

Cell Therapy Liaison Meeting
June 16, 2006

Host Organization



Original Agenda

Moderator: *Stephen J. Noga, MD, PhD*

- 1:00-1:15 – Call to Order and **Introduction** of agenda and meeting participants
- Review of Summary and Action Items from January 27, 2006 Meeting

CONTAMINATED PRODUCT RELEASE

With implementation of the new cGTP final rule in May 2005, there has been some controversy over the clinical utilization of products with positive sterility cultures, as well as how the HCT/P reporting requirements apply to these products. FDA's comments at the Pharma Conference in Las Vegas raised a concern that facilities were reporting positive cultures on distributed products as HCT/P deviations being issued under urgent medical need. However, according to the regulations in 1271.265, distributing products with positive microbial cultures is a direct violation of the cGTP regulations because the urgent medical need exception applied only for donor eligibility determinations, and did not permit release of cGTP manufactured products that failed sterility testing.

To help address this issue, ISCT is conducting a survey of current clinical and laboratory practices with regard to administration of these products. It is clear that it is relatively unusual for autologous or allogeneic peripheral blood stem cell (PBSC) or donor lymphocyte infusion (DLI) products to have positive microbial cultures. However, it is also clear that depending on the organism found, clinical practice has been to infuse those rare sterility positive PBSC and DLI products. Discussion will focus on industry survey results and relevant issues.

1:15-2:00 – **Industry Presentations**

- I. Recent ISCT survey results (*Dennis Gastineau, MD*)

Topics to be addressed:

- Define systems in use at apheresis and cell processing facilities (open versus functionally closed)

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- Describe the practices used by facilities to identify alternatives to infusion of contaminated cell products
- Outline methods of PBSC manufacture, including sterility testing, that reduce the risk of contamination (industry “best practices”) and present recent research on cell product sterility testing
- Identify contamination issues unique to products obtained from different categories of donors (allogeneic related, autologous and allogeneic unrelated)
- Compare relative risk of infusing contaminated products versus alternatives
- What are the clinical issues versus the lab issues?
- Define urgent medical need exceptions and describe the process of determining when administering contaminated products could be appropriate

2:00-2:30 – **FDA Presentation**

I. Regulatory Overview (*Ellen Lazarus, MD*)

2:30-3:10 – **Discussion of Current Thinking**

3:10-3:30 – BREAK

3:30-3:45 – **Industry Update on Homologous Use Working Group** (*Shelly Heimfeld, PhD*)

3:45-4:15 – **Industry Update on HIV and HCV NAT for HCT/Ps**

4:15-4:30 – **Future Meetings**

- Identification of date, topics, format, etc. for next meetings

4:30-4:45 – **Conclusion** (*Stephen Noga, MD, PhD*)

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Invitee List

(Those shaded in grey did not attend)

AABB

Advanced Medical Technology Association (AdvaMed)

American Association of Tissue Banks (AATB)

American Society for Apheresis (ASFA)

American Society for Blood and Marrow Transplantation (ASBMT)

American Society for Gene Therapy (ASGT)

American Society of Hematology (ASH)

American Society for Testing and Materials (ASTM)

American Society of Transplant Surgeons (ASTS)

Biotechnology Industry Organization (BIO)

Cell Transplant Society (Cell Tx)

Foundation for the Accreditation of Cellular Therapy (FACT)

International Pancreas and Islet Transplant Association (IPITA)

International Society for Biological Therapy of Cancer (ISBTC)

National Heart, Lung, & Blood Institute, National Institutes of Health (NHLBI NIH)

National Marrow Donor Program (NMDP)

Production Assistance for Cellular Therapy (PACT)

Regulatory Affairs Professionals Society (RAPS)

United States Pharmacopoeia (USP)

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MEETING SUMMARY

Dr. Noga was not available, attendees were welcomed by Shelly Heimfeld, President of ISCT and the meeting was called to order at 1:05pm.

CONTAMINATED PRODUCT RELEASE

Presentation by Dr. Dennis Gastineau

Dennis Gastineau, MD, Mayo College of Medicine, presented the results of studies conducted within the Mayo Bone Marrow Transplant program on the infusion of culture positive stem cell products and he also presented results from the survey conducted by ISCT regarding this issue (see presentation #1).

