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Final Meeting Summary of the 9th Cell Therapy/FDA Liaison Meeting
September 10, 2009
Bethesda, MD

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Host organization

International Society for Cellular Therapy
ISCT

Participating organizations: AABB, AdvaMed, ASBMT, AATB, BIO, CAP, CIBMTR, FACT, FDA/CBER/OCTGT, ISCT, NIH/NHLBI, NMDP, PACT, USP

Attendees: (**AABB**) Allene Carr-Greer, Kathy Loper, Aaron Lyss, John McMannis, Barbee Whitaker, (**AATB**) Scott Brubaker, (**ABC and ISCT**) Elizabeth Read, (**AdvaMed**) Steven Binion, Khatereh Calleja, (**ASBMT**) Thomas Joseph, (**BIO**) Jesse Seidman, (**CAP**) Zbigniew Szczepiorkowski, (**CIBMTR**) Doug Rizzo, (**FACT**) Phyllis Warkentin, Gillian Woolett, (**FDA/CBER/OCTGT**) Kimberly Benton, David Doleski, Yong Fan, Cherlita Honeycutt, Ellen Lazarus, Mary Malarkey, Richard McFarland, Jennifer Ross, Theodore Stevens, Nancy Waites, Gang Wang, M. Wells, Leslie Wheelock, Celia Witten, (**ISCT**) Kurt Gunter, Grace Kao, (**NIH/NHLBI**) Elizabeth Wagner, (**NMDP**) Julia Breyer, Traci Mondoro, Lisa Phillips-Johnson, (**PACT**) Albert Donnenberg, Jamie Winestone, (**USP**) Fouad Atouf.

Attendees were welcomed by the Co-chairs, Drs. John McMannis and Kurt Gunter. The meeting was called to order at 8:10am and Dr. McMannis introduced the speakers.

INFORMATION TECHNOLOGY IN CELL THERAPY

Presentation by Allene Carr-Greer MT(ASCP) SBB AABB

Allene Carr-Greer reviewed the definition of computer systems and aspects included in regulatory definitions of a "system." She noted that a Blood Establishment Computer System (BECS) also includes hardware, software, personnel, manuals, and standard operating procedures (SOPs). The presentation included a discussion of BECS in general and their design. These systems are designed to operate in a secure environment and generally encompass all aspects of blood banking. Electronic review, demographic checks, and recording of donor data are also included. Product inventory control and tracking applications were reviewed as well as external laboratory interface and control. Other system components such as reference laboratory operations, transfusion operations and quality assurance were reviewed in conclusion. (Slides).

Dr. Witten asked whether the systems are generally located in one facility or whether they communicate between blood establishments, with each having its own. The speaker

responded that BECS are validated systems that are a part of each licensed establishment's BLA. They are validated to perform within the licensed establishment's environment and are not typically set up to communicate with one another. Some vendors utilize user groups. These user groups then provide feedback to the vendor to revise or issue an entirely a new system.

A meeting attendee commented that there is a difference between a device used in manufacturing and a "system." Dr. McMannis asked whether the systems permitted one to further define allogeneic donors into related and unrelated categories. Ms. Carr-Greer responded yes, all products can be defined. Dr. Lazarus asked about the mechanism for transferring records. The speaker responded that accompanying records for these products generally include only shipping records, including CMV test results and, antigen history details, but she did not have up to date information on the amount of information such as what would be included in 'accompanying records' that could be managed by current BECS.

Presentation by Barbee Whitaker, PhD AABB

Dr Whitaker gave an overview of Biovigilance Systems in the U.S. Common definitions and systems were discussed. She explained that the goal of such systems is to gather data and analyze end points, permitting the early detection of safety issues, apply evidence for practice improvement and promote educational activities. Tracking of adverse reactions and errors are components of the system. Currently, most systems focus on blood, as hemovigilance systems. The hope is that these systems will expand to include cells and tissues with an end goal of safer and more efficacious transfusion and transplantation and practice improvement. Dr. Whitaker reviewed the current components of the AABB system including the initial survey and a web based data collection module for certain infectious diseases (WNV and Chagas). A total of 1600-1700 hospitals are surveyed every two years. Existing federal tracking systems and the goals of a hemovigilance system were discussed. The model is unique in that it includes public and private partnerships for both donors and recipients and a plan for tissues and organs, piloted last summer by UNOS and other organizations.

A hemovigilance system should have a standardized and centralized method of recording data and be voluntary and confidential. The system currently includes a common definition for incidents, a donor module and a recipient module. Dr. Whitaker then reviewed the National Health Safety Network, composed of 2000 hospitals. It now contains a Biovigilance module. This a partnership between AABB and CDC. Both donor and recipient adverse events are tracked. Types of reactions and the timeline for pilot studies were discussed as well. The U.S. Biovigilance Collaborative is composed of four components: blood recipient system; blood donor system; tissue and organs; and cellular therapies. (Slides).

