yes, sure. Absolutely, yes.

DR. COFFIN: I believe we have one more request for a public discussion. You can use that one.

MS. FANO: I wrote down a few comments and questions just for the record

because I didn't get a chance to respond to Dr. Vanderpool's comment which I didn't really appreciate, where he said that my comments don't apply to the real world where people suffer.

First of all, just for the record, my own parents died of chronic diseases and I know a little bit about suffering. The comment I wanted to make before I was cut off was that should an infection spread by a xenotransplantation will be causing a lot more human suffering than is currently, currently going on.

The other comment is that no guideline can account for latent or unknown infections. While Dr. Onion's study on guinea pigs is interesting, guinea pigs are not human beings. Just wanted to remind everybody that the gene therapy deaths that occurred and were reported in newspapers, the animal tests that were done did not predict the side effects that killed those patients.

The question I had, questions I had were regarding the cost of monitoring patients and the blood supply. I wonder if anybody has done any cost benefit analysis or cost analysis in general of how much the monitoring is going to cost. There were -- read certain legal journals which said that the costs would be exorbitant. Question about how to force compliance with monitoring when patients may not wish to be monitored anymore. If they tire of monitoring and decide that they don't want to be monitored. What mechanism is there in place to force compliance, if that is even legal?

I asked this particular question back in January of '98 and I never got an answer and it is, I think, important and I hope that you won't dismiss it because governments and corporations have been held liable in the case of infected blood with HIV virus and CJD and that is: Who would, here or anywhere, would agree to be held legally

responsible if a viruses did spread as a result of xenotransplantation?

I think that's an interesting question and I don't think anybody's ever answered it and I, I do sincerely hope that you won't dismiss it and make light of it because I think it is an important question that everybody should begin to think about because I think the risk of the virus spreading is, is real and I think you've all acknowledged that.

The other question is since follow up is the only hope of catching viruses, I think that's been expressed on the panel. I was alarmed that Genzyme did not think of following up with it's patients who received the Epicel treatment and I was concerned that the FDA didn't seem to have a knowledge of these patients and where they were and any kind of monitoring procedure.

Just generally, that I was alarmed by the sort of odd state of affairs here in

terms of the regulatory status and the definitions that don't seem to be clear while xenotransplant trials are still ongoing and being approved. I'm sort of puzzled as to how trials can be allowed to go forward before any kind of regulatory frame work is really fully defined and established. So, that's a lot of questions and comments.

DR. COFFIN: Thank you. Is there any further discussion that anybody on the committee would like to have? Jon.

DR. ALLAN: Can you tell us how many xeno trials are going on at the present?

DR. NOGUCHI: I don't think we can comment specifically but we could say that there are, there are on the order of a dozen or so that are active. There's different amounts of enrollment in all of them. I would like to take this opportunity to say it is not true that there is no regulatory framework for this and, in fact, the consequences of having a very active, not

only FDA regulatory oversight but public health oversight is, I think, a commitment of the government to the seriousness of the situation.

In fact, the changing definition is not one of being unclear about what we're talking about but saying exposure to animal tissue cells and potentially organs in the future, is something that we recognize as fraught with danger and, in fact, that's why we continually come to the public to ask, and to our advisors, to ask for advise and, of course, to solicit public comment and opinions. We appreciate all viewpoints and it is appropriate to always make sure that all points of view are being heard and are continually addressed. That doesn't answer the question of liability and I won't do that.

DR. COFFIN: Is there anything else? Yes.

DR. VANDERPOOL: I want to second

what Dr. Noguchi said. You can be sure that, that I will not and surely most of the people on this committee will not dismiss what has just been said because it manifests fear and alarm and concern and that's why some of us travel from different parts of the U.S. to come here to hope that these types of concerns are taken into consideration.

So rather than, I hope you don't think that I'm either defensive or hypercritical of your perspective. I think this perspective is out there and it's shared by quite a number of people and unless we are able by our deliberations to address these concerns, as I believe we are doing over time, but if we're not able to address them, then we need to change our course.

So, my point is, thank you for offering this perspective and we will keep these considerations in mind. At the same time, you heard me say that I thought that that you had over generalized at some points

in what you said earlier and I think that continues here because what else have we been about these many meetings other than trying to regulate xenotransplantation as seriously and carefully as we possibly can do and what else are we about then actually hearing of the particular regulations that have been outlined for us today yet again.

So, the regulation is occurring, there have been indications that the FDA is quick and ready to put trials on hold if there is information that is alarming concerning infectivity and so we, we can be assured that the FDA acts when it becomes aware of alarming and worrisome developments. So, I think part of what we're about is witnessing not only a careful deliberation of these risks but a willingness to act quickly and decisively if we see they're serious.

MS. FANO: I just wanted to answer that that my impression is that much of the regulation is being done in hindsight. I

think it was Dr. Allan who said if you're putting your bets on containment it's a lost cause.

I think that some of the experiments that are being done and the clinical trials that are ongoing started before there was really any regulatory system in place. As you say, it's constantly evolving but given the public health risks involved with xenotransplantation it would seem as though, if you're talking about the precautionary principal in protecting public health, that you should have these measures in place before allowing clinical trials to go forward and that there should be a very precise monitoring program set up to make sure that you know every single xenotransplant patient that's had a xenotransplant and you know their names, where they live, if you're concerned about close contacts you know who they are and what I'm saying is that it doesn't seem like that

system has been set up. It seems like experiments, clinical trials, have been ongoing without these kinds of systems in place.

