Final Meeting Summary of the 7th Cell Therapy/FDA Liaison Meeting
February 5, 2008
Bethesda, MD

Host organization

Cell Therapy Industry Attendees: John McMannis (AABB), Joe Giglio (AABB), Scott Brubaker (AATB), Khatereh Calleja (AdvaMed), Mark Sistare (AdvaMed), James Gajewski (ASBMT), Mark Bretcher (ASFA), Grace Kao (ASH), Jesse Seidman (BIO), Elina Linetsky (CTS), Dr. Warkentin (FACT), Kurt Gunter (ISCT), Shelly Heimfeld (ISCT), John Gilbert (ISCT), Bruce Levine (ISCT), Joyce Frey (ISCT), Jane Arthurs (ISCT), George Nemo (NHLBI), Fran Rabe (NMDP), Diane Kadidlo (PACT), Robert Lindblad (PACT), Aisha Khan (RAPS), Fouad Atouf (USP)

FDA/CBER Attendees: Celia Witten, Stephanie Simek, Diane Maloney, Mary Marlarkey, Richard McFarland, Steven Oh, Keith Wonnacott, Gang Wang, Ashok Batra, Leslie Kux, Patrick Riggins, Rachael Strong, Martha Wells, Teresita Mercado, Ellen Lazarus, John Bishop, Seamus O'Boyle

Attendees were welcomed by Shelly Heimfeld, PhD, ISCT President for Kurt Gunter, MD, chair, ISCT Legal and Regulatory Affairs committee, and the meeting was called to order at12:15 p.m. Participant introductions were made to benefit those that have not attended this meeting before. The last meeting summary was presented for review.

Celia Witten, PhD, MD, director of Office of Cellular Tissues and Gene Therapy, CBER, FDA, agreed with the questions that were included in the agenda and indicated that she was looking forward to the discussions. Dr. Witten reinforced that the FDA would not be able to comment on the draft *Guidance for Industry on Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs)* because it is currently out for public comment.

FDA DRAFT GUIDANCE ON CELL SELECTION DEVICES FOR POINT-OF-CARE PRODUCTION OF MINIMALLY MANIPULATED AUTOLOGOUS PBSCs *Presentation by Dr. Joyce L. Frey-Vasconcells*

Joyce L. Frey-Vasconcells, PhD, executive director of Pharmanet Consulting, summarized concerns regarding the draft *Guidance for Industry on Cell Selection*

Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs). Many of the concerns centered on points requiring clarification and a need to broaden the scope of the guidance document. According to Dr. Frey-Vasconcells, the following were among the major areas requiring clarification:

1) **Definition of the term "walking distance."** Today, many facilities are large and can be located across town, so the term "walking distance" can be interpreted differently. What if the apheresis center is contracted with the hospital? Is this acceptable?

2) **Definition of the term "same surgical procedure."** This guidance does not follow the same definition of "surgical procedure" outlined in other FDA documents, such as *Guidance to Industry Regulation of HCT/Ps Small Entity Compliance Guide*. This draft guidance appears to have narrowed the definition of "same surgical procedure," while the small entity compliance guide indicates that an HCT/P can be stored for several days between recovery and implantation as long as there is no additional manufacturing. Why does the draft guidance document only address peripheral blood stem cells and not bone marrow or other stem cells isolated with cell selection devices? This is an area that is recommended to be broadened along with addressing the use of mobilization agents. Even though FDA officials were unable to provide a commentary on the comments raised to the draft guidance document, they did state that they would take the issue of peripheral blood stem cells versus stem cells from other sources back to the agency for internal discussion (see Presentation 1).

