PACT Web Seminar 7: Question and Answer Session
Transcription from July 19, 2007
FACT and AABB Cell Therapy Standards
Speakers: Dr. Phyllis Warkentin and Doug Padley

Question 1: Can you explain the rationale for requiring that records of administration include "supplies and reagents used during administration?"

Doug Padley: Since the record of administration includes the reagents used during administration, the new standard is consistent with standard 5.9.3, which requires the lot number and expiration dates for all disposables used in procurement. Standard 5.14.1.7 requires the same for reagents used during processing. When we looked at these standards, we noticed we were missing administration, so we've added that and in addition, standard 5.5.1.2 requires that the use of critical materials shall be recorded in a manner that gives complete and accurate tracking of any given cell therapy product - and so it makes sense to track it all the way from donor selection and eligibility to administration.

One way to comply with this is to record the lot number and, to eliminate any confusion, the material number of the water bath and tracking number. If you use ACD-A or another reagent in the water bath to thaw or if a syringe is used as the container, those numbers would be good to track. And finally as part of the quality plan you need to investigate adverse reactions and so if there are some adverse reactions you need to go back and ask what lot numbers were implicated during the administration of this product. Next question.

Question 2: This question concerns laboratory testing, in particular, viral testing. Regarding the use of an equivalent accrediting body for testing, standards 4.2.2, 4.2.2.1, and 15.16.3.4.2 #2, these appear to be a little confusing to me in allowing the equivalent lab in two locations and contradicting themselves in the other two, is it the case?

Doug Padley: Standard 4.2.2 allows the lab to supply testing as long as they are accredited by AABB or equivalent and that can refer back to CMS and as specified in 21 CFR 610. The standard 4.2.2.1 discusses the specific tests indicated by the FDA in 21 CFR 610 and that must be performed in a laboratory certified by CMS and registered with the FDA with no exceptions. So I think it has to do with the FDA regulations and what they require.

Question 3: Concerning donor qualifications more specifically the autologous donor section. What are the rationales for only requiring the evaluation for risk of malaria exposure and not for other infectious diseases?

Doug Padley: Malaria was included there because it is easily addressed in the health screening. The full donor history isn't required for autologous donations because it is pretty easy to see if they've been to a malaria endemic area without administering the full donor history questionnaire. Other communicable diseases such as Dengue fever and Chagas' may be defined by site-specific facilities but they're not specifically addressed.

Question 4: Regarding screening and testing of autologous donors, what is the rationale for requiring ID Testing when these products are used for autologous use only and the FDA does not require this.

Doug Padley: I can preface this by saying this is a standard we've had a lot of questions about. There are several reasons we developed this standard. One is the need to quarantine HCT/Ps that test positive for communicable diseases during storage, whether they are autologous or allogeneic. Other concerns about the safety of autologous products include the possibility of mislabeling or other identification errors that could lead to the administration of a product to someone other than the intended recipient, and concerns about the safety of the staff handling biohazardous products. There are also concerns about the safety of the autologous donor. If we know that the donor has an infectious disease that we pick up during that testing maybe we can hold off on the treatment until the patient has a lower viral load later in the treatment, that kind of thing. Those are just a few of the things that went into the background for that standard. I'll point out that that standard is also consistent with what FACT requires. Even though they both differ from the FDA requirements, both FACT and AABB are very similar in their standards, on this topic. Is there anything you would like to add to that Dr. Warkentin?

Dr. Warkentin: Not specifically, I think that the rationale at that level was much the same and Doug has already talked about that.

Question 5: In FACT standard 4.8.2, audits shall be reviewed, reported, and documented at a minimum on a quarterly basis. How comprehensive do you expect a quarterly audit to be? In other words, can one monitor contamination of HPC products the first quarter, HPC products arriving in the outside lab, the facility keeping the acceptable temperature range, during the second quarter etc. Does each quarterly audit have to monitor all parameters or varying parameters each quarter as acceptable or more desirable?

Dr. Warkentin: This is a fairly general standard and I think the latter interpretation is more nearly what we had in mind. I would expect in looking at an audit schedule or plan within a quality management plan to have some sort of calendar that would say which audits would be performed at which time. There are certain things you would want to audit annually and other things you may want to audit more frequently. In addition, the results of the audit might trigger how often you go back to that same issue for an audit. So I don't think that the intent is that everything you do is audited every single quarter, but there is some reasonable calendar being maintained where you can get through the various things you want to audit on a sort of annual basis. But we should be looking at some of the results throughout the course of the year.

