PACT Web Seminar 8: Question and Answer Session
Transcription from October 11, 2007
Preparing for an FDA Inspection
Speakers: Drs. Adrian Gee and Nancy Collins

Question 1: Does the FDA require that you include the variance in the manufacturing record, or is that just good practice?

Adrian Gee: I think it's good practice, rather than a requirement. The requirement will be that you will be able to produce it. It makes it a lot easier when they find the variances needed and you have a copy right there, rather than tracking back to old variance log to make copy for them (FDA).

Nancy Collins: I think that it is very important to have it in both places. What we would always do is put a Xerox of the variance in the patient chart. Being able to track it and get your hands on it in a timely fashion is the most important issue.

Question 2: Is a separate SOP required for release of CMV positive product?

Adrian Gee: We have not done that. We have written into our SOPs for donor eligibility and the like, that CMV has to be handled separately from the other infectious disease markers. So we do not have an SOP for the specific release of CMV positive products, but it is part of our donor eligibility SOP.

Nancy Collins: That was the same at our institution.

Question 3: What type of review do you suggest for 1-tech labs regarding critical calculations?

Adrian Gee: It is always difficult for smaller institutions to know how to comply with many aspects of the regulations, in particular cross review. In some cases it's almost inevitable if you have an allogeneic product that's been processed and you only have one person and it has to go in immediately after processing. What I would recommend, and what we've done for most of our processing is to have an electronic worksheet that is validated that performs the calculations for you. So that you can feed the data into that worksheet and as part of the normal process it can do the calculation and you've already validated and locked that worksheet to ensure that it's doing the calculations correctly. If there's no immediate need to infuse the product then you can go back at a later time, and I think it is acceptable in such a circumstance, either to cross check the calculation at another time or find a second individual to do it when there is somebody else around.

Nancy Collins: At our institution we always used a second individual and that individual sometimes was at the end of a phone line. Sometimes they would also have access to a fax if they actually had to take a look at something. We had written into our SOP that it would be a trained individual. Sometimes that trained individual might be the physician who's actually infusing the product.

Question 4: What type of environmental testing do you perform in an unclassified laboratory?

Nancy Collins: We went around and around about this. And we finally decided that what we were going to do is we were going to do particle counts and touch plates within the biologic safety cabinets. And touch plates at certain areas outside the biologic safety cabinet, for example, within the centrifuge. We discussed at great lengths whether we should do something like particle counting or viable counting outside in the unclassified space and decided that we wouldn't know what to do with that data should be it. The problem with these is always what are your alerts and what are your action levels. I don't think that there is any consensus around the country on this. There was discussion about this at the Somatic Cell Therapy meeting. At my institution, because we were dealing within the biologic safety cabinet, when we got anything at all it just meant that we cleaned it again and tested it again. The problems with all of these, is, that of course you have to document the specific products you used between the last time you tested it. It does become a documentation problem. I think this is an area where PACT and where the other professional societies could weigh in and do studies as to practices that are common for unclassified spaces around the country.

Question 5: Dr. Collins, could you expand on how you organized your complaint file to reflect the core GTPs?

Nancy Collins: Primarily what you are going to be doing here is you're going to make certain that you talk about if it's something where say you've gotten a contamination within a hood, there you are going to want to say within your occurrence report environment, you're going to want to say contamination, cross-contamination and environment. What we would do is we would put a summary in the front of the book where we would have a very short summary of what was in that particular occurrence report, highlighting those words, which exist within the core GTPs.

Question 6: Can a warning letter be issued immediately after an FDA inspection?

Adrian Gee: I believe so. Luckily we have never been in the position where that has happened. Under extreme circumstances you can be shut down at the time of the inspection.

Question 7: How do you manage labeling controls?

Adrian Gee: We have pre-printed templates for all of the labels. Then we fill-in the specific details related to donor, recipient, etc. At the time that those templates are filled out, at least two copies are made depending on how many you would require. One of the copies goes onto a sheet that is in the processing record and that shows the information that was transcribed onto the template. And then the identical label goes onto the product itself. For more extensive products like vectors, we have a specific label check procedure where we generate the labels, they are examined by QA/QC, and we have all of the documentation showing how many labels were generated, who checked them, who cross checked them, whether the alignment of the type was right, whether all the labels were legible, how many were used, how many were returned to QC and then we shred the ones that were returned and we document that we shredded them.

