# Cell Therapy Liaison Meeting
# June 7, 2007

**Host organization**

International Society for Cellular Therapy
ISCT

**Meeting Summary**

Participating organizations: AABB, AATB, ABC, ASBMT, ASFA, ASGT, ASH, CTS, FACT, ISCT, NHLBI, NMDP, PACT

Moderator: Kurt Gunter, MD
Chair, ISCT North America Legal & Regulatory Affairs Committee

Attendees were welcomed by Dr. Kurt Gunter, and the meeting was called to order at 8:05 am. The last meeting summary was presented for review. It was announced that speaker slides would be made available online for those granting permission. Dr. Witten expressed appreciation on behalf of FDA for sharing the slides and added that both FDA and stakeholders had discovered items to work on following the last liaison meeting.

## FDA CORD BLOOD GUIDANCE DOCUMENT

***Presentation by Joseph Giglio***

Joseph Giglio, MS, MT(ASCP), CSQE(ASQ)CQA, Deputy Director of Regulatory Affairs, AABB, summarized industry's concerns regarding the Draft Guidance on Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematologic Malignancies. These included the challenges of demonstrating comparability, continued use of imported products, the requirement for NDC number on product label and the need to broaden the indications for use (see presentation 1).

***Presentation by Dr. Robert Soiffer***

Robert Soiffer, MD, Dana-Farber Cancer Institute and ASBMT President, also spoke on behalf of the stakeholders, presenting concerns with the Draft Guidance. Dr. Soiffer described the current status of umbilical cord blood transplant (UCBT) and how it was becoming a preferred alternative donor source in some cases and how outcomes appear equivalent to mismatched unrelated marrow transplants. He reviewed factors that can affect the outcome of a UCBT, including cell number, HLA disparity and clinical condition. The collection center, collection technique and storage method did not have clear effects on patient outcome. He also outlined the standards supported by ASBMT and described the role of the prospective collection of CIBMTR data in defining influential factors. Dr. Soiffer reviewed the need for patients to access umbilical cord blood (UCB) products including those collected under conditions not meeting licensure standards. He estimated 20% of units for U.S. patients come from outside of the U.S. He closed by encouraging accreditation of cord blood banks and asked the agency to consider these issues in relation to licensure of UCB products (see presentation 2).

***Presentation by Dr. John McMannis***

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John McMannis, PhD, Director, Cell Therapy Laboratory, UT MD Anderson Cord Blood Bank, discussed comparability of cord blood units. Since the Draft Guidance document allows the cord blood bank (CBB) to present comparability data for units previously collected or processed by different methods, Dr. McMannis presented an informal survey designed to provide a snapshot of practices that has been used in various facilities. The survey focused on operational procedures and questions about "GMP" compliance. The turnaround time was quite short, and nine of 21 U.S. centers responded. On the slides (see presentation 3), the number inside parentheses represents the number of centers providing that response. Most of the centers that did respond to the survey have been in operation for six to 13 years. For example, two centers reported having used the same (i.e., one) collection procedure for their operations whereas two centers reported using four different collection procedures. It is possible that some items may have been excluded from the collection procedure such as donor screening, and he noted that some centers may not have given consideration to a backup system such as the use of a mechanical freezer as back up for controlled rate freezing of products.

All centers reported using only one or two processing and cryopreservation procedures. Quality control testing was also on the survey, and four centers reported using only one procedure. One center reported two procedures during the time of operation. The availability of GMP documentation was assessed. Eight centers reported having always maintained complete documentation of the procedure for cleaning, and half of those described always documenting cleaning between products. Seven reported always documenting daily, weekly or monthly cleaning. For materials management, six of the facilities reported having procedures for quarantine and release specifications, and seven of them reported *never* measuring air particles in the laboratory during their operations. All centers reported having training documentation of all procedures, seven always had quality review of deviations and five had two-person sign-off on critical steps in procedures.

Dr. McMannis continued to explain that UCB is different than other therapeutic products as they are expected to function for >50 years and take significantly longer than red cells to detect in the periphery (20-40 days). With the average bank only transplanting 1-3% of the total UCBs in inventory, a limited number of data would be available for evaluation and possibly inhibit market entry. Non-engraftment may be due to any one of many things, including poor product quality, use of double unit transplants (in which usually only one unit engrafts), conditioning regimen, clinical course during engraftment and previous chemotherapy. It is difficult to determine the true reason in many circumstances.

