that essentially would be the opposite of what yours are. You are almost entirely self-sustaining in terms of platelet collection and get a small amount from an outside supplier.

How would such a system or could such a system work well where hospitals acquire their platelets largely from an outside supplier and very little internally.

Would the onus then fall on the blood collection center to initiate the culturing, because my sense is that hospitals would be receiving these platelets from an outside supplier at various days into the five-day duration. So there might not be adequate time.

You know, you did your culturing on Day Two. What if you get a Day Two platelet? What are your thoughts about that?

DR. AuBUCHON: You raise a very good point, Mary, that in different logistic situations one may need to use a different protocol.

In an urban setting a university hospital probably does not maintain, relatively speaking, as large an inventory of platelets and might depend on multiple deliveries daily from their blood center, and might only keep the platelet in inventory for a few

hours, not for the full storage period of the platelet.

In such a situation, I think the appropriate approach would be to work out a collaboration between the supplier and the hospital where the supplier is in the situation where they can collect the culture early on, and they would need to set up a system to rapidly identify the recipient hospital and to provide the information to that hospital to pull the unit off the shelf if it was in the hospital's hands rather than the blood center's hands at the time the culture was positive.

That is essentially what is being done in Europe, in not only the Belgian and Dutch blood centers but also in several German and Spanish blood centers that are doing this. It's the blood center that is doing the culturing.

That hasn't been the approach that was going on in this country. Our blood centers seem to continue their focus on detecting viruses. So I felt that, if we were going to do anything with detecting bacteria, it was going to have to be done in a different manner.

DR. ALLEN: This whole issue -- It's a fascinating problem, and I think the discussion this

morning has been very helpful. My personal feeling is that we are not quite ready to move forward yet.

I think, certainly, the data on the quality of the platelets, although that's not an area that I'm expert in -- Reading through the background paper and hearing the presentation and discussion this morning, I'm of the opinion that we certainly are moving forward to where seven-day platelets in terms of their quality is certainly satisfactory.

I think the issue of how one detects and deals with potential bacterial contamination is still a much more thorny issue. As I look at the list of -- and I have not read the paper by Kuehnert, the so called BaCon report, but it's a recent report.

You look at the list of gram positive bacteria. Those very likely are skin contaminants, and that 60 percent of them -- it just basically says this is an issue that ought to be aggressively looked at, because we are going to do ourselves a big favor if we can reduce those skin contaminants at the time of collection.

Nonetheless, the skin contaminants aren't necessarily the ones that are going to create the biggest problem to the patients. In actual fact, some of the cultures that were done in Dr. AuBuchon's

laboratory may not have been false positives. They may well have been true contaminants at a very low level.

They went back to confirm and, in fact, they had died off in the original. I think that certainly is not out of the question.

The gram negatives -- Forty percent of the contaminants were gram negatives, including some bacteria that I scratch my head in terms of how they got there, some of the *Serratia* species, in particular. Those are clearly bacteria that can grow to very high levels, even though they are in a refrigerated setting. They certainly can create very significant endotoxic sepsis in patients.

There is one, the *Yersinia enterocolitica*, I would guess, may have been an intrinsic contaminant in from the blood of the patient, and that's an infrequent issue, but certainly historically one that occasionally has occurred. I think those who remember the platelet collection at the NIH, I think, back in the 1970s where there was a donor with chronic osteomyelitis.

So those are other donor issue. But those gram negative bacteria bother me, and I think that is an issue that has to be dealt with.

Then one comes to the opening discussion that we had this morning on reducing risks or errors in our system and the need to begin looking at problems on a systemwide basis.

When we do that, I run right up against a problem with having individual hospitals around the country being responsible for culturing each and every unit of platelets that's going to sit around for more than three or four days.

The question that Dr. Chamberland asked, you know -- well, maybe there needs to be some sort of a system between the collecting agency and the hospitals and so on -- I think there's a lot that has to be very carefully thought through and worked out here.

I'm concerned with this system that requires us to go into every single unit of platelets, take off 5 ml aliquot, send it for culturing and so on. They are not insolvable problems. What we need is to make sure that we've got some good -- the best minds thinking about this and good research in this area.

That's maybe an area where NHLBI and the CDC and the FDA need to collaborate together to put the money out there, get the right protocols in place

to help address this so that we can move forward in the years ahead.

I think this is an exciting development and, clearly, I'm very pleased with the information on the quality of the platelets themselves, and let's see if we can address the contamination issue.

CHAIRMAN NELSON: Yes.

DR. HARVATH: I wanted to follow up on that a bit, and also to ask Dr. AuBuchon if you and Dr. Brecher and others who have taken this type of approach with the BacT/Alert system have considered combining your efforts in a multi-center approach, and perhaps approach the FDA, since you are already implementing this in your blood programs.

You mentioned that you needed an n, I think, of 13,000 for the BacT/Alert system, and I'm not sure how many times they may have asked you to sample the same unit. But would you be able to approach that n of 13,000, let's say, with the groups who are taking this approach currently in the country to combine your effort and data to justify using that particular culture system?

DR. AuBUCHON: The problems in conducting that trial -- and we did have some discussions, preliminary discussions, about it -- really related to

logistics and cost. In discussions with the agency about how this would be put together, we really faced a dilemma.

One approach would be to culture on Day One or Day Two, whatever the -- let's call it the test point of culture was -- and then culturing on a later date and using this second culture as the gold standard, anticipating that if the unit were truly contaminated, we might miss it on the Day One or Day Two culture, but we would certainly pick it up on the later culture.

The agency was of the mindset that we would need to perform that second culture on Day Five, since that's the day of outdate. Well, if we were to hold all of our units until Day Five in order to culture them, we would not be able to transfuse them essentially. We would outdate most of them.

That would then force the sponsor of that trial to not only pay for the culturing but to pay for the units, which would have been enormously expensive, well over several million dollars.

The other approach would be to allow for the transfusion of the unit on Day Six or Day Seven after culturing it on Day Five. That, however, would require an IND, IRB approval, and informed consent to

the patient, which although I would have no ethical concerns going to a patient and asking for their consent to receive a cultured unit on Day Six or Day Seven, practically that was a huge problem when you multiply it by 13,000.

So we have not proceeded along that way. I would like to propose a simplified approach whereby a second culture conducted at least 24 hours after the first one or at the time of release could be the gold standard culture against which the earlier one could be compared. But I lack a sponsor for such a trial.

DR. FALLAT: You had a very nice presentation, Dr. AuBuchon, and you make a very cogent argument that this is a big problem. I kind of share the questions about the ability to expand your hospital across the country, but we haven't heard anything more about the UVA decontamination system, and where does that stand, and where is the data on that, and is there more of that data from your -- You know, can we hear a little more discussion about what some of the other solutions to this contamination problem are, beyond just culturing?

DR. AuBUCHON: Well, those -- I think you probably will be hearing more about the psoralen inactivation systems in the future. I shared the

concern that Dr. Slichter mentioned as to whether or not platelets treated in this method will be able to be stored for seven days and yield a successful clinical result.

In vitro, it looks like they may. However, *in vivo* we already have data at five days that they are not the same as untreated platelets, and they would -- although if we have to transfuse more, that would not confer any additional risk relating to bacterial viruses, because they would be inactivated.

One always has to raise then the issue of will we have enough platelets if, all of a sudden, we are having to transfuse twice as many. Will we be able to produce twice as many platelets? I doubt it. And the other issue of the toxicity of the technique itself, particularly when you start transfusing more of this material -- does that become the overriding concern then?

DR. SLICHTER: Well, maybe I can address that a little bit about the pathogen inactivation. I mean, I think the companies that are proposing this technology have a lot of *in vitro* data and *in vivo* animal model systems that the pathogen inactivation process works, but you know, when they went before the FDA, the FDA did not ask them to do an infectious

disease trial with the pathogen inactivated product, because the numbers would have been gargantuan.

So the FDA, I think, accepted their animal model systems, their *in vitro* contamination data suggesting that the process does inactivate a wide variety of bacteria, viruses and protozoa, and then the FDA, I think rightly, wanted to concentrate on the fact of what is the quality of these products and, specifically, do they provide hemostasis.

So I think, in support of the pathogen inactivated platelets, hemostatically they are every bit as good. I think part of the reason for that is, even though the count doesn't go up as high and they don't survive as long, as I've mentioned, I think you need very few platelets in order to provide hemostasis.

So I'm not surprised that the hemostatic efficacy was similar, because after all, the counts did go up. The platelets did survive. They just were not as good as the noninactivated product.

So I think that we do have available to us two separate methods to extend storage, either detect or inactivate, and I think that, you know, although I didn't discuss it, they collected an enormous amount of adverse event data.

I mean, every time the patient reached for a Kleenex, it was recorded. Between the control and the treated arms of the trial, there was no evidence of any adverse consequences, and these people were transfused for up to 28 days, and in some of them they got a second cycle of either pathogen inactivated or control platelets for an additional 28 days, if that particular patient needed a second course of platelet transfusion therapy.

So I think there is a lot of data on the fact that there are to adverse events in the patient related to the transfusion of this product.

CHAIRMAN NELSON: Okay. If there are no other burning comments at the moment, I would like to take a break now. People can check out and what have you. If we could do it like in 20 minutes or so, so we could -- because people are going to have to catch planes at the afternoon.

(Whereupon, the foregoing matter went off the record at 10:34 a.m. and went back on the record at 10:58 a.m.)

DR. SMALLWOOD: Are the individuals present that will be making presentations during the open public hearing? Dr. Bianco and Dr. Valeri? They are out in the hall? Thank you.

CHAIRMAN NELSON: Well, someone please tell Dr. Bianco, if he doesn't come, I'm going to give his talk. Is Dr. Valeri here? We are supposed to have a committee discussion, which we have already had, sort of.

DR. SIMON: Dr. Nelson, we might in this interlude just ask, have we given the FDA -- I mean, is this what they want from us?

CHAIRMAN NELSON: Yes. You know, I could probably give an erroneous summary, but to say that the Committee is very interested in the concepts presented and the idea that it might be feasible to put in some detection systems that could be routine, if not more widespread, and if that was possible, we then could move to seven days.

Whether or not these two decisions are linked, in my mind, they sort of are. But in a way, they are a little bit separate, too, in that the issue of the function of the platelets after seven days and whether or not that increases the contamination risk is still a little bit of an open issue.

You know, I think the data that were presented were quite interesting. My understanding was that there were more -- not in transfusion medicine, but I know Dr. Yamatovian from the Cleveland

Clinic has reported on this, and Dr. Gilcher I heard yesterday from Oklahoma Blood Centers says they routinely culture platelets.