Nancy Collins: At our institution we had a simpler system. We did have a read-only file from which labels were printed out. Labels were printed out for each process and put within the patient's chart for that process. At the bottom of the patient's chart there was a checkbox along with the initials of the 1st person who made out the label the 2nd person who checked the label. The label, which went to the floor, then was identical to the label, which was actually adhered to the product. The label adhered to the product was a Xerox, when that label was taken to the floor it was signed off by the person on the floor who received it so it served a dual purpose for us, that Xerox was taken back and put into the patient's chart.

Question 8: Dr. Collins, can you respond to what type of environmental monitoring is required for apheresis collection, not processing?

Nancy Collins: Actually no I can't, I'm only involved in the processing.

Adrian Gee: I think this did come up at the Somatic Cell Therapy meeting, that the FDA did expect there to be some form of environmental monitoring. I think it would only be a very superficial type of monitoring given that these are essentially closed systems for collection. So I off the top of my head, I would say probably you just need perhaps fallout plates to see what kind of environmental contaminants you have in the collection space and some kind of documentation that you cleaned that space and that the cleaning agents are effective against the organisms that you have detected in the area.

Question 9: What type of facility controls do you recommend for a non-classified laboratory?

Adrian Gee: Ours is all classified space, so we have a very comprehensive and very labor-intensive environmental monitoring program. Again, I think based on the recommendations from the latest Somatic Cell Therapy meetings; it would be relatively similar to what I just described for the collection areas. The expectation is that you know what your environmental contaminants are, that you would focus I would anticipate, as Nancy said, on the biological safety cabinets since this is the real manufacturing area, in monitoring those when they are being used to ensure that they are operating appropriately and in showing in some way that your cleaning of both your laboratory area and biological safety cabinet is effective in reducing the types of environmental contaminants that you see in your facility.

Question 10: How do you label CMV positive products from Allo-donors?

Nancy Collins: We have that within our -- on the label which goes to the floor we don't have anything specific we have the CMV positivity is recorded within the labeling sheet which remains within the patient's production record and of course we have the original documentation from the donor eligibility.

Adrian Gee: We don't specifically label; it's in our policy that we don't specifically label but the infectious disease testing results do go to the floor with the product and would show whether the product is from a positive or negative donor. But this is usually been discussed well ahead of

time by the clinical team in selecting the donor so it's really not new information but we do make it available at the time of infusion.

Question 11: How often are environmental test (plates, etc.) performed?

Adrian Gee: What we are doing at the moment for the vector facility, which is a bit more intense than for the cell processing facility is to put the plates in for every production and they stay in for no more than four hours before being replaced by a second plate. Although we do environmental monitoring in the cell processing facility, the productions are almost ongoing all the time, we don't have the manpower to do production monitoring for every single production. The aim would be to do it for at least one production per room per week

Question 12: Dr. Gee, I was under the impression that the result of an internal audit is not necessarily disclosed to the FDA or any other inspecting organization, was I wrong?

Adrian Gee: No, that's absolutely right. What I was suggesting was to use your internal audit as a method to determine how closely you are in compliance with federal regulations. Those are confidential to your program and do not need to be released.

Question 13: Dr. Collins, I would like to ask you to elaborate a little on monitoring of biological safety cabinets, do you do it while they were in use or did you do it in between. Secondly, settling plates, when you used them outside the biological cabinet did you find those results helpful? What did you do with the data that you received from outside the biologic safety cabinet?

Nancy Collins: We did a static monitoring within the biologic safety cabinets. This was the subject of much discussion within the laboratory and the administration, but the final decision was that it was going to be a static, and not during an active phase of use. We did not use settling plates outside of the hood, we only used touch plates outside of the hood and then only in the centrifuge area and it was surprising the number of times when the centrifuge area was actually very clean. Obviously people were following the SOPs and were doing the proper cleaning between the production runs. We were trying to determine action and alert inaction levels, and by the time I left the hospital we had about two years' worth of data and were just in the process of defining at which point we should be doing more than cleaning of the centrifuge yet one more time.

****The following two questions were logged in after the written Q and A session ended. Could you please provide answers to the following questions? Question 15 is directed toward Dr. Collins.**

Question 14: When is endotoxin testing required for minimally manipulated HCT/Ps?
Adrian Gee: As far as I know endotoxin testing is only routinely required for IND products i.e. those that are more than minimally manipulated (e.g. culture for more than a few hours) or for "fresh" non cultured products that are used in non-homologous applications (e.g. marrow cells that are injected fresh but for cardiac applications). It is not required normally for Type 361 products.

Question 15: Is the Quality Plan for MSKCC still integrated with Blood Bank Quality Plan?