

**Cell Therapy Liaison Meeting Summary**  
June 24, 2005

**Host Organization**



**Agenda**

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

8:30-8:45 -- **Introduction** of FDA and Industry participants  
-- Review of Summary & Action Items from November 5, 2004 Meeting

**GENERAL FACILITY REQUIREMENTS: RECOVERY, PROCESSING, STORAGE AND FINAL RELEASE**

8:45-9:00 -- "Industry – Cells" (*John D. McMannis, PhD*)

- Review current practices in Cell Therapy Laboratories with respect to Environmental Monitoring, Cleaning and Air Quality.
- Identify the changes that must occur due to the new regulations with emphasis on risk benefit analysis

9:00-9:15 -- "Industry - Tissues" (*Scott Brubaker, MD*)

- Review current practices in Tissue Banks with respect to Environmental Monitoring, Cleaning and Air Quality.
- Identify the changes that must occur due to the new regulations with emphasis on risk benefit analysis

9:15-9:30 -- "Industry - Islets" (*Gordon Weir, MD*)

- Review current practices in Islet Laboratories with respect to Environmental Monitoring, Cleaning and Air Quality.
- Identify the changes that must occur due to the new regulations with emphasis on risk benefit analysis

9:30-9:45 -- "Industry - Genes" (*Boro Dropulic, PhD*)

- Review current practices in Gene Therapy Laboratories with respect to Environmental Monitoring, Cleaning and Air Quality.

- Identify the changes that must occur due to the new regulations with emphasis on risk benefit analysis

9:45-10:15 – FDA CBER (*Mary Malarkey, BSc and Jay Eltermann, MSc*)

- Review of the current definition/classification for facility use

10:15-10:40 -- Discussion

- Discussion and clarification of the classification in various applications (stakeholder perspectives and input)

10:45-11:00 -- Consensus

- Identification of further clarification required and determination of action points

**11:00 – 11:15 BREAK**

**QUESTIONS & ANSWER: SUBMITTED STAKEHOLDER TOPICS**

11:15 -12:15 – Industry (*Allene Carr-Greer, MT(ASCP)SBB*); FDA (*Ellen Lazarus, MD*)

1. The ***Circular of Information for the Use of Cellular Therapy Products*** has recently been revised. The revision was prepared jointly by the AABB, American Association of Tissue Banks, American Red Cross, American Society for Apheresis, American Society for Blood and Marrow Transplantation, America’s Blood Centers, Foundation for the Accreditation of Cellular Therapy, ICCBBA, International Society for Cellular Therapy, and National Marrow Donor Program. The FDA Office of Cellular, Tissue and Gene Therapies provided an observer to this working group. ICCBBA product nomenclature was used in the circular when particular products were discussed. The circular will be / has been submitted to FDA for review, along with a request that it be adopted as guidance.

Would FDA please comment on the process available for reviewing the circular? We would also appreciate FDA’s comments on the use of ICCBBA nomenclature.

2. 21 CFR 1271.65(b)(2) lists the following requirements for **limited uses of an HCT/P from an ineligible donor when there is a documented urgent medical need**. “You must prominently label an HCT/P made available for use under provisions of paragraph (b)(1)...with the Biohazard legend...and, in the case of reactive test results, *WARNING: Reactive test results for (name of disease agent or disease)*.”

This appears to be in conflict with HIPAA under a number of different scenarios - including for facilities that place the donor's name on the label and for all facilities when the donation is a directed or related allogeneic (the donor is known even if the name is not listed on the label). Even if HIPAA rules are not considered the requirement seems to be in conflict with common sense definitions of privacy.

Would FDA please comment on the need for this requirement, and whether other methods such as supplying the information in accompanying records would be sufficient?