Dr. McMannis proposed that comparability cannot be based on clinical utility. Rather, it should be based on in vitro data to try to balance having the maximum number of UCB units available for clinical use and protecting the safety of the patients receiving the product. He reviewed the MD Anderson algorithm for unit selection and suggested the following assay results be considered in support of comparability: total nucleated cells count, HLA confirmation, sterility, and either CFU growth or viable CD34 presence in the products. He then reviewed various parameters that could potentially influence the outcome and described the lack of supporting evidence for them. He proposed a system for labeling those which had been screened or tested under the old method. Dr. McMannis then described how a facility might address each comparability gap from a risk perspective and evaluate any effect each might have for GMP compliance. He ended stating that outcomes and chimerism could contribute to the data set.

There was a discussion regarding the optimal methods for determination of viability in a comparability analysis, and whether viability should be based on a comparison to previously banked unit(s) or based on a pre-defined specification. The advantages and disadvantages of different types of viability assays were discussed.

Dr. Solomon asked how accrediting agencies deal with the issue of grandfathered units or those collected before current systems were in place. Dr. Warkentin and Ms. Loper replied that both FACT/NETCORD and AABB have requirements that facilities have procedures to address such situations. FACT/NETCORD looks at current practices. AABB would require that products released meet the specifications in place at the time of release, or that appropriate procedures, including labeling, be followed. Dr. Witten added that the agency encourages the presenters and others to submit data to the docket, even if the official comment period has passed. Dr. Witten further added that while it is important to have this dialogue and exchange of ideas, the FDA can only act upon recommendations and comments that are officially submitted to the docket. She and Ms. Maloney emphasized that it is extremely important for the public to comment both positively and negatively.

During the subsequent discussion, Ms. Rabe commented on Dr. McMannis' presentation sharing that NMDP had audited about 95% of the U.S. cord blood banks, and while they did have training systems, they may not all meet GMP requirements for all phases of development, so training is an example of variation among reporting centers. A question was asked regarding how FDA might account for differences in requirements between 351 and 361 manufacturing. Dr. Lazarus responded that the GMP requirements are prescriptive in some areas and less prescriptive in other areas. Ms. Malarkey added that one should look at individual operations to determine compliance — documents, records and procedures are key. Facilities must show compliance to GMPs in order to obtain licensure. It was noted that accreditation was only reflective of the operation at the time of the accreditation assessment. Dr. Gunter suggested some sort of pilot inspection program might be helpful. Dr. McMannis suggested looking at safety data as a measure, since donor variability (and therefore, product variability) was the main issue. This is outside of the manufacturer's control.

***Presentation by Dr. McKenna***

David McKenna, MD, Laboratory Director, Cell Processing Facility, University of Minnesota, discussed his facility's experience with UCB units manufactured outside the U.S. The center has received 17% of its total 790 units from foreign banks during the period 2001-2007. Notably, the percentage has been increasing annually at a steady rate, resulting in the current rate of 33% for 2007. Dr. McKenna reviewed options for bank qualification for "grandfathering" existing banks and for banks to use in the future. Possible approaches for "grandfathering" banks include sharing engraftment data and comparing results of confirmatory quality control tests upon receipt of the product. Dr. McKenna shared the process at his center for qualifying new banks, which includes bank specific engraftment data, an inquiry and summary of processing methods, quality control test results, and shipping experiences. Currently, the process is not formalized as a questionnaire and is limited to the medical or lab director initiative. He suggested a centralized method for qualification might be a reasonable approach for these non-U.S. (non-licensed) banks (See presentation 4).

Upon discussion, Dr. McMannis asked if there were minimum values for acceptance regarding CFU and Dr. McKenna responded that they primarily looked at growth/no growth on CFU assays. Other results were dependent upon clinical situation, cell dose and other factors. Dr. Kurtzberg added that post-thaw CFU were likely more significant in her opinion.