Dr. Witten asked if the system was similar to Transplantation Transmission Sentinel Network (TTSN) or covered the same kind of adverse events. Dr. Whitaker explained that it operated in parallel to TTSN. Only reactions that included graft failures or disease transmissions were included. The next inquiry asked how long the pilot would last. Dr.

Whiteaker shared that they planned to report on it at the AABB Annual Meeting at the end of October 2009. The data would then be rolled into next year's data. The 9 site pilot was used for Office of Management and Budgeting purposes.

Presentation by Doug Rizzo, MD, MS CIBMTR

Dr. Rizzo presented a history and update on the current activities of CIBMTR. The voluntary outcomes registry is a joint effort between International Blood and Marrow Transplant Registry (IBMTR) and the National Marrow Donor Program (NMDP). It maintains a database of clinical information on autologous and allogeneic stem cell transplant recipients. The IBMTR provides scientific and statistical support for analyzing these data. The NMDP maintains a repository of stem cell donors and a recipient/donor sample repository. The CIBMTR, established in 2004, represents a research collaboration between the two organizations. Dr. Rizzo explained how the research has focused on transplant outcomes and the current center activities. Under the CW Bill Young Transplantation Program, outcomes reporting is required for allogeneic transplants when either the donor or recipient are in U.S. He reviewed the five components of the program and the stem cell transplant outcomes database (SCTOD). The transplant essential data form (TED) is used to collect data. He shared the various instruments and data that each collects. The base level form requires 30-90 minutes to complete. The data collection time points are based on pre-determined timelines. He also discussed variables that are not collected such as detailed infection data, grade 3-5 adverse events, graft processing parameters, etc. Additional system details were discussed. Dr. Rizzo then reviewed the role of an observational database in clinical research, its benefits and limitations. (Slides).

There was some discussion concerning the data collection forms--FormsNet. In this case, Dr. Rizzo explained, each center identifies a lead data collector and medical director. A multipoint verification is performed but there is no expectation with regard to data content. Safeguards are in place to avoid duplicate unique identification (ID) numbers and validation is performed within the forms and fields. When questioned about the cord blood bank outcomes report, he responded that this report is provided to banks to help them meet the need for outcome analysis and tracking. The CIBMTR is currently working with the banks to obtain the list of infused products and reconcile the data set. Most of the cord blood bank entry is not automated and susceptible to error. Several opportunities for process improvement exist.

Presentation by Julie Breyer NMDP

Ms. Breyer presented the NMDP Cord Blood Bank System, CORD Link and Traxis. She also discussed how NMDP supports these applications. CORD Link is used by twenty partner banks as an inventory and search management system. The cord blood bank source paperwork is used to determine eligibility. This documentation is maintained by the bank and the bank uses it to validate data entry. Both the locally assigned ID as well as the NMDP number are entered. The bank determines availability status. Various unit characteristics are captured. Transplant centers then use the Traxis application to perform a search. Specific criteria are displayed and the transplant center can drill down

on any of them for additional information. The donor qualification status is based on information entered by the bank in the NMDP system. Since the final qualification status is based on the bank's source documentation, the unit status can change during the process. Confirmation is performed before the unit is shipped. Transplant centers are responsible for reporting outcomes to CIBMTR, and CIBMTR provides outcomes reports to the banks. Ms. Breyer concluded with information relating to NMDP following established software development lifecycle procedures. ([Slides](#)).

Ms. Malarkey inquired about the notation of "unusual finding' on a slide. Ms. Breyer explained that this relates to a result on a question that may be of interest to a transplant center; such as culture result positive. Unusual Finding is not related to the eligibility of the product.

Presentation by John McMannis, PhD, MDACC Cord Blood Bank

Dr. McMannis presented information relating to cord blood bank informatics. A Cord Blood Information System (CBIS) was developed internally at MDAnderson Cancer Center (MDACC) for label generation and tracking, donor data collection, processing data collection and testing/reference lab data collection. Data for each cord blood unit is directly entered electronically and/or transferred into CBIS from several sources. For example, the state health service provides hemoglobinopathy screening. Donors complete a questionnaire online or on a laptop. The SPIDR is the MDACC institutional web service.   It collects maternal testing, the cord ABO/Rh result and microbiology. This system directly interfaces with CBIS. Laboratory processing data is captured real in CBIS real time. Once complete, MDACC transfers all relevant data to CORD Link.

Dr. McMannis then discussed change management with the system. Initially, evaluation includes an assessment about how the change will affect the various systems. Validation was performed in a modular fashion, facilitating modification and other benefits. The level of validation performed is based on the risk analysis performed during the change management process. The validation process, test script, and validation summary report were reviewed. ([Slides](#)).

An attendee asked the speaker whether the system was recording data or performing calculations and analyzing data. Dr. McMannis clarified that it was only data recording. . Following the presentation, the quantity of documentation was discussed as well.