3. When the first establishment obtains **licensure for a cord blood product** how will this affect other facilities that are manufacturing and distributing cord blood products?
4. 21 CFR 1271.55(a) provides a list of records that must accompany the HCT/P at all times once a donor eligibility determination has been made. A summary of records is one of the required documents. 1271.55(b) describes the contents of the summary of records that must accompany the HCT/P at all times, including (2) “A listing and interpretation of the results of all communicable disease tests performed” and, (4) in the case of a donor who is ineligible based on screening “a statement noting the reason(s) for the determination of ineligibility.”

Please explain the **rationale for requiring that the test results and/or reasons for ineligibility accompany the product during every step involved in processing and manufacturing?** Appropriate labels have been applied and personnel responsible for determining eligibility and urgent medical need that results in the product being used already have access to the necessary information.

5. An interorganizational task force is preparing a **donor history questionnaire to be used as a screening tool for allogeneic hematopoietic progenitor cell donors collected by apheresis.** The purpose of the screening is to evaluate the donor for eligibility as defined in the Donor Eligibility Final Rule and guidance document. The task force consists of representation from AABB, American Association of Tissue Banks, American Society for Apheresis, American Society for Blood and Marrow Transplantation, Foundation for the Accreditation of Cellular Therapy, International Society for Cellular Therapy, and National Marrow Donor Program. The FDA Office of Cellular, Tissue and Gene Therapies provided a liaison. The questionnaire, and accompanying documents, will be submitted to FDA with a request that it be reviewed and adopted as guidance.

Would FDA comment on this effort and on the likelihood that the questionnaire will be accepted for review along with a request that it be adopted as guidance?

#### 12:15-12:30 -- **Future Meetings**

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

**Invitee List**

(Grey font = not represented at June 14 2005 meeting)

AABB

American Association of Tissue Banks (AATB)

American Society for Apheresis (ASFA)

American Society for Blood and Marrow Transplantation (ASFA)

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)

Production Assistance for Cellular Therapy (PACT)

Regulatory Affairs Professionals Society (RAPS)

United States Pharmacopoeia (USP)

## MEETING SUMMARY

Dr. Stephen Noga began the session with opening remarks and introductions. He reviewed the previous meeting agenda from November 2004 and detailed subsequent accomplishments. The following organizations have nominated representatives for the “Homologous Use Working Group” (intended to work on the regulatory definition of homologous vs. non-homologous use):

AABB  
AATB  
ASBMT  
ASFA  
ASTS  
ASH  
FACT  
ISCT

Shelly Heimfeld has been appointed to chair this Working Group. Further details will be distributed to those organizations and nominees regarding the commencement of work for this group. This will include a teleconference and meeting schedule, a proposed working group mandate, and proposed deliverables timeline. Summaries of subsequent presentations follow.

### **Presentation #1: McMannis**

Dr. McMannis made a presentation on facilities regarding cellular therapies. He covered room classification, cleaning, and environmental control. He presented data from the ISCT facility survey from the lab practices committee (n=53) which included routine cleaning practices of surfaces, biological safety cabinets (BSCs) and other equipment. Dr. McMannis also raised the issue of it's the application of GTPs to “storage” facilities. He presented data from MD Anderson Cancer Center which processes over 1,800 products/year. He shared *product* contamination rates between 1997-2001 and highlighted process changes and facility relocations. He noted some excursions may have been traceable to facility issues such as the case of MNC enrichment processing by “air purge” under a high air flow area. Procedure modification resulted in a decrease in the contamination rate. Environmental Monitoring data (EM) was collected as baseline and included particle counts in various areas. Over 500 samples were tested. There was no correlation in the data between product contamination rates and EM results.

He concluded by suggesting that guidance documents should include discussion of room classification (both over all and in relation to study phase), “open-ness” of system, product exposure time and possible cell recovery. Cleaning practices and routine surveillance of products were also listed as considerations. In closing, Dr. McMannis raised the question of whether cell processing facilities need a comprehensive EM program and noted issues with analyzing the overwhelming amount of data.

Discussion of repeat testing of samples and possible false positives of laboratory results of EM and product surveillance data were discussed. During later discussions Mary Malarkey (CBER) agreed the data demonstrated poor correlation.

