FINAL Meeting Summary of the 11th Cell Therapy/FDA Liaison Meeting
November 29, 2011
Bethesda, MD

Host Organization:

International Society for Cellular Therapy
ISCT®

Participating organizations: AABB, AdvaMed, CAP, FACT, FDA/CBER/OCTGT, ISCT, NHLBI, NMDP, PACT, SITC, USP

Attendees were welcomed by the Co-chairs, William Janssen, PhD and Anita Szajek, Ph.D. The meeting was called to order at 12:40pm and Dr. Janssen gave opening remarks (*see presentation #1*). Dr. Janssen presented a brief overview on the challenges of early phase and late stage development and commercialization. He noted that these challenges include ancillary materials and pharmacovigilance.

ANCILLARY MATERIALS IN CELL THERAPY PRODUCTS

USP Perspective on Ancillary Materials, Selection, Qualification, Standards

Presentation by Elizabeth J Read, MD

Dr. Read began by describing that "medicines" must meet United States Pharmacopeia (USP) requirements where these standards exist and gave a historical perspective of the USP and FDA. She also explained the publications' structure and chapter designations. Ancillary materials are materials that come into contact with the product during manufacturing but are not intended to be part of the final product formulation. Examples of ancillary materials and their potential impact were discussed next. Dr. Read then reviewed the US FDA regulatory approach for ancillary materials. The USP approach of chapters, monographs and reference standards was reviewed in greater detail. The presentation also included a risk based classification model using a four tiered system.

To demonstrate the approach, Dr. Read shared scenarios for fetal bovine serum, and some cytokines and growth factors frequently used in cell therapy manufacturing as part of cell culture. She concluded by highlighting the partnership between USP and industry, plans for future chapter revisions and the USP committee approach before taking attendee questions. *(See presentation #2)*

Dr. Witten asked about the motivation for sponsors to participate in the development of standards. Dr. Szajek responded that the ancillary material issue is of concern to many developers, including sponsors of CDER products (e.g., monoclonal antibodies, others) where the ancillary materials are critical to the manufacturing process. Dr. Furstenberg

commented that standards help sponsors during product development and compliance with cGMP, where progressive specification of all aspects of product manufacturing is necessary.

Dr. Witten asked about the location of sourcing information for FBS and the speakers explained it was covered in the general chapters. She then asked about the content and purpose of specific monographs. The speakers responded that medicare and Medicaid are set up such that reimbursement is affected for tissue products.

Dr. Simek asked about the FBS standard and the procedure for its selection. The presenters explained that the various companies had voluntarily supplied product and agreed to participate as they see the project as advancing the field.

Challenges for the Cell Therapy Manufacturer

Presentation by David Stroncek, MD

Dr. Stroncek then provided examples of common challenges faced in the manufacture of phase I/II clinical trials using cellular therapy products. After describing the case facility, he reviewed a list of common ancillary materials and their applications as well as source manufacturing conditions of some of the ancillary materials. *(See presentation #3)*. Third party donors present an additional challenge. He emphasized that if these products are used, the most prudent approach would be to screen and test them as cell therapy product donors. Dr. Stroncek then concluded by describing the motivation and experience of clinical investigators. He emphasized their familiarity with basic regulations, clinical issues, and the pressure to demonstrate results and collaboration.

As the question period opened, Dr. Witten asked about the availability, cost and quality of materials. How does this tie in with the USP efforts? Is it an issue of availability? Dr. Read responded that while the USP may not help with cost, if a standard is available then this might help identify an alternate source for a material. Dr. Szajek added that there may also be the added benefit of comparisons if other suppliers were identified. Dr. Gunter added that for scale up and scale out of cellular therapy products for pediatrics, a USP grade material might have lower risk than non USP materials. He elaborated on the challenges for commercial companies, sharing examples of cytokines and the availability of clinical grade pentastarch. As industry mergers occur, supplies may be affected. Companies may not be willing or able to route funds to materials for a phase I/II study until enough market share for that material exists. Once the market exists and a cell therapy product is produced at a larger volume, then the company becomes more interested. USP may have a role in helping with supply issues by providing a market advantage.

Dr. Benton asked about FBS and adventitious viral testing. This is important for phase I/II trials and inactivation is required for shipping. Dr. Read described a situation where the FBS has been tested and released but the endotoxin was found to have exceeded the limit on the certificate of analysis. Dr. Simek added that this is a good example of the

reason a product specification or certificate is often insufficient. It is also a good reason to support a robust raw materials program. The group discussed the challenge that also exists for raw product (cellular) sources.