Now whether or not, you know, they follow a FDA approved protocol, I guess, is another thing, but the fact is that I think there are more centers that are actually doing cultures and basing some transfusion medicine decisions on these data. But the fact is it's not a -- you know, it's not a routine procedure at the moment.

I guess one of the issues is what are the steps that we would need to move to make it routine. One might be a clinical trial. I think one of the issues is the fairly high rate of false -- apparently false positive cultures, and if all of those units were discarded, it would certainly nullify the advantage of the ones that would be salvaged by the five to seven-day cultures.

DR. SIMON; I think he had that in his financial analysis, the workup of the false positives.

CHAIRMAN NELSON: Well, right. According to his, but if in fact only one culture were taken and there weren't a five-day or a culture taken later to confirm whether or not it was a false positive, if the unit was just destroyed based on a single positive

culture, then we could actually go backwards in terms of the number of units that would be -- you know, that we would lose units. Yes, Dave?

DR. STRONCEK: You know, I've sat in on some other discussions on the problem with bacterial contamination of blood, and there really isn't a lot of great data. There's a few studies, and the data we saw this morning, while it's interesting and it's hopeful, there's only -- what? -- 2000 units we saw.

So that's not -- With the low incidence, it's not a lot of data. One thing, though, I'm confused about. What if -- Maybe Jim can answer the question, or Vostal. What is involved in doing one of these protocols?

You know, superficially I would think a person would have to go through their IRB and get consent to culture blood and then extend platelets to seven days, but some -- and you may even have to go through the FDA to get an IND or something.

Are there a lot of barriers or is all this -- I didn't get that part from the discussion, and is that creating a barrier for people to do this?

DR. VOSTAL: Well, I think the studies would have to be done under IND. Jim has been talking about these studies for a couple of years now. One of

the problems we had with him going ahead and using seven-day old platelets is we weren't really sure or we didn't have any data demonstrating that the current storage condition would produce a good platelet.

You know, now he's got data that we could extend the shelf life up to seven days. You know, that opens up the door for using that extension, as he was saying, to sort of pay for the cost of the study, you know.

If you could have a detection system or you could do a trial under IND where you are going to be looking at the effectiveness of the detection system, platelets you culture at Day Two and then a confirmatory culture maybe at Day Five or two days later, and then pay for the cost of that study by reducing your outdating of the platelets.

So I think we have -- You know, we are moving toward being able to use seven-day old platelets, but I think one thing that maybe wasn't clear up front is that there are two issue.

One issue is whether the platelets will work. So it's platelet efficacy. The other issue is the detection system, you know, or decontamination system. We have to take care of the bacterial contamination problem first.

We may be doing it out of sequence that we are looking at data on the efficacy of the platelets, but we certainly would not approve any of these -- or bags for extending shelf life -- without having some kind of a system in place to take care of the bacterial contamination problem.

DR. STYLES: Could this Committee come up with some sort of statement that we endorse the continuation of research in that direction, which is that we feel that there is adequate -- this is only my suggestion -- adequate data to suggest that the platelets are effective enough at seven days that then you -- because you made a very good point. Clearly, we wouldn't go forward with any sort of decontamination if the platelets weren't any good at the end.

Maybe this Committee's role is to state that we feel fairly comfortable, if everyone agrees to that, obviously, that the data that exists supports the idea that these platelets are functional enough so that efforts to go into contamination are warranted or suggested.

DR. VOSTAL: Well, I think that would be good. It would encourage people getting into that research. You have to keep in mind that the data we

saw today was only on a single platelet storage system, and that data could be different for different bags, different manufacturers.

So we would need to see data from each manufacturer to approve them for extension to seven days.

CHAIRMAN NELSON: I also wonder if some thought could be given to the study design that might be acceptable to the FDA, given the costs that were mentioned. I know Dr. Yamatovian from Cleveland did a study in which there was a -- Platelets, I think, as I recall the study, were randomly either cultured or not, and then the patient was given standard platelets or cultured platelets, and they looked at febrile episodes. They looked at etcetera.

A study like that -- It seemingly maybe could be done with perhaps less cost if you didn't have to pay $7 million for the platelets that cultured at Day Five.

It seems to me that maybe there are study designs that could generate larger numbers at less cost that might provide data that would be useful for us to see the effectiveness of culturing platelets.

DR. HOLLINGER: I think along those same lines, I think Dr. Allen brought that up nicely, that

much of the bacteria -- some of the bacteria that are seen probably are coming from the skin.

There were, I think, some studies that at least suggested you could reduce that substantially, not entirely but substantially, by the simple method of just removing 15 to 30 -- I don't know what the exact number -- 15 to 30 ml of blood initially at the start, and that one would consider the FDA suggesting to manufacturers that they incorporate something in their technology that would do that.

It's not going to eliminate it all, and you are still going to have to have, I think, these other methodologies, whether it's pathogen inactivation or detection. But it would still give you that little bit buffer for completeness there. So I think that would be another thing.

DR. VOSTAL: That's a great idea. I think actually, it was a year ago that we had a discussion here at the Committee where we discussed the version of the 30 ml blood collected. There was a clinical trial done in Europe that demonstrated it could be effective.

There was an *in vitro* study done by Steve Wagner at the Red Cross, showed that we could model the removal of 90 percent of the bacteria in the first

30 cc's. So I think the outcome of that discussion was that the Committee recommended this is a good idea, and we encourage the manufacturers to put this in place.

The only problem with that is, you know, you have to take it on faith. We don't really have any data what the current infection rate is, and you wouldn't know if you are actually improving things or not.

MR. DUMONT: Larry Dumont from Gambro BCT. A couple of comments on Dr. Hollinger's point, and then a question for FDA on it.

First of all, on the removal of the first aliquot of blood, I think a lot of people are familiar with those studies. Actually, in France they have an interesting report where they have looked at this problem, and they said the number one danger is the skin contaminants, and the two things that need to be done to address that -- number one is proper antisepsis of the skin, and they have a national system.

So they implemented a universal retraining of all their phlebotomists, and they went out and taught people how to do it correctly and not to re-palpate after they decontaminated and things like

that.

Then they also instituted this mandatory removal of the first aliquot that comes through the needle. They were able to measure reduction in the septic transfusion reactions. Didn't eliminate it, but it was a substantial reduction. So that certainly is an effective approach.

I think the data from Johns Hopkins demonstrates that every needle puncture carries an incidence risk of about 70 per million of having a septic transfusion reaction. That's not even bacteria in the bag, but in fact a clinical septic transfusion reaction. So you can do the numbers from that, and that's in a pretty controlled situation.

My question to FDA, which they probably can't answer right here, but some of the logistics of such a clinical trial -- One of the points that Dr. AuBuchon brought up was actually consenting patients, if you were under an IRB and IND type mode.

I know there are some options where you do not have to always consent a patient with a clinical trial. So if there was an IND approved through FDA, and these could be -- trials could be set up, does the FDA think that it would be possible to have a trial where you would not have to consent every patient to

receive a seven-day-old platelet?

DR, VOSTAL: Well, that's a really tough question. I think we would have to take that to our clinical branch for discussion and consideration. I think, from my point of view, I would think there would be -- you know, you should require a consent up front.

DR. BIANCO: I think that Larry's -- Celso Bianco, America's Blood Centers -- should be taken into account, because it's not going to get worse than what it is now. If anything, it will be better or it won't work. So I think here is a situation where, if everything is done according to the current system, present rules and things like that, and if you have a way of sampling those bags that is more effective than we have today, that probably it would be worth discussing it with IRBs and all that. Thank you.

DR. LEW: The other thing I was going to add, though: Could the study design be different where, instead of demanding that they do it on Day Five and then thus using older platelets, then do it before the time of release, just before release, just doing the study design a little bit differently.

You could actually collect data on dose response to give you a hint if it's going to be a

problem at Day Five. That might be more acceptable, I think, to the public as well.

Sitting on the board -- Sitting on the IRB at my institute, I can tell you for sure we would not allow older blood without informed consent.

CHAIRMAN NELSON: Dr. Smallwood just reminded me that we are now in the open public hearing. So if anybody wants to make a comment, and is Dr. Valeri here now? Okay, because he asked -- and, Celso, you are listed, but was that your speech, what you just said?

DR. BIANCO: I have said enough. This has been a very healthy, very informative discussion. Thank you.

CHAIRMAN NELSON: Okay. Well, are there any other comments, and what does the FDA -- What would the FDA like for us to do rather than just discuss the issue?

DR. VOSTAL: The point we were actually looking for in this discussion was: The design of these trials to look at the way the bags can store platelets is such that you would do them -- As Jim was showing, you do a survival at Day Five, and you do one at Day Seven, and compare the two.

Pretty much, we all agree that there is

going to be decrease in the survival and recovery at Day Seven. Our question is: When we see these systems come to us, you know, what should be the acceptable difference? Should a ten percent difference or a 20 percent difference be adequate or should we set some kind of an absolute limit for platelet efficacy?

CHAIRMAN NELSON: I wonder on the issue of the informed consent. I agree that, you know, given where we are, the informed consent for seven-day, you would have to consent a patient. But patients might consent if it were coupled with a cultured bag.

In other words, if the patients -- If we are saying -- you explain, you know, here's the way things have been done. There is some risk. We are trying to reduce the risk by culturing the bag and reducing the -- and actually improve the detection by, you know, if there's contamination, to allow enough time actually to be sure we detect it and divert those units, so that we may give you something that's a little -- may be a little less effective in terms of the platelets, and the estimate is ten percent or something. But it may also be a little more -- a slightly likelihood that it might be a little more safe.

Therefore, it isn't that, you know, we want you to take an inferior product that may not stop your bleeding, but we want you to -- we are offering you something that we think, you know, might decrease some risk associated with the procedure.

DR. STYLES: I don't think it's a problem with the study in itself. I just think that they have to have informed consent. So what I'm hearing, though, the problem is going to everyone of these patients every time you have to do a blood transfusion. That is going to be very, very hard to do.

DR. HOLLINGER: Is Dr. AuBuchon still here or has he gone?

CHAIRMAN NELSON: He's gone.

DR. HOLLINGER: I guess he's gone. I thought i heard him to say -- and maybe one of the other Committee members or somebody here could correct me. But I thought he said that some of the blood -- I mean, they culture it on Day Two, but that presumably some of the platelets are given before they get an answer back.

If that's the case, I was wondering what he does then, let's say, on Day -- say, platelets are given on Day Three, but on Day Four, Day Five, the

culture is positive. Do they then go back and tell the physician I have a positive culture with a *staph. aureus* or something like this to the physician or the patient or -- I wasn't sure if anything was done with that information.