DR. COFFIN: Is there anything else? Are there any further questions from the FDA that, while they have us here, they'd like to pounce on us with? Any further comments or questions from the committee? If not, I think we can declare it. Oh. One more, one more comment from the public.

MR. BRESLIN: Hi. My name is Andy Breslin and I'm just here representing a concern citizen. I have two points to make and they both concern math.

One is, if you have an infectious agent with a very, very low rate of transmissibility across species which then has a much higher rate of transmissibility within that species, I think it should be mathematically intuitive that you're, and you add to that a long latency period before you

see the development of any symptoms, it should be intuitive that you can have a very, very long period where you're going to see nothing, no symptoms and then a very rapid expansion of disease and a logarithmic growth of that disease and you could, you could map that out mathematically but I think it should be intuitive that you're going to see a very long period where there's nothing happening and then all of a sudden, very, very rapid expansion of disease.

So I think that the fact that there has been no evidence of any disease transmission should not really give you very much assurance and, in fact, it would be very, very surprising considering the relatively low amount of xenotransplantation that has occurred thus far if you had seen anything yet. So, I just think that should be factored in when considering the past evidence of no transmission.

The other mathematical point I'd

like to observe is that since this meeting began about eight hours ago, 2,000 human bodies full of organs and tissues have been burned and buried and only a very relatively small percentage of the organs and tissues that have been burned and buried have been made use of in any way, shape or form and, by the end of the day, about 6,000 human bodies full of organs and tissues will be burned and buried and by the end of this year over two million bodies full of human organs and tissues will be burned and buried.

Meanwhile we're going to just continue to talk about oh, the organ shortage. How do we meet the organ shortage by increasing xenotransplantation and to that end I'd like to invite any of the corporate interests who are so concerned about the organ shortage and who are developing xenotransplantation to discuss some of the philanthropic public service campaigns they've had to increase organ and tissue

donation if they have any. That's about all I have.

DR. COFFIN: Thank you. Do we have another comment? Okay.

DR. LONG: Yes. I just want to touch the topic that Dr. Allan raised about the validity.

MS. DAPOLITO: Have him identify himself.

DR. COFFIN: Oh, can you identify yourself please and your institution.

DR. LONG: Yes. Zhifeng Long from GTI. We participated in the 7-11 study for replicate. Just to answer the question that Dr. Allan raised regarding the validity of the test. Why we perform replicate testing.

The reason that GTI has to perform replicate testing is because we push the assay to the most sensitivity so that we can detect a single copy of PERV DNA in the presence of half a million cells. The answer was performed both and point detection as

validate the assay with single copy sensitivity but we claim by doing three tests with a ten copy sensitivity, there's no way that you will miss any positive sample because the positive sample by the percentage of distribution with ten copy, you will have 99.99 percent of detecting it.

So, it's additional work to us but it's not a loss of validity to the data itself because essentially we have to triple our work.

DR. COFFIN: Any comments? Okay. Go ahead.

DR. SAVILL: My name is Corinne Savill. I work for Novartis. We are one of the companies working in the field of research into xenotransplantation. I'd just like to make some comments in reference to the last speaker but one.

Firstly, just because nobody else in the room has mentioned it, just to make the point that most people are aware that not

public? One last word, any last word from the FDA? Last word from the committee? Ah, Claudia.

DR. MICKELSON: No, no. I'm not, never mind. I just wanted to defend the use of animal models. While they may not be 100 percent predictive, it is one of the few things you have that can allow you to progress from the theoretical bench through a living whole system that can respond. But, it's in no way 100 percent predictive but it's an intermediate step that could never be gone around.

MS. FANO: Just to add to that, that from the June 3rd and 4th FDA subcommittee meetings that were held, the researchers involved in the field themselves acknowledged that even the baboon model that they had was really not a good model of the human scenario. So, the trouble with animal models is recognized even by the researchers themselves.

DR. COFFIN: They're certainly not perfect.

DR. SIEGEL: I'm sorry but just a quick note to thank very much the members of the committee, the guests of the committee. Your deliberations were extremely helpful to us. The chair, the previous chair for a well run meeting that ended on time, the commenters from the public and from, as well as the presenters. We very much appreciate today's proceedings.

DR. COFFIN: With that we're adjourned.

(Whereupon, the MEETING adjourned at 5:09 p.m.)

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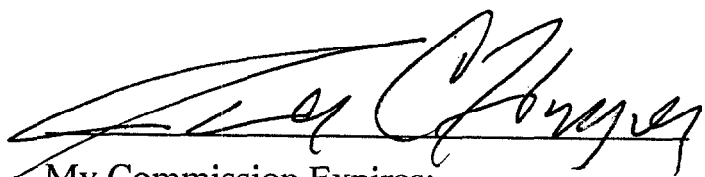
CERTIFICATE OF NOTARY PUBLIC

STATE OF MARYLAND

I, JAMES C. HARPER, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn; that the foregoing transcript is true and accurate record of the testimony given by said witness.

I further certify that I am not related to any of the parties to this action by blood or marriage and I am in no way interested in the outcome of this matter.



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