USE OF DEVICES AND MANUFACTURING EQUIPMENT IN CELLULAR THERAPY *Presentation by Dr. John Gilbert*

John Gilbert, PhD, of Piconomics spoke on behalf of ISCT, presenting a general overview of the types of devices and manufacturing equipment utilized in the production of cellular therapy products. Dr. Gilbert raised the option that equipment should be thought of as a "type" not a "brand" and provided several examples; however, this concept needs to be expanded to a full equipment typology. This prompted a discussion of whether there is a classification system for equipment and the existence of such a list. The FDA responded that it currently does not maintain a list and would be interested in reviewing one if developed by industry.

The determination of which systems are equipment and which are devices appears to be dependent on how systems are used in a cell production process flow. It may be that a particular system can be a device in one production process and equipment in another. If so, how does one tell? Does the interrelationship of equipment and reagents affect the classification? These are a few questions that may be answered by the prototype process and equipment survey that is being developed by the ISCT Devices Working Group. The template of the survey was shared with the group. While the development of the survey is still underway, it is probable that the data will be qualitative, not quantitative, with the hope that it will provide the following information:

- Allow identification of where equipment is in a process flow.
- Allow some understanding of where the requirements of equipment change — which step(s) in the sequence the equipment is utilized
- Allow one to ask if a specific component is equipment or a device — and check if that is changing based on how (which step) the equipment is being used.
- Allow one to ask how many different reagents are being used with an equipment system.

The FDA was intrigued by the survey, indicating that it would be interested in the outcome and could see the usefulness of the data. An invitation for Stakeholders to participate in performing specific parts of the survey process was extended. Some participants expressed concern that this is treading into an area of "standards." That being stated, this might be better developed along those lines, in which case the process and equipment standard could be used in reporting all descriptions of cell production processes from the beginning and we could just look this sort of information up, instead of collecting it. A follow-up step is to explore whether the European Union or ISO have standards/information that would be useful (see Presentation 2).

SPECIALTY TOPICS

Presentation by Dr. John McMannis

John McMannis, PhD, director of the cell therapy laboratory at the University of Texas MDAnderson Cancer Center, presented the industry's perspective on cell sorting and selection devices. Dr. McMannis' presentation consisted of four main topics; role of cell selection devices, decision process of which device to use, manufacturer's requirements, and 'issues'. Translational research requires a lot of time to become functional, a significant amount of funds is required, and there are intellectual property constraints, with the majority of the effort occurring during the "engineering" phase. However, high-speed cell sorting has two key benefits: high purity of cell population and enrichment of a subpopulation. In contrast, there are also disadvantages to high-speed cell sorting: single-use disposables, time, cost of equipment, cost of procedure and regulatory issues. The determination of which device to utilize in the trial depends on the type of product that is to be produced. If the product is a "361" product (i.e., minimally manipulated, homologous use only; not a combination product with a systemic effect), it does not need to be reviewed by the FDA. Therefore, the burden is on the facility to ensure good tissue practices (GTPs). Prior to selecting the device, the following factors are considered: use in a previous clinical trial, manufacturer audit, documentation review, and discussions with the FDA. The manufacturer is required to provide a certificate of analysis, which is very important; instructions for use; and changes/updates when available. The process of selecting the device is then followed by internal validation/qualification prior to use in the trial. The FDA stated that if the facility does not have the expertise in-house to perform the software validation, then it should seek external assistance. Often there are changes by the manufacturer in the equipment, reagents or software. When notified by the manufacturer of equipment changes, the equipment is revalidated/ qualified.

However, there are instances when the manufacturer change does not affect labeling, and the change would be transparent to the end user. However, if the device is used for a process other than what is stated in labeling, the change could affect the process, because the manufacturer would not have validated the change for the off-label use. Software changes are the most common changes affecting the process. The facility should require that the manufacturer provide a summary of software changes so that an evaluation of the impact on the processing can be made. FDA reminded the group that the process, not the software, should be revalidated.

A few other issues that were discussed during the meeting included the following:

- Growth factors potency — How to determine acceptability; manufacturer's information.
- Scaling up a study — What would be the biggest issue; need for more equipment.
- Cord blood products — No clear indication of what to look for in QC of product.