***Presentation by Dr. Read***

E.J. Read, M.D., Director, Cell and Tissue Therapies, Blood Systems Research Institute, next presented discussion points for unlicensed cord blood products in the post-BLA era. She opened by stating that it is possible that not all center processes are as thorough as the approach described by Dr. McKenna and suggested there might be the option for a centralized approach to cord blood bank licensing. She presented the shared goals of maximizing safety and efficacy, maximizing availability, and minimizing waste and discard of valuable units. Dr. Read divided the unlicensed products into two categories: foreign UCB products and U.S. UCB products from banks that have not yet been licensed or that have legacy units that would not meet BLA comparability requirements. Dr. Read described several mechanisms to ensure the quality of imported UCB units. Outlined in her presentation (see presentation 5), they include the individual transplant centers performing qualifications, use of NMDP criteria or accrediting bodies (AABB, FACT-NETCORD), use of foreign regulators, or using CIBMTR outcomes database. She then reviewed NMDP requirements for member and non-member banks and the contents of the NMDP donor history questionnaire. Differences in physical exam requirements for member and non-member banks, infectious disease testing, and sterility testing were also reviewed.

Dr. Read described some of the practice variations between U.S. and foreign banks, especially related to donor qualification and eligibility determination. She emphasized that NMDP cannot impose requirements on non-member banks and that data from CIBMTR would be limited for those smaller banks, given that the data collection and analysis would take significant time to format for use in the qualification process. She closed by recommending a mechanism be developed that would be palatable to all involved, establishing a formal mechanism other than BLA to qualify foreign banks and their units. The details of this approach would include potentially establishing accreditation requirements, enhancing CIBMTR's applications, and discussing issues such as enforcement and oversight. Regarding unlicensed UCB products from domestic banks, Dr. Read said an IND would be needed, but the question of how long FDA would permit this and the fate of those units that did not meet comparability would also need to be addressed. She closed by asking what the legal and reimbursement issues might be for transplant centers using unlicensed UCB units.

***Presentation by Dr. Kurtzberg***

Joanne Kurtzberg, MD, Carolinas Cord Blood Bank at Duke University Medical Center, gave a presentation on how stem cell transplant is used to correct inborn errors of metabolism. She opened by discussing these diseases and the mechanism for stem cell transplant as treatment. Dr. Kurtzberg reviewed the Duke method for donor selection, including ≥4/6 HLA match (DRB1 matching prioritized over Class I); cell dose >3 x $10^7$ cells/kg and CD34 dose >2 x $10^5$/kg; and a normal to high enzyme level upon screening. She discussed the facility's preparative regimen and GvHD prophylaxis and policies for supportive care. She then presented survival data and discussed the impact of parameters such as total nucleated cells, CD34 and CFU dose and HLA match on outcomes. She concluded that CFU and CD34 are better at predicting engraftment, and HLA match had a highly significant impact on performance status. She also reviewed GvHD occurrence and stated that HLA matching did not appear to impact GvHD, though CD34 dose was correlative.

Dr. Kurtzberg then shared details of patient response and outcome updates, including performance of the children several years out. She emphasized that early treatment was critical for most of these diseases and described a pilot program in New York to screen for several metabolic diseases at birth. She concluded that cord blood seems to be better than matched, unrelated donors for malignant conditions, and this may be the case for non-malignancies as well. She recommended that the proposed indications for UCBT be expanded to include non-malignant conditions and advised the participants that this data had been submitted to the docket and that a publication was pending and would soon be publicly available.

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## UNRELATED ALLOGENEIC PERIPHERAL BLOOD HEMATOPOIETIC PROGENITOR CELLS

***Presentation by Dr. Miller***

John Miller, MD, Senior Medical Director, National Marrow Donor Program, discussed potential regulation of PBSCs and DLIs from unrelated donors. After describing the network, he reported that NMDP currently has 88 FDA-registered domestic establishments for PBSC and DLI collection, most of which are hospital based. Most of these centers perform collection in the related setting, and the concern is that some of these centers would stop unrelated collections if licensure were required. Dr. Miller highlighted some of the issues in unrelated PBSC regulations. The safety and efficacy of unrelated and related PBSCs and marrow are similar yet regulated differently (351vs 361, HRSA, etc.). If licensure were required, requirements should reflect current data and be feasible for collection centers to implement. Finally, he noted that the importation of PBSCs is essential to meet patient needs, and the regulatory framework must permit this to continue. Dr. Miller asserted that the level and type of regulation should be commensurate with the risk posed by the product characteristics. NMDP proposed that FDA consider regulating *unrelated donor* PBSC and DLI products that are minimally manipulated, for homologous use, HLA matched and for hematopoietic reconstitution in the same manner as *related donor* PBSC and DLI products.