### **Presentation #2: Brubaker**

Dr. Brubaker reviewed AATB's position and standards on facility requirements and also presented potential changes to these. In summary, Dr. Brubaker stated AATB standards require such things as documentation of the tissue retrieval site, work surface cleaning, minimal physical plant components and documentation of sanitization procedures. The process of standard setting

by AATB was reviewed and numerous guidance documents including “Prevention of Contamination and Cross-contamination at Recovery...” were presented and summarized. Retrieval site suitability parameters were reviewed and several examples of various collection facility sites were displayed. Processing, quarantine and storage facility standards were reviewed. These included quality components, environmental control, environmental monitoring (may or may not include particle counts, personnel and work surface monitoring and equipment monitoring), and cleaning procedures. Various monitoring techniques and practices were reviewed and Dr. Brubaker also highlighted a sample template for validation of the operations. Finally, the details of a quality program including quality control, tolerance, in process controls and audits (at least annually) within the standards were included. He concluded by stating that while 21 CFR 1271 had no significant impact on AATB’s standards, the organization is considering more detailed qualification of recovery sites, potential guidance document revisions and a new one on validation and aseptic processing of tissues.

**Presentation #3: Weir**

Dr. Weir presented Pancreatic Islet cell work from the Joslin Diabetes Center. He opened with photos of the laboratory/clean room and described the tissue product receipt and processing. This includes manual dissection, enzyme flooding via ducts, manual digestions with steel balls in enzymatic solution and density gradient separation. Facility requirements, environmental monitoring and air quality monitoring practices were reviewed. Examples of compliance to 21 CFR 211 subpart C (cGMPs) were reviewed. Air quality monitoring and assessment is performed by a contract company. SOPs are in place for equipment cleaning and monitoring including calibration and maintenance. Much discussion followed regarding the regulation of these products as organs or tissues and as 351 vs 361 products.

**Presentation #4: Dropulic**

Dr. Dropulic reviewed vector manufacturing requirements for gene therapy in industry. Facility classification and design was covered extensively. General practices including procedures to minimize cross contamination, personnel and workflow operations and segregation and changeover were reviewed and discussed. Dr. Dropulic described the cases of multi use facilities and policies and procedures in place to prevent cross contamination, protect products and personnel. Biosafety level requirements, environmental monitoring practices were discussed and facility isolate data was shared. Process improvement in the cleaning procedure was implemented and these contamination rates were decreased/eliminated. He reviewed the commonly accepted model of “sliding scale” validation depending on phase I vs III in GMP settings and stressed incorporating necessary components as soon as possible in the development process.

**Presentation #5: Malarkey**

Ms. Malarkey announced that the agency would be coming forth with additional guidance documents on the GTPs and also encouraged industry to produce their own. She then took the opportunity to clarify a few topics. She explained that if a product meets ALL of the items in part 1271 then it would be classified as a 361 product and if not, it would fall under other regulations: part 820 as well as 1271, etc. Some of these would be under IND and allogeneic nonrelated products are NOT 361. If the product meets the qualifications of a “drug” regardless of its IND or BLA status, it would be held to GMPs. In the cases of conflicts between the regulations, the more specifically applicable would apply. She also reminded the group that it is acceptable not to do something defined as “appropriate” as long as one could justify why it would not apply. She added 21 CFR part 211 would apply and that specifically 211.113 (microbial contamination) would be applicable to the conversation thus far and that one might also consider “exposure” to the environment.