Mayo Experience

As an introduction to the topic, Dr. Gastineau noted that human bone marrow and PBPC transplant products have traditionally been sampled for bacterial contamination at the time of collection or after processing. A small percentage of these products have positive cultures. Due both to the criticality of the products for treatment and/or the lack of a sterility result prior to release, culture positive products have commonly been infused. However, strict interpretation of the finalized GTP regulations prohibits this practice.

The Mayo experience, which is similar to other published results, illustrates that the frequency of culture positive products is low (average <3%), the donor/patient is a significant source of the contamination, and there is no apparent clinical difference in acute toxicity or adverse reactions associated with infusion of culture positive as compared with culture negative products. Dr. Gastineau reported that 30-50% of collected autologous products would typically not be infused for other clinical reasons and the single product at their facility which grew *Clostridium perfringens* was not administered. Just over 2/3 of the patients received antibiotics as prophylaxis. Further analysis indicated that patients receiving culture positive products had equivalent short-term and long-term survival to those receiving culture negative products. The different types of organisms and the frequency of their occurrence in products were shared with the group.

ISCT Survey

ISCT developed and conducted a survey focused on the issue of the use of culture positive products in the hematopoietic stem cell transplant community. The goals of this survey were to obtain general information about current practice and to obtain preliminary information concerning experience with the safety of infusion of culture-positive products. A total of 177 responses were received (one was discarded as the response appeared random and incomplete). A total of 65,366 products from 92 respondents were represented (primarily autologous PBSC), primarily from programs with combined collection, laboratory and transplant services. The survey revealed that 90% of responding institutions have a policy for handling culture positive products, the frequency of positive products was low (1-2%), and that 67% of responding institutions infuse or release for infusion culture positive products. Testing methods used for sterility assessments were reported as 87% automated blood culture bottle systems and 8% as CFU/USP compliant. The distribution of reported organisms was also presented and consisted

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primarily of common skin contaminants such as coagulase negative staph. In culture positive products, 32% were reported to be associated with a positive culture in the patient/donor within 5 days before or after collection. Respondents reported zero deaths associated with infusion of the contaminated products. Many of the responding institutions reported implementation of changes to their collection/processing procedures with the goal to reduce the risk of processing-associated contamination; these included environmental, personnel, training and processing modifications. However, generally no changes in contamination rates were seen so the true effectiveness of these changes remains unclear. Some institutions reported a change in the sterility test methods to more automated systems did result in a decreased incidence of contamination.

Definition of a Closed System

Dr. Gastineau discussed definitions of closed, semi-closed, and functionally closed systems, noting that ultimately, 'closed' remains a relative term since nothing is completely closed as some air and starting material (blood) enter the system and may not be sterile. Variations in definitions were discussed including industry practices of referring to bag methodology as "functionally closed."

Conclusion

In conclusion, infusion of culture-positive HPC products appears to be associated with minimal toxicity when given under usual clinical practice and precautions. The type of organism detected may affect the clinical decision of whether or not to use the product. HPCs are not analogous to other types of blood products in either ease of replacement or risk of additional collections. The overall risk to the patient and donor for recollection must be balanced against the assessed risk of infusion of culture-positive products.

Presentation by Dr. Elizabeth Read

Dr. Elizabeth Read, Department of Transfusion Medicine, NIH Clinical Center, presented data from two studies conducted by her group at NIH (refer to presentation #2). The aim of the studies was to compare sensitivity and specificity between automated and CFR methods for sterility testing. The initial study was a seeded analysis evaluating organism detection and time to detection of CFR vs. BacT/Alert vs. Bactec. Mock mononuclear cell products were suspended in six common media for testing. Ten organisms in two concentrations were used. This study illustrated that both BacT/Alert and Bactec were faster relative to the CFR method in the time to detection, but overall generally gave similar final results. Another finding was that multiple antibiotics in the product medium could variably impair detection of organisms in all systems. The second study used actual products tested in parallel with CFR and either BacT/Alert or Bactec systems. The study was designed to evaluate field performance and false positives. True positive rates were comparable for all systems. False positive rates were higher with the CFR method than with the automated methods, which exhibited almost no false positives. The false positives were primarily related to high red cell counts causing turbidity in the media. Results were analyzed by both product category and organism type.

Dr. Read noted that it is highly unlikely that all true positives represent actual product contamination because frequently it is not possible to demonstrate organism growth in samples from the same product or product derived from the same parent product and processed in parallel. Given the limited volume and number of samples available for a given cell therapy product, this is a problem that is not easily resolved.