(see Presentation 3).

Presentation by Elina Linetsky

Elina Linetsky, MSc, MT, of the cell transplant center at the University of Miami Miller School of Medicine, presented the industry's perspective on equipment in the manufacturing of pancreatic islet cells. Ms Linetsky provided the group some historical background on pancreatic islet cells and the types of equipment required to process such cells. According to section 351 of the Public Health Service Act, pancreatic islet cells are biologic products. As such, prior to marketing the product as therapy, the manufacturer must demonstrate safety, purity, potency and effectiveness. Site-to-site variability is an issue with these products and manufacturing equipment may play a part in this variability. In addition, due to the complex nature of the pancreatic islet cell products, there is limited ability to characterize the final product prior to administration into the patient. Regardless, the manufacturing of pancreatic islet cells must follow manufacturing controls as stated in 21 CFR Parts 210, 211, 600, 601, 610 and 1271. Adherence to the requirements is challenging for the source material — pancreatic islet cells — which cannot be controlled in the traditional sense. Acceptance criteria have been established to mitigate some of the variables, including control of the process according to cGMP; tracking of final product to donor/tissue, qualification and validation of equipment; and lot-to-lot reproducibility. They are currently considering what additional validation will be required to support product licensure. The key piece of equipment utilized for the isolation of the pancreatic islet cells is the Ricordi Chamber. This plastic chamber, which has undergone several modifications, is lightweight, disposable and allows for full view of the contents. In addition to the Ricordi Chamber, the COBE 2991 cell processor is utilized. Although the device was not designed for islet cells, it has been used successfully as a high-capacity centrifuge in the processing of pancreatic islet cells. Ms Linetsky concluded with a few slides of devices that would be integral to the future of pancreatic islet cell production. One such device was a subcutaneous, neovascularized device for the infusion of pancreatic islet cells (see Presentation 4).

Presentation by Dr. Bruce Levine

Bruce Levine, PhD, of the Department of Pathology and Laboratory Medicine at the University of Pennsylvania, presented the industry's perspective on devices and manufacturing equipment used for production of immune cell therapy and cell expansion. In support of the facility's IND for T-cell therapy, a modified Gambro Elutra device is used. The device is the shell of the original apheresis machine that contains inner working parts modified for the isolation of T-cells. This is considered off-label use because the device was not designed to perform this specific function. Prior to using the device in the IND, the device was validated for its intended use in this protocol. The manufacturer supported these efforts by providing multiday technical training, feedback on data collected during validation and a cross-reference to the device master file.
As part of in vitro expansion of T lymphocytes, the cells are cultured in the Baxter lifecell flasks — gas permeable bags — with anti-CD3/anti-CD28 Dynal Beads. The bag is then placed on the WAVE biotech bioreactor for several days, which provides a gentle rocking motion and the exchange of gases. After the expansion process is completed, the cell culture is passed over the Baxter MaxSep magnets, where the beads are retained and the cells flow through. Currently, the process utilizes the Fenwal Harvester which is built on the apheresis machine CS3000 frame that concentrates and washes the cells. Fenwal has notified users that it will no longer be providing technical support or kits for the Harvester. The challenge is that there is not a comparable device on the market. The FDA reminded participants that there are requirements for any change in devices specified in the IND, and those must be communicated to the agency as an amendment prior to use (see Presentation 5).

FUTURE MEETING AND CONCLUSION

Presentation by Dr. Kurt Gunter

The meeting provided the opportunity to brief FDA on a sampling of devices that are currently being utilized in cellular therapy. Because device manufacturing is commercially based, many devices are being used for alternative uses, rather than their intended use. FDA representatives stated that the presentation were very informative. The group was asked to suggest future topics/areas for the next liaison meeting and submit any recommendations to Jane Arthurs at ISCT (jane@celltherapysociety.org). Dr. Gunter adjourned the meeting.