It turns out possibly, although Dr. Allen mentioned it may have just been a negative culture because the bacteria were gone at that point. But if it were really a truly positive culture, would that make a difference? Does anybody --

DR. SIMON: Yes. He would have to, I believe. From the data he gave, that hasn't happened, and the system almost always catches the positives within the day. So he has that day, and it's very -- Those that are transfused on Day Two are highly unlikely to have an adequate amount of growth to cause a problem.

DR. HOLLINGER: But, Toby, just a question. If you have some bacteria -- Again, I'm not sure how this works. If you have some bacteria in a platelet culture -- I mean in platelets, and it's given to an individual, even though it's a low concentration, I presume that once it goes into an individual, that there would be growth of t[illegible] -- potentially growth of that bacteria in the individual

at 37 degrees.

DR. SIMON: But potentially. But many of these people have no problem.

DR. HOLLINGER: I understand that, but I just wonder. I mean, is it because there are other immune mechanisms going on that are preventing that, and there are probably many of them getting antibiotics and other things?

CHAIRMAN NELSON: You know, there are all kinds of procedures associated with bacteremia. You go to the dentist. You get a proctoscopy. You get TUR, almost 100 percent of people will have -- and you know, they are cleared. These patients may not clear them quite as well, but I think a negative culture on a patient doesn't mean a thing.

DR. STYLES: You know, you were talking about all of this, but I think what Dr. Vostal said about, before any of that can even go forward, is the problem of establishing a standard of minimum platelet efficacy.

To my mind, the problem is there are so many ways of measuring platelet efficacy, and one will have to decide on whether one is going to use an *in vivo* versus an *in vitro* measure with the attendant difficulties of each one of those and the

interpretation of them.

So maybe the Committee could discuss -- Well, what is actually the question before us, I think, from reading the statement was: Is there a minimum level? My response to that would be it depends on what you want to use as your measure.

Then can we decide on a measure that we would recommend to be used, because that's really, again, I think, the first question.

DR. VOSTAL: I think we sort of accept radiolabeled studies as a surrogate for platelet efficacy, and platelet efficacy would be the way platelets circulate and stop bleeding. But those are -- If you want to do a bleeding study, it's a very large study.

So historically, we have accepted radiolabeled studies on products or on platelets that have been stored under differing conditions. So for us to evaluate these new conditions out to Day Seven, we would still look at the radiolabeled studies.

The numbers we were looking for is, you know, what's the minimal recovery, and what's the minimal survival that would be still useful as a platelet product.

I had some discussion with Sherrill during

the intermission, and she was giving me some of her ideas about that. She thinks that it's a five-day survival 50 percent, somewhere around 50 percent recovery. Did I get that right, Sherrill?

DR. SLICHTER: Yes. The point is that I think that patients don't do the same thing with platelets as normals. Okay? So what I've tried to show you is that, as soon as you are thrombocytopenic, your survival is reduced proportionate to how thrombocytopenic you are, but your recovery is, in fact, the same as in normals.

So Jaro and I were discussing at the break -- He asked me this question, and you know, I think we have five-day stored platelets. That's the accepted end of the storage interval. So I think we have to get -- If we are going to extend storage, I think it has to be the same as or better than, conceivably.

What I have, I think, already documented is that in Plasmalyte seven days is better than five days in plasma. So I think there are ways that we can get a good quality product.

So you are toying with the fact that you need very few platelets, 5-10,000. So even -- But I think that we have to give a platelet product that is as good as the patient can use.

So in other words, if the survival of the donor platelets in the patient is only two days, then I think we have to have a product that will survive at least two days in normal volunteers and expect it to be two days in patients. But, you know, some people -- their platelets survive four, five, six days between transfusions, and those are not common, because patients have a zillion things happening to them.

So I don't know that you want to have a standard that is 20 percent less for recovery and survival, say, than five-day. So I would prefer to have us think about a recovery that's relatively close to normal, because most patients can get a recovery that's pretty close to normal, and then a survival somewhere of four, five, six days.

I would be very comfortable as a clinician saying this is a good quality product. This is as much -- The patient doesn't need an eight, ten-day survival, because they never have an eight, ten-day survival. So why should we aim for that as a gold standard, and we don't have that now.

DR. VOSTAL: Just a -- I wonder if I could get you to put a number on that recovery, because some of your studies are showing recovery of 80 percent.

DR. SLICHTER: Well, yes, and as I mentioned, I'm just dumbfounded at how good the recoveries are, and I think it may be that somehow the manufacturers, unbeknownst to us, gave us a bag or a storage material or gosh knows that's better than what we've had, and also, you know, the data that I showed that the higher your platelet count, the higher is your recovery, which is an unknown, at least to me anyway, potentially biologic phenomenon.

So I would not hold this to a 70-80 percent recovery for the product, but I think somewhere around 40 to 50 percent would be fine with me.

DR. STYLES: Can you review again how you define platelet recovery? I'm sorry.

DR. SLICHTER: Yes. It's the increment which is the pre -- the post minus the pre, and then adjusted for blood volume. So 75 times the increment, because 75 ml is the usual blood volume determination. Then divide it by the number of platelets transfused.

So what you are trying to look at is, of the platelets that I transfused, how many of them circulate following transfusion? The normal recovery is somewhere around 60 to 65 percent, because normally a third of the platelets are pooled in the spleen.

So if you asplenic, it's like 90 percent. So, you know, whether -- but these donors, we have had a 90 percent recovery donor come back and be retransfused in another set of experiments, and they are still 90 percent.

I think I showed you the 5,7 day data with the Plasmalyte that, my gosh, the recovery was exactly the same in the same donor, within a few percentage points. So that's how the recovery is calculated.

So you can think of it as how many do I put in, and how many circulate.

MR. DUMONT: Larry Dumont. I wanted to comment on the number. First of all, I think one has to be really careful about the number, because there are differences between laboratories and centers when these studies are done.

Dr. AuBuchon didn't show all the details of that data, but since I designed the experiment and did the analysis, I can tell you that the two centers -- There was a significant difference between Dartmouth and Norfolk.

You know, you can adjust for that in the analysis, of course. So you have to be very careful about a specific number. I think the studies that are done to make the argument, it's imperative that those

are well paired studies because of this random problem that we have.

Then just to reemphasize, too, what Sherrill said about the differences between subjects in these normal donors. I mean, we have some donors or subjects that they may have a recovery of like 40 percent, and they always have a recovery of 40 percent, and you have others that have a recovery of 80 percent, and they always have a recovery of 80 percent.

So it's also very critical to pair things so that you can adjust for those in the analysis. So I would be very worried about an absolute recovery number, an absolute survival number without this comparative and being able to adjust for all these other confounding factors.

DR. STRONCEK: So it's too bad Jim's gone -- or Dr. AuBuchon is gone. I hope the FDA didn't pay for his ticket. It would have been nice to have him here for the rest of the discussion.

Anyway back to the study design question, I think it's going to be very -- You know, I agree. You have to get informed consent, but I think, thinking through how a person would do that -- this would be an extremely difficult study to design and

implement.

If I were going to ask my IRB to give seven-day platelets, I would not want to give them unless I had no more five-day platelets on the shelf, because we have heard there might -- We're not quite sure that they are sterile, and we don't know -- and it looks like they are not going to function as well.

So you would want to give five-day platelets first. So I would not want to have my fellow go up a route of platelets and say okay, to a patient, you can either get nothing or you can have this old platelet, you know, when you're bleeding, please sign.

So, you know, you would probably want to prospectively get everybody to consent to the protocol. The problem becomes, if you get half the people that don't -- You know, you say, well, here, there's a possibility we might give you old platelets versus another product -- you know, our standard product, which is five days.

So you know, on a Monday morning when you are short of platelets, you have eight people that need platelets. You have five products that are in date. Well, the people that don't consent to the study, they are going to get the fresh ones, and the

few people that do consent would always get the old ones, and it gets very, very tricky to figure this out.

DR. ALLEN: I think we have to be very careful. I mean, fortunately, committees don't often design studies. I think we have to be very careful in terms of how we couch this in the concept.

The frequency of contamination is not going to go up between five and seven days. What might go up or change is the level of bacterial concentration in that period of time, although, as Dr. AuBuchon and other speakers earlier said, by five days, if you've got a bacteria such as *Serratia marcescens* or one of those others listed in the study that is very happy to grow in a cold environment in a plasma enriched environment, it's not going to make any difference whether you've got levels at five days or at seven days.

Most of those bacteria can reach concentrations of 10^6 to 10^9 bacteria per ml within 24 to 48 hours. So I think we have to be very cautious about how we couch the terminology, and I think it would be very good to go back and look at what happened in the -- was it in the Eighties when they went back -- or Seventies when they went back and made

for that brief period of time -- enabled seven days? -- and see if we can tease out from the literature of those days exactly what happened and what data were available.

It's not the level of -- or it's not the frequency of contamination that's going to create the problem. I would almost wonder if in that additional period of time whether what is happening is that you are getting bacterial die-off and the endotoxin rate is going way up.

I mean, it's not a simple answer, and I'm not concerned that we are going to create a less safe environment because the frequency of bacterial contamination is going to go up between five and seven days.

I think, if the issue is one of platelet efficacy at first, I think the data are beginning to be accumulated that we in fact do have effective products out to seven days. You know, I think you can couch your patient consent very well in terms of the making available platelets to them that might -- you know, to the patient population that might not otherwise be available when they are badly needed. That perhaps is the benefits that's there.

I think the study design is very critical,

and exactly how one provides effective -- or good information to the patients as one gets informed consent is a very critical issue. But, you know, in terms of the potential risk of bacterial contamination, I think we have to look at how we couch that message very carefully also.

CHAIRMAN NELSON: Yes?

MR. NELSON: I'm Ed Nelson from Pall Medical. Just a couple of points. Point of clarification on what Jim presented: The Gordon Archer studies that he presented looking at five-day and seven-day were not data that were submitted to the FDA in their deciding on seven-days.

They reviewed data that, in fact, Toby Simon and Scott Murphy -- studies of theirs, and on average I think the five-day studies or a series of them averaged between 46 and 51 percent at five days and 40 percent to 45 percent at seven days. That's really the sort of data that I would expect to see now unless the methods have changed somewhat, which they may have.

Secondly, I sort of would like to support what Larry said about an actual, exact cutoff for approval. Depending on what patient -- or what normal subjects you pick, you can get a mean ranging from 40

up to 60. Obviously, you don't try to pick subjects, but that can happen.

So we would be more in favor of doing an actual double labeled comparison study within the same subject to look for differences.

CHAIRMAN NELSON: Thanks. A couple of maybe brief comments. If we want to get out by 3:30, unless it's anything critical, we need to break in five minutes or so.