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Presentation by Dr. Ellen Lazarus

Dr. Ellen Lazarus, OCTCT, CBER, FDA, presented an overview of HCT/P contamination prevention and biologic product sterility regulations applicable to PBSCs (see presentation #3). She described how the GTPs and 21 CFR 1271.145 apply to these products. Regulations applicable to both 361 and 351 (IND/licensure) products were reviewed in great detail. Alternate and equivalent methods for sterility testing are acceptable, if validated, and provisions for exceptions exist (part 610.12 (g)).

Discussion

Attendees asked the FDA what it would take to change the CFR method for sterility testing requirement as it has been in existence for 30 years. Participants noted that in the future, it would be preferable to avoid the inclusion of specific methodologies in the regulations; rather they should be encompassed in guidance documents. This would allow for more rapid changes to accommodate future improvements in technology and assay methods. The FDA responded that it is working on revisions to the regulations and agreed that the current language is outdated.

Dr. Heimfeld asked about requirements for validation of new/alternate methods (i.e. is the expectation that each individual manufacturing site will have to validate their method used or can they rely on the literature)?

Ms. Malarkey and other FDA representatives responded that literature references would be acceptable for 361 products, but added a facility would want to do “something” to verify procedures and results due to variation between labs. However, this would not be the case for 351 products, where the literature references would have only a supportive role. Dr. Benton explained that sufficient details about results are not always present in the reference articles. The FDA noted that it will be issuing a broad guidance document, with specific details left up to the individual facilities.

Dr. Brecher described his method for using platelet apheresis collections as a surrogate for PBSCs in microbial testing, explaining how the media and content (white cells, etc) were comparable. Rapid release assays were briefly discussed but the consensus was that these are not quite ready for clinical use or are used in other industries such as food surveillance and do not reach the level of detection needed for cellular products.

Dr. Heimfeld asked about FDA thoughts with regard to the issue of releasing culture positive products in light of the industry presentations today (i.e. culture positive cultures are being used and most facilities have not changed their practices despite the clear restrictions in the GTPs). Ms. Rabe added that it seems most culture positive products are infused anyway and 100% of the NMDP products are infused, even if they test positive, out of medical necessity.

Dr. Witten responded that FDA does not want to create a situation where patients cannot get products that they need and that benefit them. She indicated that the information presented today taken in conjunction with additional information requested by FDA (noted below) will inform the FDA as they considers next steps.

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- Information about the practices that some of the larger institutions currently use (i.e. what are the policies and procedures that “good” institutions have adopted that can be disseminated as minimum standards for other institutions to assist them to be better compliant).
- Any relevant standards for donor safety, timing, etc from AABB, FACT, or others
- A general compilation of information that currently exists on this topic

Dr. Read asked if those who belong to organizations that set standards should commence work on developing an interim standard. Dr. Witten responded that it would be useful to describe what should happen in these cases. The ‘standard’ should be that facilities must have a policy to address the issue of contaminated product release and details regarding specific aspects of that policy would be helpful.

Dr. Warkentin raised the topic of bacteremic donors ie: true positives. The FDA responded that ideally, if one discovers that the product is positive due to the donor being bacteremic, then the product should be labeled accordingly.

Dr. Brecher asked if it would seem reasonable to make this situation an exception to the current regulations. Dr. Witten then asked what the scope, limits and qualification for this exception might be. Attendees noted that the overall principle for qualification would be that there is no replacement product available in the necessary time frame; this is the best option available in the specific situation; and that this is a clinical decision made in the patient’s best interest in concert with their physician.

The option to possibly use the “urgent medical need” exception was discussed, but it was made clear that this only applies to the issue of donor eligibility and was not intended to be used for release of culture positive products. Attendees noted that there is already a mechanism for using medical and clinical discretion/judgment for transfusion centers and blood centers; would this be a mechanism/model that could be use in the case of culture positive products?

The differences between related and unrelated allogeneic products were discussed and the stakeholders suggested finding a solution that would be acceptable to both the 351 and 361 products. Dr. Lazarus responded that the agency would examine this issue, but as noted above organizations should still propose best practices to assist “outlier” institutions.

Dr. Witten suggested the organizations examine current voluntary standards and whether this issue highlighted a need that could be better addressed. The FDA noted that developing a policy/standard for the use of positive culture products would be useful and it would also be beneficial if the standard could specify what each policy should address. Dr. Strong raised the issue of consent. Many centers do not officially obtain informed consent but the patient and the treating physician are both informed. No consensus was reached on this issue. Attendees asked if there are specific reporting requirements that the FDA has for culture positive products, and if so, what is the appropriate mechanism for reporting?