Dr. Miller shared study results for 1,178 primary PBSC recipients in which donor characteristics of the minimally manipulated, T-cell depleted were studied. The study looked at the factors impacting engraftment and other outcomes in four areas: recipient related, transplant related, donor related and product related. The only distinguishing factors at day 25 were volume of blood processed, total WBC of product and total MNC of product. Adding citrate appeared as a significant factor but falls out on multivariate analysis. Of recipient related factors, age, performance status, disease risk, HLA matching and the conditioning regimen were all significant. He stated that 25% of these products were from outside of the U.S., and the factors that significantly impact day 25 neutrophil engraftment are a) volume of blood processed (univariate and multivariate analysis) and b) whether citrate was added (univariate analysis only). The only product-related factor that significantly impacts day 60 platelet engraftment is the number of CD34+ cells in the infused product. No product-related factors significantly impact day 100 overall survival.

Dr. Miller continued by stressing the importance of considering scientific and medical aspects of these patients. He presented data on 5,607 PBSC transplants, describing the incidence of serious and unexpected adverse events (SAEs) as 0.21%. After examining the details for each category, he concluded that the five SAEs would not have been avoided through additional manufacturing controls or licensure. Since the need for HLA matching is critical to a successful transplant outcome, international exchange of products remains a critical component. In 2005, 39 percent of overall PBSC and bone marrow collections (n=7,921) came from international sources, according to the NMDP. He then shared points in support of exercising regulatory oversight only to the degree necessary to protect the public health. The greatest predictor of a successful outcome remains patient disease, clinical condition and treatment regimen. Requiring a BLA under 351 for unrelated PBSC and DLI provides no added value and poses a resource drain on both international and domestic establishments, and the current controls in place for the manufacture of 361 products are sufficient for unrelated PBSC and DLI. He concluded by reiterating the request for FDA to regulate unrelated donor PBSC and DLI in the same manner as related donor PBSC and DLI, since both types have similar safety profiles, and no product related factors significantly correlate with overall survival at day 100 (see presentation 6).

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***Presentation by Dr.* Andrzejewski**

Chester Andrzejewski, PhD, MD, Medical Director of Transfusion and Apheresis Medicine Services at Baystate Health in Springfield, Massachusetts, and Immediate Past President of the American Society for Apheresis (ASFA), presented results from an informal survey the organization recently conducted . He described the process whereby the survey document was developed and then used in the solicitation of ASFA membership for information and commentary regarding potential proposed regulations. In partnership with staff from the NMDP, the survey document was constructed and then sent to all recipients of the ASFA Newsflash, an electronic news alert tool the Society has developed to communicate rapidly with its constituency. Participants were given a two-week window for responding.
The survey's purpose was to obtain information regarding the potential impact of proposed FDA regulations of HPC-A on apheresis collection facilities.

A total of 131 individuals responded, representing institutions from around the world but predominantly from the United States. Of those respondents, 115 stated that they currently collect or have collected HPC, Apheresis (PBSCs), Most reported performing PBSC collections in a hospital-based environment. A majority of respondents reported that less than half of their collections were for allogeneic use and most collected over 50 autologous units per year. Just over half of the responding participants indicated that their facility collected less than five allogeneic unrelated PBSC products per year.

Regarding the need to offer apheresis collection services, the consensus opinion was that the collection of apheresis products for unrelated patients was a valuable service for the community as well as for their individual respective centers. Although most respondents reported a willingness to establish GMP processes for unrelated PBSC collections, almost one-third stated they would be unwilling to apply for licensure. Obstacles to licensure and the subsequent potential impact on the future provision of apheresis stem cell collection services were also highlighted.

In addition, Dr. Andrzejewski reviewed selected free text comments sent in by respondents. Issues identified included the potential impact of the regulations as well as concerns about variations in testing and labeling between unrelated allogeneic cellular therapy products and conventional blood products, since both types of products are collected from normal blood donors. Additional comments included a discussion about the nature of FDA regulations, since unrelated allogeneic products and autologous products are regulated differently yet start with the same process and material. He acknowledged that the survey was nonvalidated, that only a short period of time was offered for responses and that they could not assess the "awareness" vs. the "understanding" of the respondents with respect to potential regulations.