Presentation by Grace Kao, MD ISCT

Dr. Kao reviewed the information needs of a hospital based cell processing facility. She provided a history of the program at Dana Farber Cancer Institute (DFCI) and also reviewed research and academic interactions at the facility. Product types and volumes were discussed in relation to regulatory requirements and product classification. The challenges of a system to capture such a diverse facility were covered in detail. The processing facility provides and abundance of information to both internal and external customers. The various computer systems in use by the facility were also presented as well as staff interactions with other information systems. Dr. Kao stressed that their

solution is a team approach. It is time consuming but effective. The model of a test project for electronic physician order was discussed. The final portion of the discussion included requirements of the facility for a manufacturing execution system. A timeline was developed as the facility moved in this direction. The project remains incomplete after six years of various efforts and initiatives. Project obstacles and costs were reviewed and she closed with a discussion of the urgent need for such a system in cell manufacturing facilities. (Slides).

Presentation by Albert Donnenberg PhD, PACT

Dr. Donnenberg discussed the laboratory information system evaluated by the University of Pittsburgh. He began with an overview of system requirements. He then listed advertised features for the "quality product" and "laboratory operational information." Dr. Donnenberg then described their actual experience with the software including the requirements to develop some of the records and protocols themselves. After discussing the challenges of the system, he described some of the issues facing the laboratory today and obstacles that prevent them from being entirely electronic. He then summarized the need for such a system and the limitations of such. (Slides).

Meeting attendees then discussed the percentage of effort for each of the aspects in Dr. Donnenberg's presentation with regard to clarifying those which were performed by the company and those which had to be performed by the facility staff.

Presentation by Scott Brubaker, CTBS AATB

Mr. Brubaker presented the results of an informal survey AATB recently performed and followed that with a discussion of the organization's plans to address concerns with electronic records and software systems. He reviewed the survey content and results, noting that the answer most often obtained was listed first on each slide followed by prevalence of other responses. The survey was sent to eleven contacts at a cross-section of large, moderate and small sized tissue banks that process tissue. Nine facilities responded. Each question asked about information technology functions and whether the system was developed from "off the shelf" software or was "purchased ready." Categories included HCT/P manufacturing functions such as: donor screening, donor testing, tissue recovery, storage, processing, packaging, labeling and distribution. Results for each were reviewed. Mr. Brubaker summarized the results and shared some of the commentary from tissue processing facilities. AATB has formed an "Electronic Records Task Force" which includes representatives from both tissue banks and software companies. The goals for this group were shared at the presentation summary. (Slides).

FDA OVERVIEW

Presentation by David Doleski, OCBQ/DMPQ, FDA

Mr. Doleski discussed regulatory considerations for the use of software for manufacturing HCT/P. He began with an overview of CBER/DMPQ Responsibilities, parts of the software lifecycle and aspects that affect software complexity.

Considerations for the criticality of software were detailed. Examples of computer software applications in the manufacturing environment were reviewed next. Mr. Doleski described the Good Automated Manufacturing Practices (GAMP) classification of software categories and described approaches to risk assessment. Software that contains custom applications requires the highest level of validation. He then discussed integration issues and levels or types of testing one would perform. He added that individual business assumptions may differ and data quality may vary between systems. Validation of individual components may then be combined and the integration of the full system validated. Regarding user acceptance testing, the speaker cautioned that formal testing is performed to ensure operators are capable of using the system (user friendliness, etc). Mr.Doleski then reviewed applicable regulations including recent revisions the GMPs. It was previously thought that part 11 applied to all computers but he clarified that they only apply to electronic systems where a signature is applied to the data. Operators must be trained but there is no requirement to keep training records. The speaker then shared some helpful resources and described the agency's current thinking on part 11 compliance, software validation, BLA submission content and inspections. BLAs generally do not need a lot of information about the computer system unless it affects product safety. Submissions should include descriptions of major systems and a summary of validation data conveying what data was generated, whether lots were produced with the validation runs of the system and the outcome of any such products. If the software was used to manufacture lots then the agency would want to know if those products were used. In this circumstance, it might be best to use the products (depending on the circumstances) so that one could demonstrate that the product could be released. (Slides).

Presentation by Mary Malarkey OCBQ/CBER/FDA

Ms. Malarkey reviewed inspectional findings on computer systems. For the three year period presented a total of 300-400 inspection results was presented. Only core GTP requirements apply to these inspections. Most inspectional findings related to software validation or inadequate validation. The second most common citation related to inadequate validation plan, documentation or approval. She then reviewed 47 observations from drug inspections and provided examples of noncompliance. (Slides).

The group then discussed the differences in scope of 351 and 361 products as Dr. McMannis asked for clarification. Ms.Malarkey reminded the group that while the process may be similar, only core GTPs apply to 361 products.

In conclusion, FDA agency representative responded that the official record is the one you create concurrently. The system should designate which record is used as the primary record. Print outs are acceptable if data is captured real time.