CELLULAR THERAPIES PHARMACOVIGILANCE

Cellular Therapies Pharmacovigilance

Presentation by Lisa Beth Ferstenberg, MD

Dr. Ferstenberg opened by describing the current status of reporting for HCT/Ps on form 3500A. She explained the review process and the primary focus of the transmission of infection and communicable diseases. She advocated for a dedicated group to follow up on patient outcomes for both acute and long term adverse events for cellular therapy products, which are different than those for gene therapy products. The issues, she noted, have outstripped the reporting system. She proposes a group to look at revision of the form and the addition of additional details about cell source and the capture of ancillary materials. *(See presentation #4).* Dr. Ferstenberg also advocated for the capture of indications and a reclassification of events specific to cellular therapies. The proposed categories include graft-versus-host disease, atherosclerotic or re-stenosis complications in the cardiac setting, tumerogenesis and metastases of infused cells. The plan would be to create a long term pharmacovigilance database allowing the statistical evaluation of adverse event signals.

Dr. Witten noted that it was unclear which products would be presumably covered, those under INDs, BLAs or both. Dr. Ferstenberg replied that ideally, the system would capture both. Dr. Witten then asked for examples of things that might have been learned by such a system. Regarding the situation of rogue cells found in unexpected loci, Dr. Ferstenberg replied that cellular therapy products are much more complicated because of the diseases, cell types, manufacturing differences, etc. This makes it difficult to accurately detect a signal in the database due to the low numbers. CIBMTR collects data on adverse events and longer term outcomes on a voluntary basis. They have only one form but the current landscape for cellular therapies includes several forms, the 3500A for example, serves FDA well for INDs but the speaker clarified that she was describing more of an industry wide initiative. There would be an analysis and launch after an initial pilot phase.

Attendees then asked for clarification on the relation to the database that collects data on gene therapy products. Discussions ensued regarding whether this had additional value. Given the complexity of cellular products and FDA's role, long term follow up and analysis for cellular therapy products beyond infectious disease transmission would be helpful.

Diane Maloney asked whether the lack of specificity on the reporting form was part of the problem with data capture. The presenter emphasized that the form does not give the degree of specificity that is needed. Additional identifying information on the form would help understand the issues related to cell therapy products. The follow up question clarified that this information would be helpful for both 351 and 361 type products though some is collected as part of the IND process for 351 products. The speaker added that the primary goal at this time is to begin a conversation about building such a system and improving data collection. Mrs. Maloney then asked about specific problems with the form. Dr. Ferstenberg explained at the identification of safety signals teaches the field more than just the isolated experiences of smaller groups. It permits initial exploration of ways to use them more effectively moving forward. It provides time to consider questions and the data to be collected, going beyond a discussion about the form, which was originally designed for tissues.

Dr. Simek said the form needed a purpose and the NIH/FDA GeMCRIS (Genetic Modification Clinical Research Information System) was to collect safety data on gene therapy products. Access to such data is limited so the teaching function is essentially limited to those who have access to it. She explained that a larger question was also who would compile, interpret and trend the data.

Hemoviliance

Presentation by Barbee Whitaker, PhD

Dr. Whitaker opened by describing how the infectious disease risk has dropped in the blood transfusion industry and described how this might be comparable to tissues and cells. The testing of donors has become more safe and transfusion-transmitted diseases (TTD) are less of an issue than in decades past. She shared data *(see presentation #5)* and explained that the current issues are more associated with non-TTD such as TRALI (Transfusion related acute lung injury) and TACO (Transfusion associated circulatory overload). The early 1990s saw improvements in industry testing and screening due to the response to HIV and other reported errors. SHOT is the acronym for serious hazards of transfusion and as reports increased, there was a decrease in the number of deaths associated with transfusion related adverse events. Hemovigilance looks at the "numerator" data in comparison to denominators. Few systems collect both sets of data. She described the definition and role of biovigilance and its numerous facets including donation surveillance, transplantation/transfusion surveillance, emerging infectious disease monitoring and availability or use assessment. Dr. Whitaker described how AABB and other organizations and entities have worked together to develop a hemovigilance module for the National Health Safety Network (NHSN) at CDC in the context of US Biovigilance. In the current system, the blood transfusion hemovigilance component is active; the donor hemovigilance component is in pilot stage. The tissue component has been pilot tested with the Centers for Disease Control (CDC) and they will determine the next steps. There has been some discussion regarding cellular therapy but no additional centralized action has been taken. The NHSN is now used in almost every hospital in the US for healthcare acquired infection reporting. Reporting is

required by some states. Participating facilities cannot see others' data. Groups can form for specific projects. The "system components" detail permits like facilities to benchmark performance on key measures and there is a potential for calculating rates since denominator data is collected. The hemovigilance module collects adverse reactions and incidents that could affect the patient. Dr. Whitaker suggested that this model might serve as a useful comparison for cellular therapy, particularly since it has the ability to incorporate custom fields and has extensive reports capability. Case definition criteria and categorization of reactions are also helpful. Participants may choose to join groups or not and it appears to facilitate the formation of expert groups to develop and test interventions. Dr. Whitaker wrapped up her presentation with a description of AABB's patient and donor safety center. She described the definition of a patient safety organization (PSO) and why this status is important. The high number of participants is further testament to the system's value. The challenges include funding and the limitations of matching the goals and data restrictions and governance of the system. Data collection and communication are key, she explained, as these dictate the story that gets told. The next steps are to validate some of the data elements, maximize expert working groups and develop communications and best practices.

