PACT Web Seminar 14: July 16, 2009
"Deviation Management of Type 351 and 361 Cell Products"
Question & Answer Session Transcription
Speaker: Ms. Ellen Areman

Question 1: If a cellular therapy product dose is found to be 10 percent below the specified dose and the IRB has approved administration of this product, do we need to report this as a deviation to the FDA? If yes, is the lab responsible or the Principal Investigator?

Ellen Areman: As we said if it's under IND then it's reported as a deviation from the protocol, so it would be a safety report. Generally what people do is call their FDA reviewer and explain the situation and see if they need to file an amendment to the IND describing the failure of the product to meet criteria.

Question 2: Are there situations where the four criteria for regulations solely under 361 are not clearly met? How would this product be defined - is there any 'grey area' with these criteria for 361 regulations?

Ellen Areman: As we progress into these refined areas of regenerative medicine, tissue healing, wound healing, just a whole variety of things, I think the biggest question is the 'homologous use' question. This may change over time; something that's considered non-homologous today with additional information and research may be found to be homologous. It may be found that there are cells circulating that actually are cardiac stem cells that circulate in the blood. It's not cut and dry and even with minimal manipulation there are issues about what is actually minimal manipulation and what isn't. When there is a question, if you're not sure if the product should be more highly regulated, you should speak to someone at FDA and get their ruling so that you're not distributing a product that actually should be approved by FDA.

Question 3: Would we need to report an in-process specimen that became contaminated and was disposed of if it is a 351 product under an IND?

Ellen Areman: If it's part of the product that's being used under the IND then the requirement is, for every product you need to report how it was disposed of and what happened to it; that goes under your reporting to the IND and it wouldn't be reported as a deviation.

Question 4: What are the consequences from the FDA for an unreported deviation?

Ellen Areman: It depends on if they find out about it or not to tell you the truth. They can write a 483 (an inspection failure report) and put you on notice if they do find that you distributed products that did not meet the criteria (whether the GTPs or GMPs); that's definitely grounds for a reporting. If someone is doing this on a regular basis they could even get a warning letter, they could be enjoined from distributing products. FDA does have some 'teeth' when it comes to dealing with people who fail to follow the regulations.

Question 5: For Scenario Three, wasn't this an IND? Isn't it reported as a safety report for the IND?

Ellen Areman: It was but I guess we were kind of talking about it as if it were a product that was actually available. And you're right it is an IND product, that there are no tumor vaccines that have been licensed yet. I should have said 'a licensed tumor vaccine' as a scenario, even though that doesn't exist, but I was referring to it as if it were a licensed product.

Question 6: For an investigational 351 product, if a deviation does NOT affect safety (only purity or potency), do you still need to report to the IND as a safety report? Or is just reporting in the annual report sufficient enough?

Ellen Areman: My interpretation is that if there was nothing that actually affected the clinical trial, you could report it in the annual report. So for something where it didn't meet the dose, it really depends on what the effect was on the clinical trial itself. If there was something that would affect how many patients would be treated; say that a product didn't meet the dose requirement and they would have to add another patient to the trial, that would be something that would need to be reported immediately and not waiting for the annual report. So if it has any effect on conducting the clinical trial I would say it should be reported. Again if you have an IND you have a relationship with or the PI has a relationship with the reviewers at the FDA, and whenever there's a doubt the best thing is to contact them and say: 'do I need to file a safety report or can I just put this in my annual report?' It doesn't hurt to communicate verbally with them and get their input.

Question 7: In Scenario Three, is the incident required to be reported on a BPD since the permission to release was obtained prior to distribution?

Ellen Areman: I don't think it matters whether there was permission to use the product. The product did not meet the safety criteria, so I don't think that has anything to do with it. I would say it would still need to be reported.

Question 8: Are GTP deviation reporting requirements the same as BPDs?

Ellen Areman: No the methodology for doing the reporting is the same, but the reasons for reporting are slightly different. The GTPs only talk about deviations that relate to a transmission of communicable disease or contamination of a product; they don't deal with potency, or purity, or identity as the GMPs do.

Question 9: For HCT/P (361 products) that have positive sterility-results - are they reportable to FDA if distributed?

Ellen Areman: Yes obviously they are capable of transmitting disease so they should be reported.

Question 10: In Scenario Three, was the tumor a licensed product? Otherwise it should be reported as a safety report or in the IND annual report?

Ellen Areman: Yes my mistake. I should have said 'hypothetically a licensed tumor vaccine.'

Question 11: How is bone marrow regulated?

Ellen Areman: That's a difficult one. Bone marrow is not actually regulated. Bone marrow comes under the oversight of HRSA, which treats it more like an organ let us say. So bone marrow is not regulated as an HCT/P unless it meets other criteria. If it's more than minimally manipulated or non-homologous etc., then it gets kicked over to the FDA. This is something that is very difficult to understand; it has to do with legislation way back when bone marrow transplantation was first being used and before there were any cellular therapies to speak of. Somehow it went under the auspices of HRSA which is not a regulatory agency. That's all I can say; it's a very complicated subject because now people are using bone marrow cells the way they are using other cells, for cell therapy products, and in some cases they're regulated and in some cases they're not. I hope that someday FDA will actually clear this up so that people will know what to do about it.

Question 12: In one of your early slides, it states that all deviations of 351 products under IND must be reported whether or not it was distributed. Will you clarify, as it seemed you indicated that it did not need to be reported if it had not been distributed.