Ms. Malarkey made a slide presentation reviewing sections of part 1271 and definitions of HCT/Ps. HCT/Ps that are classified as drugs fall under parts 210, 211 for GMPs and 820 for Quality Systems. Due to the broad scope of the regulations, most of the GMP regulations would apply to those products which are not solely regulated under section 361 of the PHSA. These regulations apply to entire “manufacturing” process of HCT/Ps and not just to the “processing” component of the process. Therefore, recovery is included. She clarified that “where appropriate” means that a facility must document when it is NOT appropriate and the requirement is deemed appropriate if the nonimplementation could reasonably be expected to result in the HCT/P not meeting its specified requirements relating to disease transmission or the inability to carry out any necessary corrective action. Facility requirements, processes, environmental control and monitoring and records were also included. Ms. Malarkey reviewed related cGMP requirements regarding facilities, operations, sanitation, production and process controls.

Ms. Malarkey recommended consideration of product exposure in a “controlled environment” and validation or verification of a “closed” system. She recommended eliminating practices that would be considered unacceptable under either regulatory scheme (351 vs. 361) regardless of facility classification such as the case of processing multiple donor cells at the same time.

Regarding the use of unclassified air handling in a facility – she raised the consideration of minimal manipulation, more than minimal manipulation and non-homologous use applications. These parameters are a function of *changing the characteristic of the product – not of how much processing occurs*. Monitoring and cleaning were also discussed and Ms. Malarkey stated she could see from the data previously presented that environmental monitoring might not be helpful in some cases. She said there could be a reasonable argument that an unclassified room would be acceptable if there was data to demonstrate this, the system were closed, and if such were presented on a case-by-case basis. It is difficult to make across the board applications as some manipulations might occur in a BSC and be acceptable for those products/processes.

Regarding the phase of an IND affecting facility classification requirements, Ms. Malarkey stated that this is really an issue of sterility. “The question is sterility assurance and there is no difference in the IND phase, perhaps it could be due to other reasons, but not related to IND phase.

Regarding the topic of recovery in locations not under the direct control of the processing facility and the issues of monitoring and cleaning these: basic procedures require that the area is assessed and segregation of different donors and tissues is maintained. Cleaning is key. “Hospital cleaning” and documentation is acceptable as long as controls needed to prevent cross contamination are in place. In the event of recovery occurring during the “third case of the day” for example, it is acceptable to require documentation of the cleaning that is routinely performed by the operating room staff between cases. Regarding unrelated products (under cGMPs), an audit obtaining information such as a task log, etc would be acceptable. FDA GTP regulations require document retention of cleaning records for 3 years. This would apply. Other examples of compliance include completion of a “form” included with the recovery/collection kit and accepting label claims of a sanitization agent, if the manufacturer’s instructions for mixing, application and contact time were followed. She clarified that one would want to ensure the collection facility meets the specifications set by the manufacturing entity. This can be accomplished by inspecting the recovered product immediately upon arrival: Is the container leaking? Is the label intact, legible, etc? Was it received at the appropriate temperature? Are there any visible signs of contamination? By looking at operations up front and deciding what is and is not appropriate for each product and manufacturing specification, each facility should be able to design processes to ensure adherence with the GTPs.

The group discussed these topics and the suggestion was made to develop a cord blood collection guidance document. Dr. Noga suggested acceptance criteria for various products might also be helpful. It was the consensus of the group that acceptance criteria for unrelated and related products and collection facilities would be most useful and the suggested format style was “Q and A” addressing unrelated products, degree of manipulation, verification of processes/procedures and clarification of “where appropriate.” Regarding environmental monitoring, Dr. Gastineau suggested a guidance document with a graduated approach to EM would be a useful resource. Drs. McMannis and LeMaistre agreed to draft a guidance for facility compliance for acceptance criteria for related and unrelated products as well as for EM, facility classification and cleaning effectiveness.