DR. DOPPELT: One quick question. We've been focusing mostly on platelet numbers and survival, and what really counts is the function of the platelets. So my question is how difficult is it to do *in vivo* tests for the function of the platelets?

I mean, for example, is the correction of bleeding time of value?

DR. SIMON: I tried doing those studies for many years, and I think others would agree, they are very difficult to do. But they can be done. I think they have -- Sherrill has shown more through evaluation of hemostatic effectiveness, because the bleeding time studies were just nonreproducible and difficult to do.

DR. STYLES: And the bottom line really is need for further transfusions or platelets. That's

why those endpoints, I think Sherrill showed -- Dr. Slichter showed were -- Those are the ones they looked at where the clinicians' bottom line was going to be do I need to give them more platelets because of this or are they having red cells or more bleeding complications; because those -- You mentioned the bleeding time is pretty inaccurate, risk for -- risk of bleeding. That's been done over and over in a lot of surgery studies.

DR. FALLAT: Well, I couldn't agree more that this is not the forum to be developing a protocol. But I think we have clearly demonstrated that we have a major problem here with infection and that we have a real need to try to extend the time.

So we have three different problems, extending the time and correcting the contamination by either culturing or by perhaps using a decontamination method. The fourth problem is we don't have enough money to do it.

I would suggest that the FDA sponsor a workshop which would combine industry, academia, and the various blood banks and so forth to really hassle out these issues and really in that forum decide how best to proceed. I don't think this is the forum to do that.

CHAIRMAN NELSON: Thank you. I agree.

Okay. Let's break now and come back at 12:30, and we will try to end by 3:30 this afternoon.

(Whereupon, the foregoing matter went off the record at 11:39 a.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(12:37 p.m.)

DR. SMALLWOOD: I would just like to remind all of the speakers, if you have presentations to make, I hope you have seen the gentleman over here to my left to have your presentations loaded onto the computer.

We have a full session this afternoon. I would also like to advise speakers to please speak as long as necessary, but to move quickly through the program, because our Committee members will be leaving, and we do want to give full consideration to this topic. Dr. Nelson.

CHAIRMAN NELSON: Thank you. The first topic is bacterial and fungal contamination of human tissue intended for transplantation. To introduce the topic, Dr. Ruth Solomon from FDA.

DR. SOLOMON: Good afternoon. This is the final topic of this BPAC meeting. This topic is being presented today to inform the BPAC members about recent reported cases of bacterial contamination associated with musculoskeletal tissue allografts.

FDA is concerned about transmission of communicable disease by human tissue intended for transplantation, since we regulate this tissue. Next

slide.

As you may know, there has been a recent report of sepsis and death in a young recipient of fresh osteochondral tissue allograft from a cadaveric donor following knee surgery that he had. The organism that was cultured from his blood was *Clostridium sordellii*.

For those who are a little rusty on their microbiology like I was, *Clostridium* is an anaerobic, spore forming bacillus that is normally found in the human GI tract.

Investigations of this case were performed by the Minnesota Department of Health, the CDC, and FDA. There have been additional reports of bacterial and fungal contamination of tissue allografts. Next, please.

To give you a preview of this session, I will be summarizing the current and future FDA regulations that address this issue. Then Mary Malarkey from our Office of Compliance at FDA will talk about microbial contamination and cross-contamination during processing of tissue, including the guidance that recently published.

Dr. Marion Kainer from CDC will update us on CDC's ongoing investigation of allograft associated

infections. We will also hear presentations from Dr. Ted Eastlund who will present the tissue bank perspective, and Dr. Michael Lemp who will present the eye bank perspective. Next.

FDA has been regulating human tissue intended for transplantation since 1993 when it issued an Interim Rule. The interim rule was then finalized in 1997 and became effective in January 1998. It is codified in 21 CFR Part 1270.

The legal authority for our promulgating these regulations is Section 361 of the PHS Act, which states that the Federal government can propose regulations that control communicable disease introduction and spread.

The main focus of the interim and final rules was on donor screening and testing for HIV, Hepatitis B and Hepatitis C, because of concerns about imported tissue for which donor screening and testing were not being done.

With that as its main focus, there are very few requirements in the current regulations that address processing. Next slide, please.

1270.31(d) in the current regulations says that there shall be written procedures prepared, validated, and followed for prevention of infectious

disease contamination or cross-contamination by tissue during processing. Infectious disease agents can include, but are not limited to, bacteria and fungi. Next slide.

Compliance with 1270.31(d) and all requirements in Part 1270 is determined during inspection of the tissue establishment. Recently, we promulgated some additional final rules under 21 CFR Part 1271 which published January 2001 and became effective in April.

These regulations require that tissue establishments register with the FDA and list their products and update the registration and product listing annually. Next slide.

As you probably know, FDA has proposed two regulations which we have received comments on and are in the process of finalizing, but they have not been finalized yet. These are the suitability determination for donors of human cellular and tissue based products, a proposed rule that issued in 1999, and current good tissue practice for manufacturers of human cellular and tissue based products, inspection and enforcement, a proposed rule which was published in January 2001.

I would now like to briefly review some of

the requirements in the GTP proposed rule. Remember that these requirements are not currently in place, but they would become effective after the GTP proposed rule is finalized.

These are the sections of the proposed rule that I think focus on the issue today: First of all, the GTP requirements are intended to prevent the introduction, transmission and spread of communicable disease through the use of cell and tissue products, by helping to ensure that the products do not contain communicable disease agents and that the products do not become contaminated during manufacturing. By manufacturing, we mean recovery, processing, storage, labeling, packaging, and distribution. Next, please.

Then another proposed requirement is that establishments should establish and maintain a quality program whose functions would include: Investigating product deviations and complaints; ensuring that appropriate corrective actions are taken, both short term and long term; performing audits at least annually; and reporting the findings to management. Next, please.

In addition, there would be requirements to have process controls. The establishment would have to control and monitor manufacturing processes to

ensure that each product is not contaminated and is manufactured so as to prevent transmission of communicable disease by the product.

There would be in-process monitoring and control: Representative sampling; control of the product until required inspection and tests were completed and specific requirements were met. Next, please.

There would also requirements for process validation when the results of a process cannot be fully verified. Validated processes would have to be monitored to ensure that the specified requirements continued to be met.

When any changes to or deviation from a validated process occurred, revalidation would be required, and any process related claim in labeling or promotional materials would be based on a validated process. Next, please.

There would also be requirements for receipt and distribution of tissue products. There would be procedures established for receiving and accepting or rejecting products for processing, distribution or any other step in manufacturing. Each incoming product would be inspected for contamination. Next.

In addition, there would be requirements for tracking; that is, maintaining a method of tracking a tissue product from the donor to the recipient and vice versa, from the recipient to the donor. Next, please.

Lastly, there would be requirements for reporting to FDA of adverse reactions involving the transmission of a communicable disease, if the adverse reaction was fatal, life threatening, could result in permanent impairment of a body function or permanent damage to a body structure, or necessitated medical or surgical intervention to prevent permanent impairment.

Also product deviations that could lead to an adverse reaction would also be required to be reported to FDA. Just to remind you that at the present time adverse events following tissue transplantation are not required to be reported. They can be voluntarily reported through FDA's MedWatch system. Next.

Although we are not asking the Committee to vote on any particular questions, we would like to have a general discussion of possible mechanisms to prevent bacterial and fungal contamination and communicable disease transmission by human tissue, and these possible mechanisms will be presented by Dr.

Kainer.

FDA and CDC investigations are ongoing. Dr. Kainer will mention that currently investigations are being performed to identify risk factors associated with *Clostridium* infection post-allograft transplantation. CDC is working with states on that.

In addition, CDC is working together with AATB to do a survey of tissue banks to determine current processing methods and quality control procedures.

Lastly, the goal is to develop sterilizing methods which would eliminate bacteria, fungi and bacterial spores without adversely affecting the tissue allograft quality.

We are going to be holding questions until the Committee discussion, but the next speaker, who is Mary Malarkey, cannot stay until the end, and she will address questions immediately after her talk.

CHAIRMAN NELSON: Thank you, Dr. Solomon. Are there any questions or comments directly related? Okay. Dr. Malarkey.

MS. MALARKEY: Good afternoon. I am pleased to be here today to participate in this session about a very important topic for FDA, and that is our concerns regarding microbial contamination and

cross-contamination of tissue during processing. Next slide, please.

To that end, I would like to speak about what we've been doing over about the last ten months. That is the evolution of our concerns; what the current thinking is at FDA, and this includes what current industry thinking is as well; some information sharing and gathering activities that have been underway and the results of those activities; and finally where we are going in the future. Next slide, please.

In late 2000 there was an *E. coli* transmission by cancellous bone chips. A sample was taken in the operating room and cultured, and following surgery the next day the patient developed signs and symptoms of sepsis.

The blood cultures on the patient were positive for *E. coli*, as were the culture results from the preop culture. Wound re-exploration was necessary, and the patient did recovery but, of course, required antibiotic treatment and a longer hospital stay, and one can expect not a very pleasant outcome altogether. Next slide, please.

FDA was not notified of this incident, and it came to light during an inspection in May of 2001.

Many of the items associated with this incident were documented on the FDA 483, which is our list of inspectional observations.

At that time, we realized that the manufacturer had withdrawn some, but not all, of associated tissue from the same donor. I should say that during the course of the inspection, that was done. So a total recall was performed. Next slide, please.

The result of this was a Class 1 voluntary recall because of the harm that had been caused and the potential harm that additional units of tissue could have caused to potential recipients. Class 1 is our most severe designation in terms of health hazard evaluation.

We published this in our FDA Weekly Enforcement Report, as is required under our regulations under Part 7, on August 1, 2001, and I should say that this is an ongoing investigation with respect to the tissue bank. So I can't comment much further on what is going on in that regard. Next slide, please.

Around the same time we became aware of a voluntary recall due to potential mold contamination. This affected about 1300 units of tissue. Again, this

is an ongoing investigation. So the same applies. And of course, the very tragic fatality in Minnesota more recently, and we have become aware of other transmissions, if you will, as identified by our colleagues at CDC. Next slide.

Our current thinking: Well, the industry standards -- and I'll go through some of those in a moment -- speak to control and prevention of contamination and cross-contamination of tissue during processing with respect to microbial agents.

As Dr. Solomon said, our current regulations require validation of -- well, preparation, validation and following of procedures in this regard. Next slide, please.

Now I have excerpted some of the industry standards. These are certainly not all inclusive, but some that I feel that speak to the subject at hand today.

From the American Association of Tissue Bank standards for tissue banking, we have -- The expectation is the standard operating procedures manual will establish a list of organisms which necessitate discard, sterilization and/or disinfection of tissue.