Ellen Areman: Well because we're talking about a non-conforming product that's part of an investigational new drug application, there are requirements for those products to meet all of the criteria whether they are distributed or not. So it's not the same as a product deviation it's more a listing of products that failed to meet the requirements. As I said before, depending on what the reason for failure, or what the problem is, it could just be listed on an annual report, and there's a place on the annual report that says something like: 'how many products were discarded because they did not meet requirements?' When it comes to an IND there can't be just batches that are ignored because they didn't meet criteria, because you're trying to prove that a drug is safe and effective even with biologics. That's why all of those have to be reported. As I said also, in any case, in any product, it should be recorded; you should have a mechanism for dealing with products that don't meet criteria even if they don't get distributed. This talk was specifically about reporting deviations to the FDA; that doesn't mean other deviations shouldn't be followed up and dealt with, and that FDA couldn't come in and say, 'you have all of these product failures and what are you doing about it?' So if they don't come under deviation reporting, but they do come under quality issues, they would need to be followed up on, investigated, risk-analysis done, the normal quality assurance to make sure quality products are being produced.

Question 13: If you infuse an allogeneic first degree relative HCT/P product that is positive for Hepatitis under urgent medical need with permission from the Lab Medical Director, physician, and patient, is this a reportable deviation?

Ellen Areman: I'm saying yes because it still meets the criteria. There's nothing that I know of in the regulations that says 'if the product is administered with permission, if it meets the criteria for a biological product deviation, then it doesn't have to be reported.' I could be wrong, but I don't recall anything that says that that would mean the product doesn't have to be reported.

FDA Comment from Sharon O'Callaghan: To clarify the question that you received about the positive Hepatitis: there is a regulation that allows for exceptions for donor eligibility criteria. If a donor is considered ineligible because of positive viral-marker testing, that product collected from that donor can be used, but there are provisions for labeling that have to be met; that it has to be labeled for autologous use, or first or second degree use. It has to be labeled that it has the potential for transmission, it has to be labeled that it has a positive marker. There are provisions for using that type of product. Because of that, a deviation report would not be required, as long as the product is labeled appropriately and all of the appropriate approvals have been met prior to distribution of the product.

Scenario Poll Question Results and FDA Comments:

Scenario 1: Frozen autologous peripheral blood progenitor cell product transported from the Cell Therapy Lab to patient care unit for infusion. Product placed in water bath for thaw. During the thawing of product bag a small leak was noticed by the technologist. The bag was clamped and the cells were transferred to another bag. A sterility sample was removed from the bag and the cells were infused with permission from the Laboratory Medical Director and patient physician. Sterility testing from the bag was negative for microorganisms.

1. Is this a 351 or a 361 Product?
(Note polling results were not displayed for this question. Results are Ms. Areman's comment.)

	Response Percent	Response Count
351	N/A	N/A
361	N/A	"Majority by a long shot said it was a 361 product"

2. Is this a product deviation?
(Note polling results were not displayed for this question. Results are Ms. Areman's comment.)

	Response Percent	Response Count
Yes	N/A	"A little less clear, though the majority who voted decided it was a deviation"
No	N/A	N/A

3. Should a BPD report be submitted to FDA?

	Response Percent	Response Count
Yes	48%	42
No	52%	45

FDA Comment from Sharon O'Callaghan regarding Scenario #1: Anytime there is a broken bag or a leak in a bag identified during the thawing process, FDA has determined that that's not really associated with manufacturing. So that event, the way it was described, is not a reportable event.

Scenario 2: Unrelated cord blood under IND is received by transplant hospital. Upon thawing the cord blood unit in the laboratory routine ABO/Rh testing is performed on the product. The ABO/Rh results do not match the type reported by the Cord Blood Bank. The unit is not infused and subsequent investigation determines that the unit was mislabeled with results of another cord blood unit.

1. Is this a 351 or a 361 Product?

	Response Percent	Response Count
351	92%	72
361	8%	6

2. Is this a product deviation?

	Response Percent	Response Count
Yes	92%	72
No	8%	6

3. Should a BPD report be submitted to FDA?

	Response Percent	Response Count
Yes	31%	28
No	69%	62

FDA Comment from Sharon O'Callaghan regarding Scenario #2: I just wanted to make the point that in determining whether an event is a deviation, distribution is not part of the algorithm. Distribution comes into play when deciding whether or not to report it to FDA, but when you determine whether there's a deviation, you use the criteria for 351, which are, was the safety, purity or potency affected, and was there a deviation associated with the GMPs or applicable standards? Or you use the criteria for 361, which are, was there deviation from the core GTPs, was there potential for transmission of communicable disease or contamination? So the distribution piece of the deviation itself doesn't come into play until you're deciding whether or not to report.

Scenario 3: During the manufacturing of an autologous tumor vaccine in a Class 10,000 clean room the air handling system shutdown for 4 hours. Due to urgent medical need production was continued and the product was infused. All Lot Release testing passed including gram stain testing (taken after air handler shutdown). Approval for release obtained from the Lab Medical Director and Principle Investigator prior to issuance of the product. Environmental monitoring performed during shutdown was outside of acceptable limits. 14 day sterility testing of product was negative.

1. Is this a 351 or a 361 Product?

	Response Percent	Response Count
351	95%	86
361	5%	5

2. Is this a product deviation?

	Response Percent	Response Count
Yes	97%	77
No	3%	2

3. Should a BPD report be submitted to FDA?

	Response Percent	Response Count
Yes	72%	62
No	28%	24