In the discussion of some of the labeling issues, Dr. Lazarus presented a few slides on label requirements. The FDA authority over this comes from section (502) (a), Section 505 (d)(7) and 21 CFR 201.57. Current content requirements include: description; clinical pharmacology; indications and usage; contraindications; warnings; precautions; adverse reactions; dosage and administration; supply, storage and handling information; and clinical studies and references. General biologics labeling and IND labeling requirements (21 CFR 312.6) also apply. Specifically for HCT/Ps, Dr. Lazarus stated a biohazard legend, donor eligibility provisions and label controls would apply. Regarding the question of labeling issues it was clarified that the final consignee is the transplant center and the need of a guidance document for labeling was discussed. The FDA is working on this now and the final document will be forthcoming. Dr. Witten (CBER) stated the scope would be included in the document, specifically as to whether it applied to cord blood or not. She reaffirmed that recommendations would be in line with the regulations. Additionally, Dr. Witten offered that some areas, such as pancreatic islet cell issues, may warrant discussions with groups rather than individuals.

## QUESTION SUMMARY

Allene Carr-Greer (AABB) presented the following questions prepared by the stakeholders.

1. The ***Circular of Information for the Use of Cellular Therapy Products*** has recently been revised. The revision was prepared jointly by the AABB, American Association of Tissue Banks, American Red Cross, American Society for Apheresis, American Society for Blood and Marrow Transplantation, America’s Blood Centers, Foundation for the Accreditation of Cellular Therapy, ICCBBA, International Society for Cellular Therapy, and National Marrow Donor Program. The FDA Office of Cellular, Tissue and Gene Therapies provided an observer to this working group. ICCBBA product nomenclature was used in the circular when particular products were discussed. The circular will be / has been submitted to FDA for review, along with a request that it be adopted as guidance.

Would FDA please comment on the process available for reviewing the circular? We would also appreciate FDA’s comments on the use of ICCBBA nomenclature.

Drs. Witten and Lazars lead the discussion stating that the true question is “how” this should be reviewed. That is to clarify what the intent of the document is so that the agency can compare it to requirements. For example, as a label extension, label requirements would apply including Section 502 and 505 giving authority over false or misleading information. 21 CFR 201.57 contains specific requirements on content and format for such things as “package inserts” for prescription drugs and 21 CFR 610 subpart G contains information on biological containers and package labels. 21 CFR 201.25 (Bar code label requirements) includes NDC numbering and 21 CFR 312.6 addresses “labels of INDs”. HCT/P labels are covered in 21 CFR 1271 and include items such as biohazard labeling, accompanying

records, summary of records and donor eligibility. "In general the circular of information contains many but not all of these elements and FDA would consider also whether it would stand alone or be accompanying the product. Is it only for HCT/Ps or is it also meant to supplement 351 regulated products (other regulations apply)?" The answers would differ for HCT/Ps, 351s and BLAs. The Investigators Brochure contains information on adverse reactions, etc and the protocol typically includes information about the study, measurements and follow up. There are elements of commonality with 351 products. Dr. Witten suggested users review the December 2000 proposed rule (**Docket No. 00N-1269, CDER 9663. Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels**).

Regarding ICCBBA nomenclature, regulations for this do not apply as the products are not regulated as "blood". Tony Stifano (CBER, Asst to the Director (Mary Malarkey) for Labeling Policy and Medical Communication added that this makes nomenclature a non-issue. In conclusion it was decided that the document would be submitted with a request that it be considered acceptable for the "intended" purpose and the initial FDA review of the COI would identify any limitations for intended use.

2. 21 CFR 1271.65(b)(2) lists the following requirements for **limited uses of an HCT/P from an ineligible donor when there is a documented urgent medical need**. "You must prominently label an HCT/P made available for use under provisions of paragraph (b)(1)...with the Biohazard legend...and, in the case of reactive test results, *WARNING: Reactive test results for (name of disease agent or disease)*." This appears to be in conflict with HIPAA under a number of different scenarios - including for facilities that place the donor's name on the label and for all facilities when the donation is a directed or related allogeneic (the donor is known even if the name is not listed on the label). Even if HIPAA rules are not considered the requirement seems to be in conflict with common sense definitions of privacy.

Would FDA please comment on the need for this requirement, and whether other methods such as supplying the information in accompanying records would be sufficient?