Further, basically, the regulation under

1270.31(d) is reiterated within their standards. That is, there must be written procedures that are prepared, validated and followed with regard to this issue. Next slide, please.

Microbiological culture samples should be taken prior to any treatment of the tissue with disinfecting agents or antibiotics, and this is, of course, to guard against false negative results from the incoming tissue.

Also cells and/or tissues with bacterial contamination may be released, but only if adequate measures are taken to identify and eliminate those microorganisms.

The one thing that is somewhat lacking, we believe, in the current standards for tissue banking is, if microbial testing is performed in-house at the tissue bank, there is very little guidance on how that should be performed, what the methodology should be, the sampling techniques, etcetera.

On the other hand -- next slide, please -- there is an AATB Technical Manual that was published in 1992 on musculoskeletal tissues, and this goes into great detail on requirements for microbial testing and sampling methodologies.

One of the important discussion points in

this document is the importance of bacteriostasis and fungistasis testing. Again, for those of you who aren't up on your microbiology, what this is is -- It's an evaluation of any inhibitory effect that the test article may have on recovery of microorganisms during the course of a sterility test, put in simple terms.

In this case, it is very important, since antibiotic soaks and soaks in other bacteriostatic rather than bacteriocidal agents is often performed. Also, there is discussion of the various sampling methods such as destructive versus swab testing. Next slide.

Now in regard to the EBAA standards, we are talking here, of course, about other than *in situ* recovery -- that is, if a whole globe is taken and then further processed in a biological safety cabinet.

The standards are not very specific, but they do give information on equipment cleaning and maintenance, but they don't really go into environmental controls or validation with regard to this processing.

We do understand that microbial cultures of eyes are generally not taken at tissue banks -- excuse me, at eye banks, and that's not the issue I'm

trying to get through here. It's just the processing itself and controlling any further introduction of contamination to the tissue. Next slide, please.

Well, what do our regulations say? Well, Dr. Solomon already addressed 1270.31(d), which is very important here.

There is also -- next slide, please -- a very important definition of processing under 1270.3(p). Basically, processing is any activity performed on tissue outside of recovery, and this would include any steps to inactivate and/or remove adventitious agents. Next slide, please.

There is also 1270.31(e), and this speaks to verification rather than validation. That is, if you are using current processes that are part of technical manuals, for example, that you would want to verify the effectiveness of those procedures. But it wouldn't necessarily necessitate, if you will, full validation. Next slide.

So just to reiterate, processing includes all activities performed on tissue outside of the realm of recovery. So this then would include testing, microbial testing, both pre- and post-processing, and any other activities that are undertaken on the tissue even at the procurement site,

such as storage or labeling. Next slide, please.

So in summary, we believe that the current regulations do require validation or verification of these procedures to prevent contamination or cross-contamination of tissue during processing with respect to microbial agents, and we believe that the current industry standards support that thinking. Next slide.

What have we been doing since these concerns arose? Well, we have taken on several information sharing and gathering activities. In regard to tissue banks that we have found some problems with in this regard, we have sent Untitled Letters.

These are regulatory letters which describe our current thinking and our expectations. They don't quite rise to the level of a warning letter or a more serious action, but they do warn firms that these are our expectations.

We recognize that guidance would be necessary to the industry in regard to our current thinking, and we began some outreach programs in this regard, both internal and external. Next slide, please.

In terms of gathering of information, we sent a request to all the FDA district offices and

asked that, during the course of their inspections of tissue banks, they would review and document certain issues. This began about mid-August of 2001.

The next few slides go over the request that we gave to the field and asked them to address during the course of the inspections and documented in the reports. I won't read through each and every one of them, but basically we wanted to know if the firm has procedures in place in this regard; whether the procedures are validated or verified based on the scientific literature; -- next slide -- are the procedures being followed; some questions regarding microbial testing, how it's performed, what standards are used, what types of sampling methods are used. Next slide.

Finally, is there any evidence of release of contaminated tissue, and finally, how are the finished products labeled? Next slide.

IN terms of outreach, we participated on a panel at an AATB one-day validation symposium back at the end of November. I want to say, this was a very intense program, quite intense, very well put on program, and provided a lot of information to the tissue industry.

We are also going to be involved in the

presentations at the AATB annual meeting about a week from now, and Dr. Kainer from CDC will also be there. So the Department will be well represented. Next slide, please.

I should also say that we also are doing internal training with regard to the field investigators with all of these new developments to keep them abreast of our current thinking.

Probably very, very new is our Guidance for Industry which was actually just published or just issue March 8. This is the Guidance for Industry on validation of procedures for processing of human tissues intended for transplantation. A notice of availability was published in the Federal Register Wednesday, March 13th.

What I have done for the Committee is there's some manila envelopes that should be in front of you that contain copies of my slides, because I think there were updates, as well as the guidance and the Notice of Availability for your information. Next slide, please.

Now just briefly what the guidance says. It gives our current expectations with regard to viruses, bacteria, fungi and TSE associated prions. We say that currently we expect that procedures will

be prepared, validated and followed to prevent contamination or cross-contamination of tissue during processing by viruses, bacteria and fungi.

We talk about validation versus verification, what that means, and we give some broad examples about how these studies may be undertaken. Next slide, please.

With regard to TSE associated prions, we acknowledge that technology is not quite there to do full validation studies. However, we expect, as technology progresses, that this requirement will be readdressed.

For those tissue banks that are currently engaged in high risk processes with respect to TSE, we strongly encourage heightened screening and recovery procedures be put into place to minimize the risk, and we speak very briefly as to the current regulations and the proposed GTPs with regard to commingling and pooling. Next slide, please.

Finally, we let industry know that these procedures and data wills be reviewed during inspection, and any deficiencies will be noted on the FDA Form 483. Next slide.

The Notice of Availability that just published the day before yesterday: We are soliciting

comments on this guidance, but this guidance was issued for direct implementation due to the public health concerns involved here.

We are asking industry, if they would, to submit information on what current methods are in place, and we wish to have further public discussion on this issue and hope for -- We recognize that we will need more additional, specific guidance in the area of bacterial and fungal contamination of tissue. Next slide.

With regard to our information gathering, the results there -- and I want to stress that current resources as they are do not permit us to do an exhaustive review of all establishment inspection reports that are prepared as a result of inspections of tissue banks. This was a project that we undertook because of the current situation.

We reviewed 60 establishment inspection reports with regard to the information that we requested from the field. This is a small percent -- It's not everyone out there, obviously, the whole universe. So I also want to stress that.

I've done the breakdown here also to show that a lot of these sites aren't really doing any processing. There's distributors and testing labs for

donor screening activities that would not be considered processors. Next slide, please.

With regard to the problems identified, again I want to qualify this, and I'm not saying that these problems are everywhere or they are completely lacking. There are different degrees, as is always the case, but we did see in our review that there is lack in many cases of full validation or verification of procedures in this regard.

There also seems to be a lack of clarity as to what processing is. This was especially at eye banks, for example, that do the whole globe and then do further processing, and also at procurement sites where, for example, bacterial testing is performed on the tissue after recovery.

Unfortunately, also we saw in some cases procedures are in place, but they are not always being followed. Next slide.

We did see problems with microbial testing: Lack of verification or validation of sampling and testing procedures. For those of you who are familiar with destructive versus swab testing, both have their pluses and minuses.

With destructive testing, you are really evaluating the entire test article, but you can only

really use a representative sample of the entire lot. So what is a representative sample is one of the big issues here. To be representative, one has to assume that the process is consistent and uniform. That is consistent form time to time, and uniform with respect to each piece of tissue being treated in the same manner.

IN regard to swab testing, you can actually look at 100 percent of tissue with this method. However, it has its own drawbacks, mainly the recovery of whatever is of interest from the test article, and then the ability to recovery from the swab into the microbiological media. So in the biopharmaceutical industry we have seen data anywhere form 30 to 80 percent recovery in this regard.

Lack of bacteriostasis and fungistasis testing: As I mentioned earlier, this could lead to false negative results, and this is a big concern. Even for contract testing, we weren't always sure whether this was addressed, this inhibitory effect of the test article. Next slide.

We saw some inconsistencies at times in handling of incoming positive microbial results. There are often various procedures in place, depending on what the microorganism is it that is identified as,

but in some cases we saw that there is some retesting, reprocessing, and reworking going on until the desired results are obtained.

So, in fact, there is very little rejection of tissue. We understand that it's very precious, but in some cases it may be in the best interest not to perhaps proceed with processing of certain tissue. Next slide, please.

So finally, where are we going? Well, clearly, we believe we need to develop more specific guidance in respect to this area, and we do want to work with industry and other scientists in the agency as well as in the Department at CDC to develop this guidance.

We will continue to monitor the validation and verification procedures and activities in industry through inspection and surveillance, and we are prepared to take enforcement actions as necessary. This is never our preference. We would much prefer that industry take heed and do what is right here, and I think it's really up to all of us, industry, regulators and scientists, to ensure the safety of the tissue supply.

On my final slide -- last slide, please -- I have got some -- where you can get the guidance

document on the CBER website. The Notice of Availability is also under the DOCKETS Website, and I believe for the Committee I have put that website on the last slide.

Thank you.

CHAIRMAN NELSON: Thank you. Any questions? Dr. Schmidt?

DR. SCHMIDT: It used to be common practice for the orthopedic surgeons to have a freezer outside the operating room, and they know what they put it, and they took it out.

Now I expect with the current financial climate at the hospitals, the administrators would rather buy them a freezer than sign up with a licensed organization to get their material for them. I'm curious as to are they part of the industry? How many of them are there?

We have an orthopedic surgeon, and I wonder if he would speak to the status of that. Does this fall through the cracks?

DR. DOPPELT: I'm the orthopedic surgeon. It used to be in years past common practice for small hospitals and so forth to keep, for example, femoral heads, say, for grafts in other patients.

As the whole field has progressed in terms

of the need for various serologic testing and sterility testing and so forth, basically, those places have essentially dried up. They don't exist, because number one, they can't afford to do all the testing. Number two, neither they nor the hospitals want the liability, if they are not going to follow all the rules that are basically promulgated. So, basically, they don't exist anymore.

DR. CHAMBERLAND: I may have missed it, but can you give us some sense of what the denominator is in terms of number of tissue banks, and I believe also isn't there a differentiation between those that are licensed and -- or just so what is the universe of tissue banks that we're dealing with? Then also some sense of, up until these recent events, what FDA's ability has been to perform routine inspections and whatever?

I would imagine you can only inspect per year some fraction of what's out there.

MS. MALARKEY: Unfortunately, I am unsure as to exactly how many registered banks we have currently. Dr. Solomon may have that information. I do know that with the 1271 registration rule, actual tissue processors were supposed to all have registered by a given time, and then there is a three-year

implementation for other cellular therapy based sites to register.