Dr. Andrzejewski indicated that ASFA leadership plans to publish results from the survey, which would then be publicly available. He closed by stating that the regulatory architecture and guidance related to cellular therapy products collected by apheresis techniques should rest on a foundation of patient and donor safety and medical, scientific and quality rationales that are evidence-based in their derivations.

***Presentation by Dr. Lazarus***

Ellen Lazarus, MD, Medical Officer, Division of Human Tissues in the Office of Cellular, Tissue, and Gene Therapies, CBER, provided a review of FDA’s approach to the regulation of hematopoietic stem/progenitor cells (HPC). She described how this approach was unique because it is tiered (i.e., risk-based). The regulatory approach has three goals: 1) prevent

unwitting use of contaminated tissues with the potential for transmitting infectious disease; 2) prevent improper handling or processing that might contaminate or damage tissues; and 3) ensure that clinical safety and effectiveness is demonstrated for most tissues that are highly processed, used for non-natural purposes, combined with non-tissue components, or that have systemic effects on the body. HPC from cord blood and peripheral blood are "human cells, tissues, or cellular or tissue-based products" (HCT/P), and regulations at 21 CFR Part 1271 apply to all HCT/P, including HPCs. Furthermore, certain HPCs are subject to additional regulation, including GMP and biological product licensing requirements. Currently, there are two tiers: 1) those regulated solely under HCT/P regulations if *ALL* "kick down" factors apply and 2) those that are regulated under HCT/P regulations *AND* premarket review (BLA) if product does not meet all "kick down" factors. "Kick down" factors are codified in 21 CFR 1271.10(a) and include minimally manipulated; intended for homologous use only; not combined with drug, device, or biologic (exceptions apply); and does not have a systemic effect (exceptions: autologous use, use in first- or second-degree family relative, reproductive use).

Dr. Lazarus then reviewed the types of HPC products that are currently subjected to IND/BLA requirements. These products are HPC and bone marrow that are more than minimally manipulated; intended for non-homologous use; or combined with drug, device or biologic. She then described the agency's phased-in approach and that in January 1998, the agency issued a Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood HPCs and a Request for Comments. The Federal Register stated this applies only to unrelated allogeneic minimally manipulated HPC for hematopoietic reconstitution, and comments were solicited on the establishment controls, CMC controls, and processing and product standards. Only data on cord blood was submitted to the docket, thus draft guidance only related to cord blood was published in January 2007. She then reviewed the list of regulations to which all HPC are subject and the additional regulations of HPCs under IND and those that would apply to licensure. Dr. Lazarus closed by summarizing the current considerations regarding unrelated, allogeneic HPC, A (see presentation 7).

During the discussion of peripheral blood derived HPC products, a request was made for clarification of "who" would be responsible for compliance and "who" would be responsible for holding the IND for the use of non-licensed products in the post-licensure era. FDA responded that this is currently an open issue. Dr. Witten asked who determines donor eligibility, and following the discussion on this issue and its variations, Dr. Lazarus called attention to the question of who labels the unit. Dr. Warkentin added that in the case where an allogeneic apheresis product serves as part PBSC (HPC, A) and part DLI, the issue around labeling is even more complicated. The discussion concluded with several open questions: Dr. Heimfeld inquired about the justification for treating products differently, such as NAT requirements for blood and HCT/P products. Dr. Gunter raised the issue of different regulatory requirements between bone marrow and the other products. Dr. Read asked if there were any alternate mechanisms in other industries that might serve as models.

Dr. Gunter concluded the meeting with a call for suggestions for future meetings. Dr. Witten stated that in the absence of other topics, the agency would be interested in information related to the use of devices in manufacturing — not necessarily from the manufacturers but rather a discussion about what items are important for consideration regarding a device how they are evaluated and used, and what manufacturer information is relied upon. Regarding acceptance, what items are worrisome but accepted? Stakeholders were advised to notify FDA if they intend to pursue this topic so that the appropriate people can be invited. The meeting was adjourned at 12:00 pm with the next meeting to occur in January 2008.