FDA representatives responded that a guidance document would be forthcoming in the near future. Placement of biohazard labeling in the accompanying records would not be sufficient. The guidance document will clarify what is meant by "label" and discuss affixed vs attached labels. It might be acceptable in some situations to have attached tags. The intent is so healthcare providers can have access to the information readily and act upon it. The agency is also aware and respectful of donor privacy and will consider that as well.

3. When the first establishment obtains **licensure for a cord blood product** how will this affect other facilities that are manufacturing and distributing cord blood products?

The agency representatives responded that licensure of a product would define the specifications for products produced by the particular licensee it would not affect other facilities. These products would be regulated as biologics and that at any time any manufacturer can submit a BLA. There may be an alternate approach for unrelated cord blood products meeting the requirements of homologous use and minimal manipulated. Regarding the question of the first licensure forcing others to obtain an IND, the agency responded that it will come out with a cord blood plan to include what needed to be done as well as the time frame and that this would be the action/regulation that would affect other centers more than licensure of a cord blood product being granted to one facility .

4. 21 CFR 1271.55(a) provides a list of records that must accompany the HCT/P at all times once a donor eligibility determination has been made. A summary of records is one of the required documents. 1271.55(b) describes the contents of the summary of records that must accompany the HCT/P at all times, including (2) “A listing and interpretation of the results of all communicable disease tests performed” and, (4) in the case of a donor who is ineligible based on screening “a statement noting the reason(s) for the determination of ineligibility.”

Please explain the **rationale for requiring that the test results and/or reasons for ineligibility accompany the product during every step involved in processing and manufacturing?**

Appropriate labels have been applied and personnel responsible for determining eligibility and urgent medical need that results in the product being used already have access to the necessary information.

Dr. Lazarus clarified that the intent of this requirement is that the information will be available when needed for purposes of prevention of disease transmission and in the event of a need to release the product immediately. When other processes / procedures are in place to assure the information is available then a hard copy does not need to “accompany” the product. Examples of acceptable alternatives given include 1) the ability to fax the summary of records in advance to each location, and 2) computerized records containing the summary are available at each location.

5. An inter-organizational task force is preparing a **donor history questionnaire to be used as a screening tool for allogeneic hematopoietic progenitor cell donors collected by apheresis**. The purpose of the screening is to evaluate the donor for eligibility as defined in the Donor Eligibility Final Rule and guidance document. The task force consists of representation from AABB, American Association of Tissue Banks, American Society for Apheresis, American Society for Blood and Marrow Transplantation, Foundation for the Accreditation of Cellular Therapy, International Society for Cellular Therapy, and National Marrow Donor Program. The FDA Office of Cellular, Tissue and Gene Therapies provided a liaison. The questionnaire, and accompanying documents, will be submitted to FDA with a request that it be reviewed and adopted as guidance.

Would FDA comment on this effort and on the likelihood that the questionnaire will be accepted for review along with a request that it be adopted as guidance?

Dr. Lazarus noted that the donor history questionnaire will be a welcome submission and if submitted in time might be appended to the final Donor Eligibility Guidance. However, it can also be reviewed separately from the guidance.

Upon conclusion, Dr. Noga permitted Dr. Edward Snyder to present a brief proposal. Dr. Snyder proposed to the FDA that the agency “recommend guidance that facilities be accredited by agencies acceptable to the organization.” With regenerative medicine and the increasing use of cellular therapies there is the potential for numerous groups working independently without close monitoring of these [less traditional] activities. Reference was made to the IOM report’s recommendation and the topic of transferring this paradigm to the cellular therapy setting was proposed. Discussion ensued. Regarding the request to consider it for the September 15-18 Somatic Cell meeting, the agency agreed it was too large a topic for the current liaison meeting and that while September might be too soon for such a discussion, the agency was willing and open to further consideration of this topic.

The meeting was adjourned at 12:35pm and Dr. Noga closed with appreciation for everyone’s attendance, responsiveness and openness and open exchange.