It is also important to note that, as my slide indicated, not all of them are full service tissue banks or necessarily performing processing. So I would defer to Dr. Solomon.

DR. SOLOMON: Okay. We have currently 460 registered establishments in our database. Eighty of those voluntarily registered. They were not required to register now, but would be required to register when all of our rules are in place -- for instance, reproductive banks and hematopoietic stem cell banks.

Of the -- So that leaves us with about 380 that had to -- were required to register. Out of those, we recently tallied that more than half of them either distribute only or test only.

On the form that they have to fill out to register, we ask what functions they perform. So we wanted to know how many distribute only and test only for some inspection priority purposes, and also we have also heard that the Congress and the public are saying, you know, why do you have 460 banks when we only expected you to have about 150 tissue and eye banks.

I think, based on the people that have

joined the -- voluntarily joined the professional organizations in the industry, but I think that distributors and test labs would not be likely to join AATB or EBBAA. So that might account for some of the discrepancy in the numbers.

DR. CHAMBERLAND: And then, Dr. Solomon, up until recent events what has been your capacity to do inspections of the banks that you are aware of?

DR. SOLOMON: Do you want to take that?

MS. MALARKEY: I was going to say, I think as of now we have inspected all of the tissue banks that are full tissue banks. Is that -- about 160-some, based on that math when you take out the distributors and testing labs.

I think it is fair to say that we cannot get out to every one every year, and there is some priority given based on the activities and based on their prior history. If we saw problems, we would obviously want to go back in a more timely fashion.

DR. SOLOMON: But I believe currently the aim is to inspect every two years.

MS. MALARKEY; Yes.

CHAIRMAN NELSON: You reported a couple of instances, one of which was only detected during an inspection. Do you think that there -- What do you

think the level of unreporting of recognized events might have been, and what is the plan to correct or get all of events reported, investigated?

MS. MALARKEY: Well, I believe the -- In answer to your first question, I don't really know what the universe is out there; that is, how many times this has occurred without our knowledge. I believe that Dr. Kainer has some information perhaps on that.

I certainly don't want this to sound like we believe it's a rampant problem, but it is out there.

In respect -- I'm sorry, sir, your final question?

CHAIRMAN NELSON: Well, I guess the guidance or after these rules are promulgated, theoretically, that would more effectively required reporting, I guess.

MS. MALARKEY: Yes. Certainly, the adverse events, as Dr. Solomon stated, would be reported. So that would give us an idea when this occurred, and we would be able to act on it.

DR. DOPPELT: I'd just like to say that I think the issue of data gathering and reporting is a serious issue and a potential - and a clear gap in

the entire system.

The AATB does inspect banks and requires that they have an adverse file -- you know, any problems with the tissue that they have distributed. The problem is that they send out a form with the tissue that the hospital is supposed to report back to, and they may or may not get it, and they can get it, and they may or may not get a response.

So the system is there, but it doesn't respond very well in terms of getting that information back, and I think, clearly, one of the things is that somehow you have to develop a system where, if there is a problem, at least the AATB is notified, the CDC, FDA, etcetera; because if you are going to try and establish trends, you would like to do it early on, not two years after the fact.

MS. MALARKEY: Absolutely.

DR. DiMICHELE: When you cited the evolution of concerns, you started in the year 2000. Yet I'm assuming that tissue banks have been in existence for a while. I don't know how long, and maybe you can educate me on that.

I'm just trying to understand what the previous history has been, you know, in the absence of regulation in terms of infections. I guess maybe what

people are thinking is that there have been infections. There just hasn't been systematic reporting, and we just don't know what's happened before this time. Is that --

MS. MALARKEY: Well, as Dr. Solomon says, we have been regulating the tissue industry since the early Nineties, 1993, and the focus initially was more on the transmission of viral infectious disease agents such as Hepatitis C, B and HIV.

I can't speak to what happened pre-regulation, but that has been the focus, and our attention has certainly gone elsewhere as a result of recent -- more recent events.

CHAIRMAN NELSON: Okay, thank you. The next presentation is Dr. Marion Kainer from CDC.

DR. KAINER: Could I have the first slide, please? Good afternoon. Thank you for allowing me the opportunity to update the Committee on these infections.

Musculoskeletal allografts includes tissues such as bone, tendon and menisci. In 1999 650,000 allografts were distributed in the United States. This compared to 350,000 in 1990. Next slide.

Once consent is obtained from a donor,

tissue is procured by sometimes several tissue procurement or organ procurement organizations. They can involve skin banks, eye banks, solid organs, as well as musculoskeletal tissue.

One tissue procurement organization may send tissue to several tissue processors. Thus, a single tissue processor may then distribute it to several tissue distributors, and then it gets implanted into multiple patients. One donor can give rise to about 130 tissues.

The tissues you see down at the bottom are bone, tendon, meniscus, and bone screws. Next slide, please.

In November of 2001 a 23-year-old man in Minnesota had reconstructive knee surgery using a femoral condyle -- that is a bone-cartilage -- allograft. Three days later he developed pain in his knee. There was rapid progression to shock, and he died the following day. Blood cultures obtained premortem grew *Clostridium sordellii*. Next slide.

The tissue came from a donor who I will refer to as Donor A. That donor had no signs of sepsis. He had no risk factors for *Clostridial* infection. The body was refrigerated 19 hours after death, and the tissue was procured 23.5 hours after

death. A single tissue procurement organization was involved, and all tissue was sent to a single tissue processor who I will refer to as Tissue Processor A. Next slide.

A total of ten tissues were implanted into nine patients located in eight states. That includes the patient in Minnesota. We contacted the health care providers of all recipients of the tissue, and identified one additional symptomatic patient, a 17-year-old who had a femoral condyle and meniscus implanted.

He developed septic arthritis and fever with absolutely no response to first generation cephalosporins which have no anaerobic cover. He was admitted to hospital eight days after surgery with a dramatic response to ampicillin-sulbactam, an antibiotic which has got excellent anaerobic cover. No anaerobic cultures were taken.

There were 19 non-implanted tissues still at Tissue Processor A, and these were cultured at CDC. *Clostridium sordellii* was isolated from two tissues, one fresh femoral condyle and one frozen meniscus. Of note, all processing cultures at Tissue Processor A were negative.

Let me just take you through some tissue

processing. The tissue bank receives unprocessed donor tissue. It is debrided and this is a knee showing after initial debridement. Then different parts are taken out of the knee to get the parts which you want, and this was trying to get the patellar tendon.

This is the femoral condyle. This is what was implanted into the Minnesota patient who died, and meniscus tissue. Okay.

Now let me take you through what happens at Tissue Processor A. At Tissue Processor A you get the allograft, and at the same time there is a bit of companion tissue which may be a sliver of cartilage, for example, from a femoral condyle. Those are processed identically.

After the debridement, you have the allograft, the femoral condyle or the meniscus and the companion tissue, and they are placed into a working container.

This antibiotic solution is added. In the container you still may have residual vegetative forms of *Clostridium* species, and you also may have *Clostridium* spores. After some time -- next slide -- the antibiotics will kill the vegetative forms of the *Clostridia*. They will have no effect on the

Clostridium spores. Next slide.

After having been soaked in this antimicrobial solution, the allograft tissue is packaged. The companion tissue is cultured. The companion tissue is placed into a culture medium, and you may also have a transfer of some of the *Clostridium* spores, and over time -- next slide -- you will have growth of those *Clostridium* spores into vegetative forms, and that is how you detect a positive culture. Next slide.

Now let's go through this again. Same process. Next slide. But instead of just transferring the actual companion tissue, you are now transferring antibiotics as well. So what happens now?

You get some of the *Clostridial* spores germinating, becoming vegetative, but they get killed by the antibiotics, and therefore, the cultures are negative, something which we call bacteriostasis, and so one would not know that you had *Clostridial* spores present. Next slide.

So we hypothesized that the discrepancy in culture results between Tissue Processor A and CDC were due to bacteriostasis. That is, that there was residual antibiotic transferred along with the

companion tissue.

Another fact is that the companion tissue may not be representative of the whole allograft, partly because it is statistically only a small sample, but also the surface area-volume relationship is such that you may have much better penetration of the antibiotic-antifungal solution into smaller companion tissue than you do into the actual allograft.

This would result or explain in the false negative results, which Tissue Processor A experienced.

CDC published in the December 7th MMWR the case in Minnesota and also alluded to four other cases of septic arthritis due to contaminated anterior cruciate ligament allografts, and we solicited additional case reports. I will now discuss these additional cases.

First of all, the definition: For purposes of this report, an allograft associated bacterial infection was defined as: A surgical site infection at the site of an allograft implantation occurring within 12 months of allograft implantation in an otherwise completely healthy patient who has no predisposing risk factors for infection, such as

diabetes.

Cases could be culture negative if they were diagnosed by infectious diseases physicians or surgeons and you had diagnostic such as a knee aspirate or operative findings which supported the diagnosis of a surgical site infection.

We excluded any cases where the only organisms isolated were *Staphylococcus aureus* or *Staphylococci spp.*, since these are common causes of surgical site infection, and we did not want to contaminate our sample, unless in these cases -- sorry, back on slide -- unless there was additional epidemiologic or microbiologic evidence suggesting allograft contamination.

By epidemiologic evidence, I mean that you had two recipients who had *Staphylococcus aureus* and they both had tissue from the same donor. That would be the additional evidence. Next slide, please.

We ascertained cases by notices on electronic list service, through the MMWR, Food and Drug Administration, and through some state regulatory authorities. As of March 11 we had a total of 14 cases of allograft-associated infections which met the preceding case definition.

Thirteen or 50 percent of these allograft-

associated infections were due to *Clostridium* species. Twelve of those were due to *Clostridium septicum*, one due to *Clostridium sordellii*. The *Clostridium sordellii* was the patient who died in Minnesota.

Of note, 11 of the 13 or 85 percent of the implicated allografts came from one tissue processor, Tissue Processor A.

Now to what tissues were involved: Tendons required for ACL reconstruction, eight; two femoral condyles; two bones; and one meniscus. Most of these were frozen. The femoral condyles were fresh.

Now in 11 or 85 percent of these 13 cases, additional evidence implicated the allograft as a source of infection. That is, there was a common donor or cultures of nonimplanted tissues were positive. All 13 allografts were processed aseptically, and there was no terminal sterilization for any of these.

Now to some of the clinical features of these patients. These are young patients. The median age was 35, ranging from 15 to 52. Symptom onset occurred at a medium of 8.5 days, but ranged from two to 85 days.