Question 6: Did the company accreditation manual soon to be released for the new FACT standard?

Dr. Warkentin: The short answer is yes. The clinical portion, I should say that each of the portions, clinical and collection and laboratory portions they are being independently written by the group that divides the standards. So the clinical one is finished and awaiting approval. The laboratory one is very nearly finished and the collection one has a way to go, but the plan is that

we will be publishing these on the website of FACT as soon as they are approved by the oversight committee. So I envision that within the next few weeks that the clinical section should at least be up and certainly by the end of the summer the laboratory portion will be.

Question 7: In the small program, what is the best way to review processes that are only performed by only one or two staff members? This also applies to the QM oversight.

Dr. Warkentin: There are probably are a lot of ways you could approach this in a small program. One thing that many of them do is utilize the other resources within the institution for quality management so that if somebody is involved in quality management at the nursing level in the transplant program or in another portion of the laboratory that the portion of the plan that applies to a larger entity could be applied to within the cell therapy lab. And can become an inactive part so you can use people with quality expertise in the institution. It is important that the person not review his or her own work. I think in the worst situation it would be possible to review one's own work in a time and place distant from when the work was actually done so that you take on the role of a quality reviewer on a day when the work was your own. And that is obviously not optimal and I think some other places have used maybe reviewers from the blood bank or someone who has some of the same expertise or experience from a different area, but they can review specific things. So I guess getting help from other areas is the most appropriate for a small program.

Doug Padley: I think, the key, like Dr. Warkentin said, is that you shouldn't be reviewing your own work. That's the key and there are lots of ways to do that. So I think you want to avoid having someone do the technical review and then find the quality reviewer in the audit is no the same person.

Question 8: Is a cross walk available describing the new changes in due standards between the second and third editions of the FACT standard?

Dr Warkentin: There is a crosswalk available we, I'm just looking. I thought we had maybe put it in the document, but maybe not. It is available; you could contact the FACT office for a copy of that.

Question 9: Is there a list of top ten deficiencies for AABB inspections?

Doug Padley: I don't know the answer to that. If someone from AABB is listening maybe they could send me an answer. Otherwise I suggest that this person go to standards at AABB and ask that question there. They might be able to help. [See additional material submitted.]

Question 10: What constitutes major changes that are to be reported to FACT annually?

Dr. Warkentin: I think the minimum would be a new building, a new program director, a new laboratory director. Sort of leadership changes, facility changes, in general we would consider in a relatively moderate to large sized program one staff member one way or the other would not

necessarily be a major change unless it dropped the program below the minimum number of people that were necessary to do the work. Probably if an entire laboratory left that would be a major change. Also, it would be a change if you had been doing your own processing for example and now decided to contract out the laboratory part to another laboratory even though that laboratory would be accredited to provide services to many programs it is still important for FACT to know that the change had occurred. Not every major change is necessarily going to trigger a re-inspection or a change in accreditation status but it is just a matter of making sure that the program continues to comply with standards throughout the period when they are accredited.

Question 11: Since we are a processing and storing facility what responsibility do we have in ensuring that the collecting and administering facilities follow the AABB *Standards*?

Doug Padley: To answer this question, agreements are probably the best way to deal with outside agencies involved in activities like collection and infusion. You should have an agreement with the clinical site for example, and it doesn't necessarily have to be a written agreement, but an agreement that says they are going to follow the AABB requirements for the infusion. So maybe if you want the nursing service to record the lot number of the tubing set you need to make that clear in the agreement with them. And then follow that up with some due diligence, maybe an occasional audit or something that says, "Yes we told them they need to follow these standards and we have evidence that they are following these standards."

Question 12: How were the standards addressed in the autologous HPC collection that was shipped to a further manufacturing facility, manipulated and then returned to the autologous donor for infusion?

Doug Padley: In general terms, this is probably covered in agreements because you're going to have this outside place do something to a product. So you need an agreement with them about what you are going to do with those cells and how they're going to treat them and what they are going to do with them, you need agreements with the patients, so the patients know what's happening with their cells. If it involves frozen shipping you need to look at the standards for shipping. What needs to be monitored, temperature-wise, during that shipment? Receiving the product comes under the topic of "raw materials received," so for example when the cells come back to the laboratory you have a process for receiving those into your inventory and you have a process for tracking that it's the same unit that went out and all those kinds of things. So this actually covers quite a number of the standards. If you break it down into the sections, there is probably a standard in each chapter that applies.

