

Cell Therapy Liaison Meeting, January 27, 2006

Bethesda, MD, Summary

Attendees were welcomed by Stephen J. Noga, MD, PhD, ISCT FDA Liaison and the meeting was called to order at 8:15am.

HIV and HCV NAT for HCT/Ps

M. Allene Carr-Greer, MT(ASCP)SBB, deputy director, Regulatory Affairs, AABB, presented an overview of the first topic - HIV and HCV NAT for HPC Donors. HIV-1 and HCV NAT testing has been performed on HPC donors as a part of donor eligibility determination, with many regulated establishments interpreting manufacturer's instructions in package inserts differently from FDA. Package inserts list the licensed claim for donors of whole blood and whole blood components (and source plasma) to include testing by individual donor testing (ID) or pooled testing. Additional categories of donors are described as other living donors and organ donors (heart-beating) and cadaveric (non-heart-beating) donors. For these additional categories of donors, the licensed claims allow for ID testing, with no licensed claim for pooled testing. Many regulated establishments have tested samples from HPC donors in mini-pools (MP), as they do for other donors of blood components. The product has been considered to be a component of blood and the sample to be tested is a peripherally collected plasma sample. However, language in the draft guidance "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" issued May, 2004 includes hematopoietic stem/progenitor cell donors as an example of "living donors of HCT/Ps". The discrepancy in interpretation of the manufacturer's instructions became known after the effective date of the final rule on Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (May 25, 2005). The final rule requires "...using appropriate FDA-licensed, approved, or cleared donor screening tests, in accordance with the manufacturer's instructions..."

FDA is still considering the appropriate actions for establishments to take if they have released to inventory, or for distribution, HCT/P products that were tested in pools instead of individual donor testing.

Susan L. Stramer, PhD, executive scientific officer, American Red Cross, summarized an analysis of data gathered from multiple blood and HPC centers. Included in the analysis were the test results for samples of donations of HPC donors collected from geographically distinct US collection facilities from the time of NAT licensure to the end of 2005. The goal of the analysis was to determine the infectious disease marker prevalence/incidence rates for donations of HPC donors to qualify these donations for MP NAT by demonstrating equivalence to blood donation types already included in the intended use statements for licensed NAT assays, and prove that the risks associated with MP NAT as compared to ID NAT for HPC donations are no greater than the difference between MP and ID NAT for donations of whole blood. 171,574 donations with minipool NAT and serology results were analyzed, using autologous whole blood donors from the ARC system as the control. Confirmation testing was used to identify false positive results.

Stramer concluded that 1) overall comparison of prevalence rates shows no difference between control groups and HPC donations, 2) there are no significant differences in incidence (as determined by NAT yield) observed between control groups and HPC donations, and 3) there is no additional risk of MP NAT for HPC donations as compared to the control groups for which MP NAT occurs. The data will be separated and submitted to the appropriate manufacturer (Gen-Probe or Roche) in support of modifying package inserts to include a claim for MP NAT of HPC donations.

FDA encouraged publication of the data so it can be referenced for public discussion. Data that FDA receives from a manufacturer in support of a package insert modification will not be available, from FDA, for public discussion.

Representatives of the various cellular therapy organizations present for the meeting discussed the various reasons why this issue is important to them.

- Increases in complexity of testing should be offset by increased patient safety, but this is not apparent in the requirement to perform individual donor NAT testing for donors of HCT/P products.
- Increases in testing costs should be offset by increases to patient safety, but this is not apparent in the requirement to perform individual donor testing.
- The process for NAT testing is highly automated. Manual intervention to separate HCT/P samples from whole blood samples intended for minipool testing will increase errors associated with testing without an apparent increase in patient safety.
- Individual donation testing has a higher rate of false reactive results than minipool testing.
- Facilities that have minipool test results do not know whether to report this issue to donors and patients, or how to respond to questions concerning the significance of the individual donor vs. minipool test results.

FDA commended the efforts of the various organizations to get the word out and work with their members and FDA toward resolution of the issue. FDA is carefully considering the stated concerns. The rule on donor eligibility is clear regarding requirements to follow manufacturer's instructions when using a licensed test. A guidance document would not change this.

Attendees at the meeting did not consider it appropriate to stop NAT testing while awaiting issuance of the final guidance on donor eligibility.

FDA noted that some differences donor populations (HPC vs whole blood) are relevant to NAT. For example, G-CSF could potentially change the quality of the specimen.

Discussions of modifications of product labeling are discussions between FDA and manufacturers.

Sue Stramer was hopeful that the data could be in the hands of the manufacturers by March.