Many of these patients required multiple

reoperations, often requiring removal of the allograft. They required prolonged intravenous antibiotic therapy, and some had serious complications from the pick lines or central lines, including secondary bloodstream infection, embolization of the pick lines, and several required total knee replacements because of ongoing pain and stiffness and, as we mentioned before, there was one tragic death.

Now to the non-*Clostridium* species infections. There were 13. Eleven of these were due to gram negative rods. Two were culture negative, and five of these are polymicrobial. In eight or 62 percent of these infections, additional evidence implicated the allograft, i.e., a common donor or microbiology. We are still investigating the others, because we have not contacted all the other recipients of those tissues.

Now what about the allograft implicated here? Ten were tendons used for ACL reconstruction, which were frozen, one fresh femoral condyle, one bone which was freeze dried, and one frozen meniscus. Three allografts were reported to have undergone irradiation.

Now nine patients had allografts which

originated from six tissue processors which are currently AATB accredited. Fifteen patients had allografts which came from two tissue processors which are currently non-AATB accredited, and in two patients we still have not traced back which tissue bank actually did their processing, because just because something is labeled as one tissue bank doesn't mean they did the processing. Next slide.

So of tissues processed at Tissue Processor A, 85 percent -- accounted for 85 percent of cases of the *Clostridium* species infection, and 54 percent of the total cases of allograft-associated infections.

So what are factors which may have led to the release of contaminated tissue at Tissue Processor A? First of all, they used an antibiotic/antifungal cocktail or solution, and that is nonsporicidal. Their pre-packaging cultures had a false negative result. They did not perform any pre-processing cultures, and they went outside industry standards with respect to tissue retrieval time limits.

So let me just go through what happens to tissue. You have a death of a donor. Tissue is procured. Tissue is processed, and tissue is released.

Tissue Processor A used an antibiotic/antifungal solution which is nonsporicidal. The cultures, which are taken post-processing, were false negative because of bacteriostasis. They did not take pre-processing cultures. They did not take procurement cultures, and there was a significant time lag in terms of before the tissue was procured.

So this combination of events probably led to the contamination -- contaminated tissue being released by Tissue Processor A. How could you avoid this? Have a sporicidal method, by far the simplest method, but it's not as easy as that.

Ethylene oxide is associated with poor penetration of tissue and has also been associated with immune-mediated synovitis. Gamma irradiation, particularly at high doses, can impair the biomechanical properties of tissues.

So in the past it's very much been trying to get a balance between the need for sterility and the need to keep biomechanical function. There are, however, some new technologies which are focus of research and development.

There are some promising low temperature chemical sterilization methods which appear to be sporicidal and which don't affect the biomechanical

properties of tissue, once implanted.

I will now describe the steps which were provided to Tissue Processor A by CDC to reduce the risk of allograft-associated bacterial infections:

Whenever possible, to use a method that can kill spores to sterilize tissue. If a nonsporicidal method is used, it is important to remember that aseptically processed tissue is not sterile, and health care providers should be informed regarding the risk of bacterial infection.

So if you are using a nonsporicidal method, how can one decrease the risk of releasing contaminated tissue? One: Culture tissue before suspension in the antimicrobial solution. You, therefore, don't have a problem of bacteriostasis.

If *Clostridium* species or other bowel flora are isolated, all tissue from that donor that cannot be sterilized should be discarded.

Second, culture methods should be validated to ensure that residual antimicrobials do not result in false negative results, and performing both destructive and swab cultures should be considered to increase sensitivity. The recommended time limits for tissue retrieval should be followed.

After receiving a report of a potential

allograft-associated infection, remaining tissue from the donor should not be released until it is determined that the allograft is not the source of infection.

Health care providers of recipients of tissue from implicated donors should be contacted to determine where there are additional cases, and a sample of nonimplanted tissue which underwent the same processing method as the implicated allograft should be cultured by an independent laboratory using a validated method, so we don't run into a problem of bacteriostasis again.

Other steps were included: To perform a one-time audit of unreleased tissue inventory to estimate the proportion of unreleased tissue inventory that may be contaminated with microorganisms or spores.

So in conclusion, to reduce the risk of allograft-associated infections, if nonsporicidal methods are used, then process and quality control measures should be in place to reduce the risk of releasing contaminated tissue, but the best way to move forward is to have methods to sterilize tissue that do not adversely affect the functioning of tissue when transplanted into patients. Thank you.

CHAIRMAN NELSON: Thank you very much, Dr. Kainer. Questions? Yes?

DR. DiMICHELE: Thank you for all that wonderful information. I have two questions.

The first is with respect to Tissue Bank A and potential predisposing problems to what happened. I noticed in the last report that the tissue -- that basically, when you had to go back for tissue verification, you went to the medical examiner, suggesting that this body was in the care of the medical examiner.

The question in another document of patients who die a traumatic death with respect to predisposition to *Clostridia* has been raised. I'm just wondering whether the victim or the person who died, the cadaver from whom these tissues came -- was he a trauma victim? Do you know? And is there any question as to whether harvesting from trauma victims actually increases this problem?

My second question relates to the fact that -- again, the question I asked before, in that there hasn't been a lot of bacterial contamination problems at least presented to anyone in CDC or FDA before. Even in the case finding data that you presented, there doesn't seem to be quite consistent

clustering.

In other words, given all the tissue banks that are involved, there haven't been many that have been implicated and, certainly, this one that's been overimplicated and everything that we are seeing. Is this, in your estimation, an isolated problem or is this a more global problem that we are dealing with?

DR. KAINER: With respect to the harvest of tissue, the donor for -- Donor A -- he did not die of trauma. So that does not represent a risk factor.

There have been some studies performed by other investigators, some from overseas, which show that the chance of finding positive blood cultures or bone marrow cultures at the time of procurement increases in patients who have died -- in donors who have died from trauma, specifically for *Clostridium* species, in particular.

That does not happen so much for the other bacteria, and the time interval from donor death to tissue recovery also -- The increase in *Clostridial* species -- It's predominantly *Clostridial* species which increase with that time interval.

With respect to your second question, there is currently no centralized required reporting system. It is -- I don't believe that we have an

epidemic, but we are certainly seeing much larger numbers when we had initially thought, partly because clinicians never used to even consider the allograft as being a source of infection.

Most orthopedic surgeons involved in the care of these patients believed that the allograft they implanted into their patients was sterile. So they would never have even reported it in the past. So I don't necessarily think it's a new problem, but something which probably has not been recognized.

You now have an industry which is greatly increasing the number of allografts from 350,000 in 1990 now to 650,000. I don't -- Even though there is a cluster around one tissue processor, and I think there was a combination of events at that particular tissue processor which led to the release of contaminated tissue, but the problems are still, I believe, something which the whole industry needs to take note of. There are at least eight tissue processors involved at the present time.

Does that answer?

CHAIRMAN NELSON: Are there any guidelines, either by the Association or FDA or anybody, about which donor, if you will -- that's what you call the person who died -- the characteristics.

In other words, how soon after death the tissue must be taken or any characteristics.

I assume, if he died of sepsis, he wouldn't be acceptable. But if he had a gunshot wound to the abdomen or, you know, something like that, are there any guidelines that pertain to which donor is an acceptable donor?

DR. KAINER: My understanding is that there are industry guidelines from the AATB which specify the time limits for tissue retrieval, and my understanding is that you can retrieve up to 24 hours after death if the body had been refrigerated at 12 hours after death.

With respect to whether you can reject a donor or not, I'm not entirely sure whether the industry guidelines specify those details, but the next speaker will probably be able to assist with that question.

DR. ALLEN: Two or three quick questions.

Let me just confirm what you said early on about this one tissue donor. He was not refrigerated until 19 hours after death?

DR. KAINER: That is correct.

DR. ALLEN: And what is the potential within a tissue processing plant for contamination and

subsequent transmission of the contamination to other specimens rather than intrinsic contamination? Was there any evidence of that based on your examination of the processing unit?

DR. KAINER: We had the opportunity to observe some of the processing at Tissue Processor A, and there really did not appear to be a lot of opportunity for cross-contamination of tissue at Tissue Processor A. I believe the tissue came in most likely contaminated, and then the process there failed to eradicate or reduce the number of *Clostridium* spores efficiently.

DR. ALLEN: And given that Processor A had a large bulk of the *Clostridial* infection subsequently, that was -- it was a problem inherent in their processing methodology, as you described, that enabled that?

One other final question. How frequently or as a standard of practice are antibiotics with a broad range of coverage used for the recipient at the time of surgery, and does that in fact mitigate some potential low level contamination of tissues that are being implanted?

DR. KAINER: So far, most -- There is no orthopedic guideline as to what antibiotic to use, but

probably 95 percent of the orthopedic surgeons involved in these cases have used a first generation cephalosporin, Cephalozolin, one dose.

If patients have received a femoral condyle, that operation is more painful. They stay in hospital a little longer, and they may have additional doses of cephalozolin, maybe up to 48-72 hours, but that is a standard preoperative antibiotic cover given.

DR. ALLEN: Yes, and that really is much more to do with the prevention of a nosocomial surgical wound infection rather than contaminate -- you know, dealing with contamination.

DR. KAINER: That is correct.

DR. ALLEN: Thank you.

DR. DOPPELT: Yes. I might just add: After most orthopedic surgical procedures, including allografts, usually you give Anceph, either one dose or for 24 hours, depending upon the case. If they are penicillin allergic, it's Vancomycin.

So usually, but it's not given assuming that there is going to be some transmission of disease. It is given just in the usual course of management.

In regard to -- If I can just add one

thing in regard to the donor screening, I believe Dr. Eastlund has some words on that, but there is a uniform donor screening form that we use as well as do OPOs. So there are strict criteria that you are supposed to follow in terms of no evidence of infection and no sepsis and so forth.

In this particular instance, Bank A, they did not adhere to the standards in the industry, which is -- or they were sort of splitting hairs, let's say. As you pointed out, the body is -- the donor body is supposed to be refrigerated as soon as possible, preferably within 12 hours, and the procurement is supposed to be done and completed within 24 hours.

So in this particular instance, the information that Dr. Kainer has is that the body wasn't refrigerated until 19 hours. Procurement, I believe what you were saying was that it started at 23 1/2 hours.

So that's kind of splitting hairs and, depending upon how large the procurement is, it could go for several hours. So they would have been outside the window for refrigeration, also outside the window for actual time of retrieval.

DR. CHAMBERLAND: Do either you or do FDA have any estimate of what proportion of the universe

of tissue processors Tissue Processor A accounts for? In this particular investigation, to date it's accounted for a little more than 50 percent of the identified infections, but I am curious as to, number one, what proportion of the processing market does it encompass.