Dr. Warkentin: I would just add that probably in the agreement section too you would want to know how the agreement, that whoever did whatever they were going to do to the cells told you what they did and also that you had an idea of the safety of the product when its back in the laboratory.

Doug Padley: I might add one more thing. One of the questions we went over in the AABB teleconference a while ago for these standards as a great way to address future issues is that in

the agreements, you can define who owns the cells at the various times. So if the cells are damaged in shipment, who takes liability, or if the patient dies during that treatment where do those cells end up when they're in either place? So agreements are nice just as a way to lay out expectations before you undertake something.

Question 13: What are facilities using for continuous monitoring of cryopreserved cells during transport?

Dr. Warkentin: I think the most common thing is the data logger. Kind of a system where a device can be placed in the shipping container and a record is kept and it can be downloaded either at the receiving end or it can be shipped back to the sender and that record can be downloaded on the computer and a record can be printed out.

Doug Padley: I'm aware of at least two companies. Data logger is one company's brand and I have just forgotten the name of the other company. But there are at least a couple of those that offer that similar down to the liquid nitrogen temperature.

Question 14: If the product needs to be processed within 36 hours, how would it be tested, evaluated, and etc? What if they were called a vaccine after manipulation?

Doug Padley: Something like this, I believe AABB standards would apply to a product like this even though it is probably under IND or it may not be under IND. I think, once again, having an agreement would be the key. So what our lab is going to participate in and what's going to happen and frankly, this may be a place where the laboratory wants to request a variance. If you say AABB standards requires this but the process doesn't allow it, but we've addressed it in another way and it would cover the standards, then you can send it to the committee. We would look at that at either say, "Yes, this makes sense," or ask for more information. So if a protocol-specific activity makes it hard to follow the *Standards,* contact someone at AABB and we can try to work with them to make sure that we are meeting the intent of the standards, if not the letter.

Question 15: Will a guidance document be available from FACT?

Dr. Warkentin: Yes a guidance document will be available. I think somebody asked about when it would be available. We are actually going to post it on the website in order to allow the different sections to be posted as soon as possible after they are completed. We are also nearly finished with the guidance document for the NetCord FACT standards and we have not had guidance for Cord Blood. So I think it is going to be really helpful to have this guidance document. The base of it was prepared during the preparation of standards, so that should not take very much longer until that is also ready for publication.

Doug Padley: I received a message that the FACT second to third edition crosswalk is available for download on the FACT website.

Question 16: In AABB Standard 5.14C, if you currently do not do colony assays what would be an example of a potency assay?

Doug Padley: Well Standard 5.14C applies for products other than HPC, Apheresis, HPC, Marrow, and HPC, Cord, so non-hematopoietic cells such as dendritic cells, mesenchymal stem cells, stromal cells. So there may not be sort of a traditional assay for that or it may not be "applicable" or you can show some evidence that maybe flow cytometry correlates with activity so up-regulation of a certain marker shows potency. So if there is an assay, you are required to test perform a potency assay, and if you just don't have one, I think you need to have some evidence that we tried to use another one and none of these worked. But maybe even cell counts are enough for potency in an early stage trial. I think the key in that one is that it applies to non-hematopoietic cells and the potency assay is required, "if applicable."

Question 17: If HLA-C Typing is not available from the collection facility for distribution, what is the responsibility of the transplant facility?

Doug Padley: I assume this is the cord blood and the cord blood HLA-C typing was required at confirmatory typing. So I would think that this would have to happen earlier and if they didn't have HLA-C typing, this would have to be noted at the time of the confirmatory testing. You can always bring things under exception and document that there's an exception. Most of them have variances or deviation reports or something where they can just document what they did or didn't follow in the standards for that case.

Dr. Warkentin: For the FACT standard they don't specifically say which loci need to be tested at what time so I think that the transplant program makes its decisions on what kinds of testing are required what the best kind of evidence available is at the time. It's a little bit left more to the clinical team to make its medical decisions.

Question 18: When were the FACT guidance documents posted on the website?

Dr. Warkentin: Maybe my FACT colleagues that sent in that they have the crosswalk on the website already, would have a better date than mine. But just in general I would say certainly by the end of the summer you should be expecting at least two thirds of it on the website.