Dr. Witten asked about the volume of reports thus far and the time course for adverse events. Dr. Whitaker responded that the timeframe varies. Some are immediate and others take up to one month. Some events, such as bacterial contamination, might be reported shortly after. A review of TRALI and TACO cases is now in progress. Over 1,000 AEs and even more incidents have been reported over the past two years. Most are febrile and non hemolytic allergic reactions. Acute respiratory reactions and hemolytic reactions have been reported and these acute reactions appear to have more variability in reporting. Dr. Witten asked about the relationship of reporting to FDA. Dr. Whitaker explained that at this time there is no reporting to CDA as CDC is waiting to see how the reporting and analysis goes. There was discussion about whether these issues were related to technical or political challenges. Change control is also an issue. When functionality is developed for data sharing with FDA, the hospitals will report to FDA through some affirmative step. CDC will not report events to FDA due to restrictions to its NHSN mandate. Dr. Simek added that the gene therapy reporting form had to be acceptable to FDA as did the medical language. The computer language issues, such as HL7, have also been worked out over the years.

Robert Lindblad noted that once a product is FDA approved, it should be consistent. He asked how the system might then work for cellular therapy products in which there is a relatively low volume and highly variable products. Dr. Whitaker explained that bringing together the groups in the community who would be reporting and using the data was key to its success. Consistent terminology, such as ISBT 128, is also critical.

Regarding validation, attendees asked about under reporting. While reporting should be good for those who do report, there is a concern about under reporting. The community is now focusing on raising awareness in this regard.

CHALLENGES TO CELLULAR THERAPIES DEVELOPMENT AND POTENTIAL AVENUES FOR FDA HELP IN OVERCOMING THEM

Presentation by Kurt Gunter, MD

Dr. Gunter opened by describing some of the current issues facing the field with a focus on what could be done to move the field forward. The scientific issues include immunological barriers, challenges in optimal product formulation and limitations with the current animal and laboratory models. *(See presentation #6).* In the manufacturing and quality realm, challenges include the inclusion of ancillary materials; product characterization and stability; scale up, process controls and manufacturing changes; and the lack of reference standards for products. Commercial cell therapy products have a manufacturing focus and it can be a challenge for scale up or technology transfer to other sites. The clinical challenges include potentially imprecise dosing, limited surrogate end points and few pivotal studies with poor or absent controls statistical challenges. The model for clinical trials is often based on what an investigator can afford so the statistical data may be difficult to interpret. Pharmacovigilance and length of follow up are also limitations though some cell therapy product donors are followed longer than that of the pharmaceutical industry. Regarding policy, Dr. Gunter explained that the public may possess unrealistic expectations about time to market for a product in research and this challenges the legitimacy of the industry. The risk affects both patients and the field. There is limited global harmonization and compendia standards. The financial and buss models are challenging because access to capital is limited for phase I/II trials. The cost of goods is high and reimbursement is often difficult to obtain or absent. Partnerships can be difficult due to the unique nature of the industry and unconventional business models of many therapies, particularly in the autologous setting. In conclusion, he noted that the nation faces an aging population and there are unmet medical needs. The lifetime cost if spread out over the entire patient lifetime, may be less than perceived. Some adult stem cell therapies have shown proof of principle and some products have made it to market successfully. Recent pharmaceutical deals in the industry also show promise. He urged attendees to consider the challenges and consider addressing them, even if in another forum.

Stephanie Simek noted that the challenges listed are the same as those seen by FDA. Dr. Witten asked about the role of FDA and industry in the setting of ancillary materials – what is needed and would be seen as helpful? Dr. Read asked if the ICH quality by design guidances were being viewed by OCTGT as applicable or useful for cell therapy products. Ms. Simek noted this approach is most appropriate for development of small molecules. While some parts work well, others would be difficult for cell therapy as parts of the process may not be as well controlled and may not fit the same model because of the variability in cellular products. Dr. Read added that in some ways, every process has a wide design space with high variability. The end products are also variable. Ms. Simek commented that OCTGT uses a case-by case approach in their reviews. FDA and stakeholder participants agreed that public presentation of product development case studies by sponsors is helpful to the community. The closing discussion focused on the benefit for common information on ancillary materials and that public expectations are

always difficult to manage. Dr. Lindblad suggested the pharmacology/toxicology model might be helpful as we learn from others moving forward. The group discussed ways to try and reach the public as well as challenges to such messages. Patients may receive incorrect information. There is also a need to build enthusiasm to obtain funding. Some of this difficulty is created by our own funding system. The FDA attendees noted that the CDER Learn website might be helpful.
http://www.fda.gov/Training/ForHealthProfessionals/default.htm

In conclusion, Dr. Janssen asked for recommendations for future topics. Richard McFarland proposed tissue engineering in cellular therapy. A second suggestion was information on translational officers at major universities.