Then just also for my own information, is Tissue Processor A a discrete entity located in one physical location or is Tissue Processor A some sort of a corporate entity that might have multiple -- offices is not the right word, but facilities located around the country?

DR. KAINER: I'll answer the second question first. Tissue Processor A predominantly processes tissue all at one site, but I believe they have arrangements with some other tissue processors who also process some of the tissue. All this tissue was processed at one facility -- all the implicated tissue was processed at one facility.

With regard to market share or denominator data, I have attempted to get that information, and I'm not privy to it. I'm sorry. But my understanding is that they have a reasonably large market share for the femoral condyles and the menisci, and a relatively -- a smaller market share for the anterior cruciate

ligament tendons.

DR. DOPPELT: I believe that's right. I think that Bank A does a fair amount of banking of, let's say, fresh frozen in situations where you want viable chondrocytes or you want the viable chondrocytes and a menisci or something.

I don't know -- I'm not privy to their absolute numbers, but I believe it's a fair statement -- maybe Dr. Eastlund when he speaks can add to it, but I think that there are about 73 or 75 accredited -- AATB accredited tissue banks which probably accounts for about 98 percent of the tissue that's distributed and used in the United States.

So if you sort of work backwards, overall they probably represent a fairly small part of the market share.

In regards to that, I would just add one other thing. I mean, I think this is an exceptionally important issue, and you know, we need help from wherever we can get it. But I would point out that in terms of the incidence of infection, if you look at -- Dr. Kainer has identified 26 or so. Now there may be some more, but let's say 26 over three years, and there is roughly now about 850,000 grafts done a year.

If you do the math, that turns out to be

about .001 percent. infection rate. If you look at surgical procedures in general, you've got 500,000 post-op infections in about 25 million procedures done a year, which represents about two percent.

So in this particular instance, the infection rate related -- or associated -- I shouldn't say related -- associated with allografts is .001 percent compared with the general surgical infection -- post-op surgical infection rate of two percent. And the orthopedic community, depending upon what cases you are doing, it could be anywhere from, you know, one or two percent, maybe even lower if you are just doing arthroscopic procedures. So --

CHAIRMAN NELSON: I noticed in your database you excluded people who had an underlying condition, and, you know, many people who have a knee replacement, I guess, don't have an underlying condition, but there are circumstances where somebody had some immune deficiency. So they might even be more susceptible.

I wondered, do you think that that may have affected the total numbers that you -- I understand why you did it, and it's right to do it that way, because you wanted data that were clean and that were -- and to estimate, you didn't want to

contaminate it with what could have been an endogenous infection.

Nonetheless, when you start to estimate the rates and .01 percent, it may be higher than that if we take into account a more susceptible patient population.

DR. KAINER: Sure. There were multiple patients who were excluded because they had underlying conditions, and we just did not want to include them in this database. So these are 26 patients where they were healthy patients undergoing elective procedures, not life saving procedures, elective procedures to improve the quality of life.

Unfortunately, for most of these they ended up having a far worse quality of life than they had prior to surgery.

DR. LEW: One thing that might help if you are going to do this prospectively to try to gather data, particularly if you are saying it's such a rare event, that if you could include in it collection of the organism, only because it could address the issue if there is something in the manufacturing process, and then patient-to-patient contamination, you could do the genetic testing and see.

Antibiotic profile is sometimes useful,

but for *Clostridium* I don't think so. So, you know, that might be worthwhile, particularly if it is rare enough. You could really get a lot of data from clusters.

DR. KAINER: We have collected this data retrospectively. Unfortunately, most of the isolates were not available for genetic fingerprinting, although two of the cases which were reported in the December 7th MMWR of *Pseudomonas aeruginosa* -- they were genetically identical in pulsed-field gel electrophoresis.

DR. STYLES: Just a quick comment about what you were saying about surgical infections. My impression is that overall those are underreported, and I suspect from the data that you have said that some of these infections are underreported.

I think it behooves the orthopedic community or any of the communities that use tissue bank tissue, if you will, to really ramp up their reporting of incidents, because I think what may be happening is surgical infections that are being attributed to the surgeon could in essence be not their fault.

I mean, I feel sorry for the orthopedic surgeon that had cared for this unfortunate patient in

Minnesota, and I think that it would actually be to their own benefit to -- and would be helpful in determining not only the true incidence of problems but how the FDA's interventions actually impact that, to go back to the actual communities using the tissues and say let's try and gather more data here because, you know, just my experience with these sort of things is these infections in a number of cases could be related to a variety of things and are not generally reported or further explored.

DR. DOPPELT: Well, yes, I agree. I think there may be more cases, and I'm sure if Dr. Kainer investigates, we will find that there are some more. But let me just say that, in terms of post-op infections, it's not that it isn't being reported. It is being reported. It's just not being reported to the right people.

Every hospital has their own infection control program. So they know about every infection. Each department has their monthly QA reports in which they go over their infections.

The problem is that the tissue banks that are providing the tissue aren't getting the information back. The CDC isn't getting the information back. The FDA isn't getting the

information back.

So you know, that goes back to what I had said before, that we have to somehow develop a system where this information is reported to the interested party so they can take action appropriately.

DR. HOLLINGER: Are there -- You mention at the bottom there -- you said there are methods to sterilize -- Are there methods to sterilize tissues that would not adversely affect the things, and what was -- For example, what --

DR. KAINER: There are some. I know that there is at least one company which has got a low temperature chemical sterilization method, and I believe that they have validated that and have implanted bone with that, and I believe there is some soft tissue about to -- Some soft tissue is also about to undergo that.

Certainly, Tissue Processor A is actually working very hard at trying to get to that as well, but they haven't implemented it as yet.

DR. CHAMBERLAND: Just in follow-up to some of the comments that were made about reporting, can you share with us, are there any discussions underway within CDC, CDC-FDA collaboratively, in perhaps trying to consider what possible approaches to

perhaps more active or systematic surveillance might be undertaken to try and get a better estimate of what the true level of allograft-related infection might be?

DR. KAINER: Ideally, what we would really like is to have a very simple system for clinicians to report to, so that they have sort of like a one-stop shop. They would report the condition once, and it goes to all the relevant right people instead of asking the Commission to report to six different people, the consequences being that they don't report any at all.

Any such system requires a motivation of people. It is voluntary, and also requires resources. But it is something we are certainly very interested in exploring wider, also in conjunction with the American Academy of Orthopedic Surgeons.

Tissue processors would like to have from tissue processors denominator data so that one can actually work out the rates of infection, and not just denominator data of total tissue but also by type of tissue and type of processing, so that one can identify what processing method is a problem and then can remedy that.

So that is what the idea system would be,

but then there are proprietary issues, and it is confidential market share information which tissue processors may not want to share.

So there are some challenges ahead, but that would be the ideal system, to also have the denominator data, so that patients and health care providers can have informed consent about what is the actual risk.

DR. SOLOMON: Could I comment? As I mentioned before, reporting of adverse events is not currently a requirement, but we have proposed it. We have received several MedWatch reports on tissues, but again that's voluntary.

I also would just like to comment that, if we discover a case of contamination on inspection, if the inspection is ongoing, we are not at liberty to make that public and to share that information.

DR. CHAMBERLAND: You can't share that with state and local health departments or CDC, if you are investigating?

DR. SOLOMON: I don't believe we --

DR. CHAMBERLAND: So those entities would have to independently -- through an independent source learn that information, if there were adverse events associated with allograft transplantation. They would

have to come to other entities through another channel?

DR. SOLOMON: As I said, right at the beginning of an ongoing investigation we could not make that information public. If we issued a warning letter, for instance, that is public information, and there is some data that we have shared with Dr. Kainer, but I just wanted to make the point that we are somewhat restricted in what we can make public.

DR. LINDEN: On the issue about reporting, in New York we do have mandatory reporting for adverse events, and we license the transplant sites as the hospitals as well as the tissue banks.

Unlike the blood banks which are really excellent in the reporting, the tissue banks -- it's erratic. There are some that report a ton of trivial things, but in this particular case there were a couple of these events that did occur in New York that were not reported to us. Tissue Bank A is licensed by New York and didn't report these to us.

So even if you have a mandatory reporting requirement, that doesn't mean people are necessarily going to report. I agree absolutely that sharing of information, however we can get people to report it and share that between public health agencies, would

be a really, really positive thing to happen.

DR. HOLLINGER: I think you're right, and I think that, you know, one of the problems is that the tissue banks as well as other organizations don't get the reports from the clinicians or the people who see the problem in the first place. That's really one of the big issues.

Part of that is because of the questions that are often asked clinicians and others to do. You know, sometimes these require a fair amount of information which I -- It depends on what you want your adverse reports to say.

If you are looking for an early surveillance of problems that are occurring, then you don't have to ask a lot of questions. I know you like to have it. People like to have it for reports and look at this and so on. But if it's for an early surveillance, then it doesn't require a lot of information. Got an infection, and here's what it is, and then it's a requirement then, I think, of the tissue bank and so on when they start seeing things or even other organizations to then go back and try to ferret out a lot more of that information.

I find sometimes that there is just -- You know, you sit down and you say I don't have the time

to go through this, and you end up not doing it rather than at least sending some information off to the organizations that could use it.

CHAIRMAN NELSON: I was rather struck with the importance of *Clostridium sordellii* in this, and I wondered. You know, one method to alert to a problem, if somebody got a *Yersinia* blood culture in somebody who was transfused, that would immediately send a bell that, you know, maybe it was the transfusion.

I wondered to what extent *Clostridium* in a post-operative patient should alert the fact that it may be the allograft rather than, you know, a bacteremia or operative infection or something. Do you have any sense on that?

DR. KAINER: We have actually collaborated with the Emerging Infections Network, and the questionnaire has gone out to 500 infectious disease physicians to actually report all *Clostridium* infections and what proportion of those were actually allograft associated.

So we will, hopefully, get some data on that.

DR. STRONG: Strong, Seattle. I might also mention that, although a lot of tissue banks do

get reports -- for example, in Seattle I think about 95 percent of our transplant records are returned, but it's generally cosmetic things: Did they like the way it looked? Was it packaged properly?

We rarely get the longer term follow-up clinical information which is really the important information.

DR. DiMICHELE: Two questions. Are there standards for non-banked tissue that's transplanted, you know, taken out of someone and put right back into someone else, hearts, kidneys, you know, those kinds of organs?

Secondly, are there other international standards that might be helpful in helping us reestablish our own in this country?

DR. KAINER: With respect to standards for organ transplantation, I'm really not the best person to answer that at all, and I'm not aware of many additional standards internationally.

I know that in Australia they don't -- there is some work going on at the present time in revising some of their standards, but I haven't done a call-out to the international community yet. But representatives from AATB probably will be able to answer that question.