REGULATION OF DEVICES

John McMannis, PhD, director, Cell Therapy Laboratory, UT M.D. Anderson Cancer Center, provided an industry perspective for the second topic related to regulatory pathway(s) for devices. In his introduction McMannis pointed out that a recent CBER list of Hot Topics included “ Devices used to make/process cells and tissues”. He emphasized that most cell therapy research is being done in academic centers (relatively small Phase I/II protocols in single centers with fewer than 20 patients) while under the review of IRBs and FDA via the IND process. Concerns have arisen within industry regarding the line drawn on what is / is not a regulated medical device and what regulatory pathway the device would be subject to. Issues arise around how to divide equipment into what is a cell therapy device and what is ancillary (scales, incubators, etc). Industry perspective is that most devices are ancillary to the process of developing a cell therapy and are not part of the final product, or are washed out of the final product. They do not constitute a “critical control point” in the manufacturing process, (ie, quality can be assured by subsequent steps in the process) and should not be required to have special or specific approval related to the particular cell therapy under development. Devices used in developing a cell therapy are as varied as those used in cell separation, selection, washing and culturing, as well as centrifuges, incubators, reagents, growth factors and cytokines, storage bags and solutions, filters and analysis tools such as infectious disease test kits, cell counters, flow cytometers and particle counters. He relayed case studies and explained how difficult it can be to determine which equipment is critical.

It seems most are ancillary and are washed out of the culture before the final product is prepared. Almost all are not “critical” control points. Other issues to consider:

- How are devices with multiple applications or intended uses regulated?
- How can study sponsors secure approvals if manufacturers have not?
- Can BLA oversight cover the production process and associated materials?

McMannis cautioned against regulating specific components of a system, for specific tasks, as that would tie the hands of researchers and inhibit “tweaking” or refining of processes.

An overview of FDA medical device regulation was provided.

In a response to a question from FDA, McMannis explained that the definition of “critical control point” used in his presentation is that point at which the quality of a product cannot be assured by subsequent steps in the

process. FDA encouraged any working group that might form to look at the regulatory pathway for devices to cover the entire scope of devices.

FDA added that regarding the regulatory option of the BLA sponsor including necessary device information and data in the IND/BLA for the cell therapy product, the group could obtain information about the type and extent of data that is generally required for clearance or approval, to be able to evaluate whether it would be feasible for individual sponsors to generate these data. Relevant devices may also have blood applications and looking at this will help focus the group's attention. For example, look at the type of device and how it is used in blood. Then examine how it was handled previously as a model.

In response to a request for assistance in interpreting FDA's designation of something as a "hot topic" FDA explained that device regulation was one of a number of things FDA is focused on and FDA welcomes thought or input into these issues.

In summary it was agreed that the work group would be assembled and any work product would be sent to FDA. A workshop was suggested, as it would provide the proper forum for a more thorough discussion of the issues.

"HOMOLOGOUS USE" WORKING GROUP SUMMARY

Shelly Heimfeld, PhD, Fred Hutchinson Cancer Research Center, president-elect, ISCT, provided an update on the Homologous Use Working Group that formed following the Cell Therapy Liaison Meeting held November 2004. The working group's mandate includes definition and explanation of "homologous use" to the cellular therapy community and simplification of the interpretation in a way that is equally applicable to all types of cells. His presentation emphasized that the manufacturer makes the same product, no matter what the intended use will be. Questions under current consideration by the working group that were presented to FDA include

- Can the manufacturer of a 361 HCT/P product make the product without stating its intended use, potency, or any clinical efficacy?
- Can the intended use be generic and not clinical application specific?
- If a 351 HCT/P product has one single approved clinical efficacy indication, will the manufacturer be allowed to make the same product for other non-homologous use indications (a 361 product)?

Heimfeld proposed that, with the following proposed clarification added to the current definition - *intuitive or already clearly documented clinical evidence for efficacy in a specific clinical application* – an HCT/P that is currently on the BLA track and has established clinical data behind it (see third bullet above) should be able to make the "shift" to a 361 product.

One of the primary goals of the working group will be to draft a guidance document to further clarify “homologous use” for the cellular therapy community. When completed, the document will be submitted to FDA.

During the follow-up discussion it was noted that the diagnosis and intended use of the product may not be known by the releasing facility. It was noted that this is similar to the current situation with IVIg.

The workgroup was encouraged to continue developing the guidance document and to engage FDA on such issues as those posed during Dr. Heimfeld’s presentation.

The meeting was adjourned at 12:10pm.