Dr. Benton responded that 351 products should be reported under the IND mechanism. Products regulated at 361 products would be reported as described below. Given the nature of the issue,

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some enforcement discretion might be used. Dr. Heimfeld asked whether there are any requirements regarding sterility testing status for the labeling of products, as current practice generally does not include this information. It was also noted that for non-cryopreserved products, sterilities would be pending.

FDA also provided clarification of specific issues concerning the reporting of deviations related to release of products that have positive culture results. The agency stated they are currently considering potential exceptions or clarifications to the regulations and will issue guidance on this in the near future. For now, the following represents the requirements.

According to the agency:

- If 361 products found to have a positive result for microbial testing, either before or after release of the product are distributed, **an HCT/P deviation report is required.**
- If there is reason to believe, upon investigation, that the donor was bacteremic and therefore the test result is explained as such, these particular products may be distributed under the provisions for urgent medical need in 21 CFR 1271.60(d) or 1271.65(b). Positive microbial test results received on the product should be reported in the summary of records if known before release. An HCT/P deviation report would not be required if 361 products are distributed under the urgent medical need provisions of the regulations.
- Products may be collected or issued under the “urgent medical need” exception. This exception only applies to donor eligibility criteria (such as infectious disease testing and bacteremia of the donor as described above), and would not be reported. The products issued under urgent medical need would not be reported as deviations when distributed for use, but must be labeled with the appropriate biohazard label. Positive test results received on the product would be reported in the summary of records. The provisions for use of products in cases of urgent medical need are not applicable to products in which the donor passes eligibility but the product does not meet specification or acceptance criteria. Examples would include a positive microbial test.
- Donor eligibility requirements do not apply to autologous donors. However, if product testing (including microbial testing of the product) is performed the reporting requirements described above apply.
- Reporting for 351 products being collected under an IND should be reported according to the IND protocol.

Furthermore, the FDA reminded the group that only distributed products should be reported. Email address for questions and deviations is hctp_deviations@fda.hhs.gov

If a determination can be made that a positive culture test result was incorrect (supported by sufficient data and documentation), then this would not have to be reported to the FDA.

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INDUSTRY UPDATE ON HOMOLOGOUS USE WORKING GROUP

Dr. Heimfeld reported that a group spearheaded by ISCT with various stakeholders is working to develop a document on the definition of homologous use. A draft document was delivered by the working group to the advisory group for comment. The advisory group noted that the suggestions outlined in the document should be broad rather than specific. The working group is currently in the process of finalizing this document. The expectation is that this final document will be given to the FDA for comment and will serve as a starting point for discussion. The ultimate goal is the creation of a guidance document from the FDA with a clearer definition of the intended use of the homologous/non-homologous categorization for GTP vs. GMP designation.

INDUSTRY UPDATE ON HIV AND HCV NAT FOR HCT/PS

As follow up to the last meeting, Dr. Strong asked for clarification of NAT methodologies for both PBSCs and tissue products. He reported that the data from the previous meeting had been submitted to both manufacturers and they will be encouraged to submit it in a timely manner to FDA. Dr. Solomon reminded attendees that the Office of Blood Products approves the test but may not immediately recommend the agent be used for testing (for feasibility reasons) but rather only “when available.”

According to the agency, if NAT testing was performed on pooled samples, instead of individual samples as specified in the manufacturer’s instructions, HCT/P deviation reports are required for hematopoietic stem cells derived from peripheral or cord blood distributed for use in first-degree or second-degree blood relatives (related allogeneic) under 1271.350(b). Single-summary reports should include dates and number of products tested in minipools, as well as the number of products the facility has released and intends to release (still in storage), as medically indicated. FDA emphasized that they want one summary report per facility, rather than one report per product. Additional information may be obtained by emailing HCTP_deviations@fda.hhs.gov

FUTURE MEETINGS

The participants of this meeting decided that the next cell therapy liaison meeting should be held sometime during the first two weeks of November at the AABB National Office.

Topics were solicited and FDA representatives suggested as a topic for the next meeting : how to deal with the international movement of products. Issues might include donor evaluation ; screening, testing and collection process differences ; operational issues ; border issues ; harmonization between countries ; testing laboratory acceptance ; and other issues. Additional topic requests may be emailed to the ISCT Head Office (ashka@celltherapysociety.org).

The meeting was adjourned at 4:25pm